General Psychiatry

Effects of ketamine in electroconvulsive therapy for major depressive disorder: meta-analysis of randomised controlled trials

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ABSTRACT

Background The use of ketamine in electroconvulsive therapy (ECT) has been examined in the treatment of major depressive disorder (MDD); however, there has been no systematic review and meta-analysis of related randomised controlled trials (RCTs).

Aim To examine the efficacy and safety of ketamine augmentation of ECT in MDD treatment.

Methods Two reviewers searched Chinese (China National Knowledge Infrastructure and Wanfang) and English (PubMed, PsycINFO, Embase and Cochrane Library) databases from their inception to 23 July 2019. The included studies' bias risk was evaluated using the Cochrane risk of bias assessment tool. The primary outcome of this meta-analysis was improved depressive symptoms at day 1 after a single ECT treatment session. Data were pooled to calculate the standardised mean difference and risk ratio with their 95% CIs using RevMan V.5.3. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to assess the whole quality of evidence.

Results Four RCTs (n = 239) compared ketamine alone or ketamine plus propofol (n = 149) versus propofol alone (n = 90) in patients with MDD who underwent a single ECT session. Three RCTs were considered as unclear risk with respect to random sequence generation using the Cochrane risk of bias. Compared with propofol alone, ketamine alone and the combination of ketamine and propofol had greater efficacy in the treatment of depressive symptoms at days 1, 3 and 7 after a single ECT session. Moreover, compared with propofol alone, ketamine alone and the combination of ketamine and propofol were significantly associated with increased seizure duration and seizure energy index. Compared with propofol, ketamine alone was significantly associated with increased opening-eye time. Based on the GRADE approach, the evidence level of primary and secondary outcomes ranged from very low (26.7%, 4/15) to 'low' (73.3%, 11/15).

Conclusion Compared with propofol, there were very low or low evidence levels showing that ketamine alone and the combination of ketamine and propofol appeared to rapidly improve depressive symptoms of patients with MDD undergoing a single ECT session. There is a need for high-quality RCTs.

INTRODUCTION

Electroconvulsive therapy (ECT), which is also known as electroshock therapy, is an effective treatment procedure for major mental disorders, including schizophrenia, bipolar disorder and major depressive disorder (MDD).[1] General anaesthesia renders unconscious patients free from muscle paralysis and/or even recall and is wildly applied to all ECT procedures in clinical practice.[2] Duration of seizure activity, recovery and haemodynamic parameters could be affected by the choice of anaesthetic agent for ECT. Thus, there is a need to determine the optimal choice of anaesthetic agent for ECT from several agents, including ketamine, propofol, etomidate, sevoflurane, ethohexital and thiopental.[3]

Ketamine is an N-methyl-D-aspartate (NMDA) antagonist with a rapid antidepressant effect.[4,5] Despite its risk of potential adverse drug reactions (ADRs),[6] increasing randomised controlled trials (RCTs) have reported that ketamine was significantly superior to placebo in reducing depressive symptoms in patients with unipolar or bipolar depression.[7–11] Ketamine is often used in ECT and can cause a favourable seizure outcome by inducing action and increasing seizure duration.[12,13] However, ketamine could cause delayed recovery, as well as induce transitory psychotic episodes and cardiotoxicity.[14]

Given the correlation of propofol with reasonable haemodynamic response to ECT, it has become increasingly popular in ECT anaesthesia.[15] However, propofol has limitations with respect to reduced seizure duration and increased seizure threshold.[16] The combination of ketamine and propofol has been successfully employed for various anaesthetic procedures.[2] This could be attributed to the following: (1) ketamine can mitigate propofol-related hypotension and (2)

propofol can mitigate ketamine-induced recovery agitation and vomiting. Thus, the use of the combination of propofol and ketamine has theoretical benefits, including obviating the need for opioid coadministration and minimising the propofol dose.

There have been several RCTs[12 17–19] on the use of ketamine alone or ketamine plus propofol in a single ECT treatment session for patients with MDD; however, they have reported inconsistent findings. A recent meta-analysis of seventeen RCTs found that ketamine alone did not increase the antidepressant ECT effect; moreover, ketamine combined with other anaesthetics has a short-term advantage with respect to improvement of depressive symptoms at the early ECT stages[20]. These findings are consistent with those of another meta-analysis.[21] However, this meta-analysis[20] did not include RCTs with a single ECT session.[12 17–19] Notably, there has been no systematic review or meta-analysis exclusively investigating the effectiveness and safety of adjunctive ketamine with single ECT treatment in patients with MDD. Thus, we aimed to perform a meta-analysis to examine the effectiveness and safety of ketamine alone and that of ketamine combined with propofol in patients with MDD undergoing a single ECT treatment.

METHODS
Search strategy
This meta-analysis was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.[22] As recommended by recent meta-analyses,[23 24] English (PubMed, Embase, PsycINFO and Cochrane Library databases) and Chinese (China National Knowledge Infrastructure and Wanfang database) databases were independently searched by two reviewers (X-ML and Z-MS) on the same day to retrieve studies published in Chinese and English journals from their inception to 23 July 2019 using the following search strategy: ('depression'(MeSH) OR depressive OR depressed OR depression) AND ('electroconvulsive therapy'(MeSH) OR ECT OR electroconvulsive therapy) AND (NMDA OR ketamine OR glutamat*OR N-methyl-D-aspartic acid) AND ('propofol'(MeSH) OR propofol). Reference lists of the retrieved trials,[20 25–28] relevant reviews and meta-analyses were manually searched to obtain missing RCTs.

Eligibility criteria
The inclusion criteria were as per the following PICOS acronym: *p*articipants: patients with MDD diagnosed using any criteria; *i*ntervention versus *c*omparison: (1) ketamine alone versus propofol alone in ECT and (2) ketamine + propofol versus propofol alone in ECT; *o*utcomes: the primary outcome was the improvement of depressive symptoms at day 1 after a single ECT treatment measured using standardised rating scales (including the Montgomery and Asberg Depression Rating Scale[29 30] or the Hamilton Depression Rating Scale (HAMD)).[31 32] As

recommended by a previous meta-analysis, HAMD was preferred to other scales in studies using multiple rating scales.[27] Key secondary outcomes were (1) improvement of depressive symptom at days 3 and 7 after a single ECT session; (2) the improvement of suicide ideation; (3) seizure duration and recovery times, and (4) ADRs. Study design: only RCT with a single ECT session. Studies with multiple ECT sessions (≥2 times) were excluded.[33–46] Observational studies, conference articles, case report/series and meta-analyses and systematic reviews were excluded. Moreover, multiple-intervention studies, including ECT combined with acupuncture or Chinese herbal medicine, were excluded.
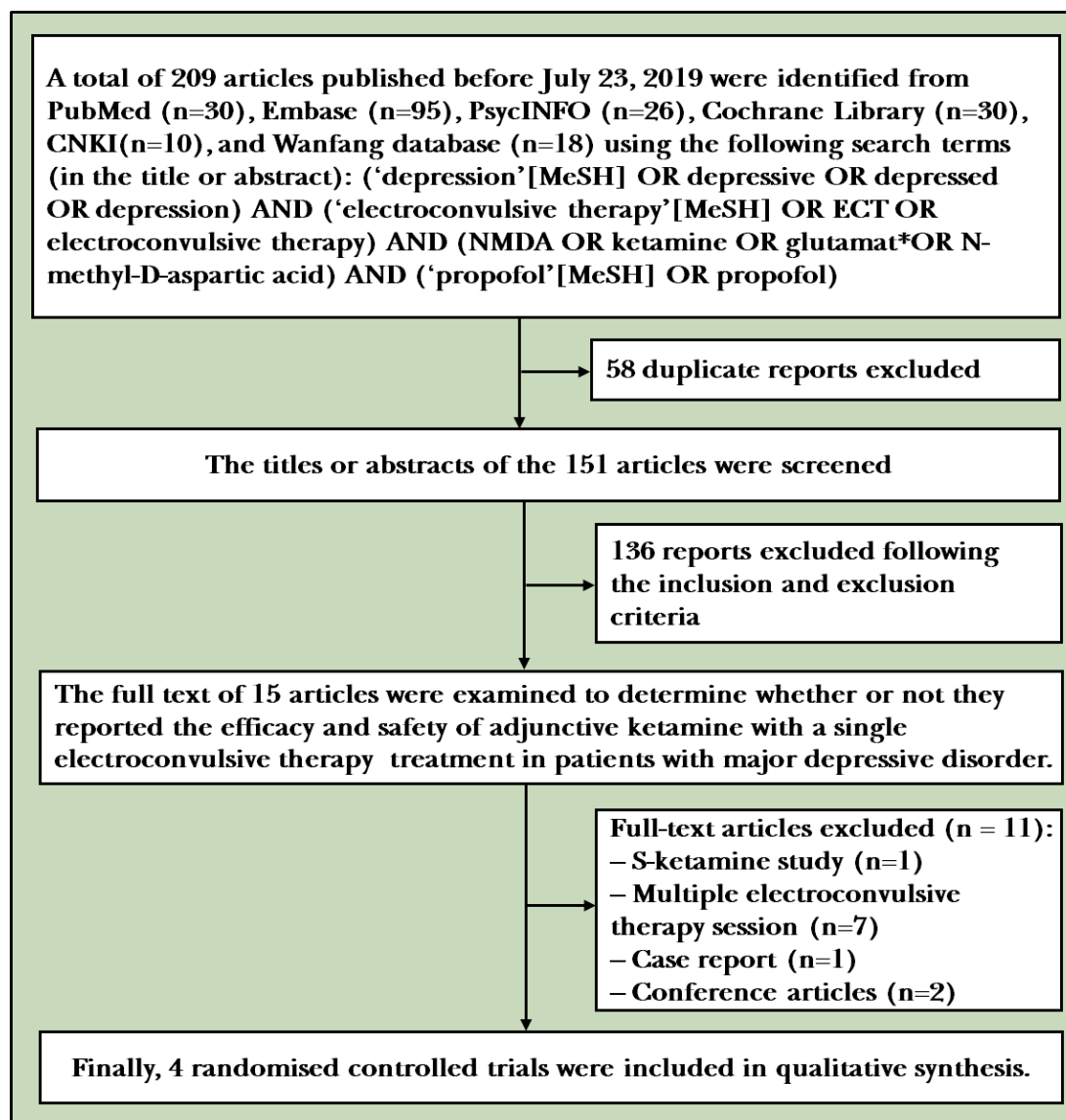
Data extraction
Two reviewers (X-ML and Z-MS) independently extracted and checked data. During the data extraction process, disagreements were resolved through discussion and consensus or with the involvement of a senior reviewer (HH). Study authors were contacted by email or telephone to obtain more meta-analysable data. The WebPlotDigitizer V.4.1 (https://automeris.io/WebPlotDigitizer/) was used to extract data from figures and/or graphs of the included RCTs as described by a recent meta-analysis.[47] Missing SDs were calculated from test statistics or using the mean (SD) of the remaining studies.[48] Three RCTs[12 17 18] with three treatment arms compared propofol with ketamine alone and with ketamine combined with propofol, separately. We included propofol arms twice in the aforementioned respective analyses and used half of the number of patients in the propofol arms.[49]

Statistical methods
Two reviewers (X-ML and Z-MS) independently analysed data of the included RCTs using the Review Manager V.5.3 (http://www.cochrane.org) based on the PRISMA statement.[50] Standardised mean differences (SMDs) with their 95% CIs and risk ratios (RRs) with its 95% CIs were calculated. SMD values over 0.8, 0.5–0.8 and 0.2–0.5 represented large, medium and small effect sizes, respectively.[51] All meta-analysable outcomes were pooled using a random effects model.[52] The Q statistics and I^2 were used to assess between-study heterogeneity with a p value of <0.1 in Q test and I^2 of ≥50% indicating significant heterogeneity.[53] In case of a p value of <0.1 or I^2 of ≥50% for the improvement of depressive symptoms at day 1 after a single ECT session, a sensitive analysis was conducted to examine the robustness of meta-analytic results after excluding an outlying study (SMD≤−3.50).[17] Funnel plots and Egger's test[54] were applied to investigate the possibility of publication bias. All meta-analysable primary and secondary outcomes were considered significant with alpha set at 0.05 (two-sided).

Quality assessment of each included study
Two reviewers (X-ML and Z-MS) independently conducted quality assessment of each included study using the Cochrane risk of bias[55] and the Jadad scale

A total of 209 articles published before July 23, 2019 were identified from PubMed (n=30), Embase (n=95), PsycINFO (n=26), Cochrane Library (n=30), CNKI(n=10), and Wanfang database (n=18) using the following search terms (in the title or abstract): ('depression'[MeSH] OR depressive OR depressed OR depression) AND ('electroconvulsive therapy'[MeSH] OR ECT OR electroconvulsive therapy) AND (NMDA OR ketamine OR glutamat*OR N-methyl-D-aspartic acid) AND ('propofol'[MeSH] OR propofol)

58 duplicate reports excluded

The titles or abstracts of the 151 articles were screened

136 reports excluded following the inclusion and exclusion criteria

The full text of 15 articles were examined to determine whether or not they reported the efficacy and safety of adjunctive ketamine with a single electroconvulsive therapy treatment in patients with major depressive disorder.

Full-text articles excluded (n = 11):
– S-ketamine study (n=1)
– Multiple electroconvulsive therapy session (n=7)
– Case report (n=1)
– Conference articles (n=2)

Finally, 4 randomised controlled trials were included in qualitative synthesis.

Figure 1 Flowchart of the literature screening.

(range = 0–5).[56] The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system[57 58] was applied to examine the overall evidence levels for all meta-analytical outcomes.

RESULTS
Search results
We identified 209 hits from the aforementioned databases (figure 1); among them, 58 duplicates were removed. Subsequently, 151 articles were screened for titles and abstracts with 136 reports being excluded according to the inclusion and exclusion criteria. Next, 15 full texts were examined with 11 articles being excluded as follows: an S-ketamine study (one trial), multiple ECT sessions (seven trials), a case report (one trial) and conference articles (two trials). Finally, four RCTs with a single ECT session were included in this meta-analysis.[12 17–19]

Study characteristics
Four RCTs (n = 239), which compared ketamine alone or ketamine plus propofol (n = 149) versus propofol alone (n = 90), were included.

Ketamine versus propofol
Four RCTs (n = 178) compared ketamine alone (n = 88) versus propofol (n = 90). The mean age was 48 (range: 41–55) years in two studies with available data; moreover, 44.8% of the participants (range: 36.7%–51.9%) in three studies with available data were men. None of the studies reported the mean duration of illness (table 1).

Ketamin+propofol versus propofol
Three RCTs (n = 122) compared ketamine+propofol (n = 61) with propofol (n = 61). Only one study with available data reported the mean age (56.5 years); moreover, 39.8% of the participants (range: 36.7%–42.9%) were

Table 1 Summary of studies included in this meta-analysis

Study (country)	Blinding	Diagnostic criteria	Measures on depression	Sex*: male (%)	Age* (years) (range)	Intervention group: mean dose (mg/kg), patients (n)	Control group: mean dose (mg/kg), patients (n)	ADs	Observation time (days)	Jadad score
Wang et al, 2012 (China)[17]	SB	DSM-IV	HAMD	18† (45.0)	56.4† (NR)	1. Ketamine (0.8), n = 16 2. Propofol (1.5) plus ketamine (0.8), n = 16	Propofol (1.5), n = 16	ADs	7	3
Xu et al, 2013 (China)[18]	OL	NR	HAMD	20 (44.4)	39.5 (24–60)	1. Ketamine (0.8), n=15 2. Propofol (1.5) plus ketamine (0.8), n=15	Propofol (1.5), n=15	NR	7	1
Yalcin et al, 2012 (Turkey)[12]	NR	NR	NR	46 (51.1)	NR	1. Ketamine (10 mg/mL), n = 30 2. Ketofol‡ (10 mg/mL), n = 30	Propofol (10 mg/mL), n=30	ADs	1	2
Zhao et al, 2016 (China)[19]	OL	ICD-10	HAMD	29 (51.8)	41.03 (NR)	Ketamine (1.5), n = 27	Propofol (2), n = 29	ADs	1	2

*Available data were extracted based on mean baseline value of each included trials.
†Number of patients were the data from the completion of the trial because the randomly assigned data were not clear.
‡Ketofol was prepared as a 1:1 mixture of ketamine 10 mg/mL and propofol 10 mg/mL mixed in a 20 mL syringe.
ADs, antidepressants; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; HAMD, Hamilton Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; n, number of patients; NR, not reported; OL, open label; SB, single blinding.

men in two studies with available data. None of the studies reported the mean illness duration (table 1).

Quality assessment
In the Cochrane risk of bias (online supplementary figure 1), three RCTs (75%, 3/4) were judged as unclear risk with respect to random sequence generation. The Jadad scores ranged from 1 to 3 (mean = 2.0) with only one RCT (25%) being considered as high quality (table 1). Online supplementary table 1 summarises the overall evidence level for all meta-analytic primary and secondary measures, which ranges from very low (26.7%, 4/15) to 'low' (73.3%, 11/15).

Primary outcomes
Ketamine alone was superior to propofol with regard to the improvement of depressive symptoms at days 1 (SMD: −2.37, 95% CI −4.50 to −0.25, I^2 = 90%, p = 0.03; large effect size), 3 (SMD: −3.94, 95% CI −5.08 to −2.79, I^2 = 0%, p < 0.001; large effect size) and 7 (SMD: −2.98, 95% CI −3.94 to −2.01, I^2 = 0%, p < 0.001; large effect size) after a single ECT session (figure 2). After excluding an outlying study (SMD≤−3.59),[17] the significant difference disappeared (SMD: −1.88, 95% CI −4.49 to 0.74, I^2 = 92%, p = 0.16).

Similarly, the combination of ketamine and propofol was superior to propofol with regard to the improvement of depressive symptoms at days 1 (SMD: −2.99, 95% CI −3.94 to −2.04, I^2 = 0%, p<0.001; large effect size), 3 (SMD: −3.87, 95% CI −4.97 to −2.77, I^2 = 0%, p<0.001; large effect size) and 7 (SMD: −3.08, 95% CI −4.04 to −2.11, I^2 = 0%, p < 0.001; large effect size) after a single ECT session (figure 3). None of the studies examined the relationship between ketamine used in ECT and suicide ideation.
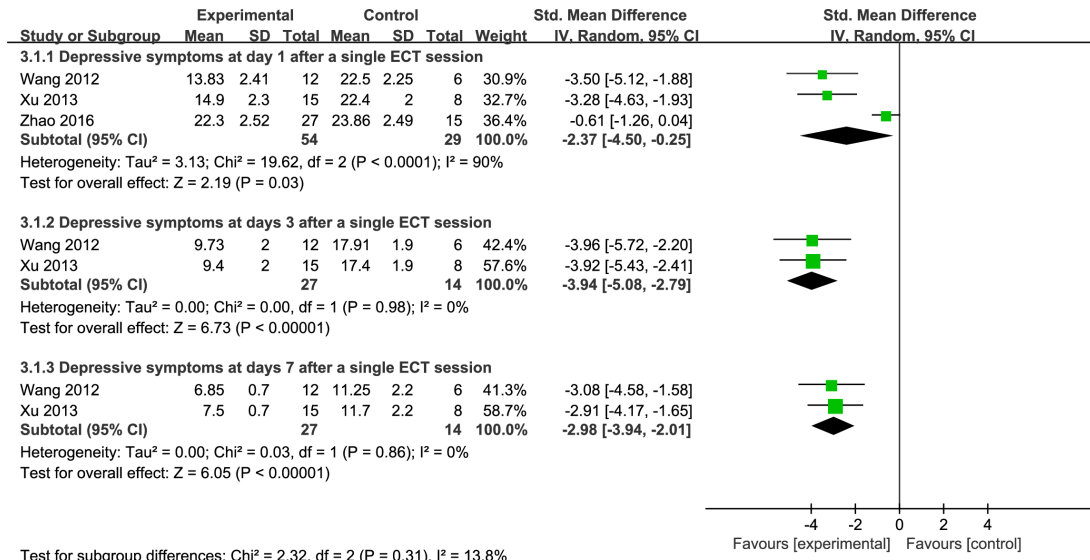
Secondary outcomes
As shown in table 2, ketamine alone was significantly associated with increased seizure duration (SMD: −2.11, 95% CI 1.54 to 2.67, I^2=0%, p<0.001; large effect size), seizure energy index (SMD: −1.74, 95% CI 0.97 to 2.51, I^2=0%, p<0.001; large effect size) and eye-opening time (SMD: 2.73, 95% CI 1.53 to 3.94, I^2=64%, p<0.001; large effect size) compared with propofol.

Similarly, ketamine combined with propofol was significantly associated with increased seizure duration (SMD: −2.11, 95% CI 0.55 to 3.67, I^2=84%, p=0.008; large effect size) and seizure energy index (SMD: −1.71, 95% CI 0.95 to 2.47, I^2=0%, p<0.001; large effect size) compared with propofol. There was no group difference in the eye-opening time (SMD: 1.78, 95% CI −0.31 to 3.86, I^2=88%, p=0.09; large effect size).

There was no significant difference regarding hypertension between propofol and ketamine alone (p=0.51) and between propofol and ketamine combined with propofol (p=0.65). There was no group difference regarding nausea and vomiting between ketamine and propofol alone (p=0.78) (table 2).

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.1 Depressive symptoms at day 1 after a single ECT session								
Wang 2012	13.83	2.41	12	22.5	2.25	6	30.9%	-3.50 [-5.12, -1.88]
Xu 2013	14.9	2.3	15	22.4	2	8	32.7%	-3.28 [-4.63, -1.93]
Zhao 2016	22.3	2.52	27	23.86	2.49	15	36.4%	-0.61 [-1.26, 0.04]
Subtotal (95% CI)			54			29	100.0%	-2.37 [-4.50, -0.25]
Heterogeneity: Tau² = 3.13; Chi² = 19.62, df = 2 (P < 0.0001); I² = 90%								
Test for overall effect: Z = 2.19 (P = 0.03)								
3.1.2 Depressive symptoms at days 3 after a single ECT session								
Wang 2012	9.73	2	12	17.91	1.9	6	42.4%	-3.96 [-5.72, -2.20]
Xu 2013	9.4	2	15	17.4	1.9	8	57.6%	-3.92 [-5.43, -2.41]
Subtotal (95% CI)			27			14	100.0%	-3.94 [-5.08, -2.79]
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 6.73 (P < 0.00001)								
3.1.3 Depressive symptoms at days 7 after a single ECT session								
Wang 2012	6.85	0.7	12	11.25	2.2	6	41.3%	-3.08 [-4.58, -1.58]
Xu 2013	7.5	0.7	15	11.7	2.2	8	58.7%	-2.91 [-4.17, -1.65]
Subtotal (95% CI)			27			14	100.0%	-2.98 [-3.94, -2.01]
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%								
Test for overall effect: Z = 6.05 (P < 0.00001)								

Test for subgroup differences: Chi² = 2.32. df = 2 (P = 0.31). I² = 13.8%

Figure 2 The ketamine group versus the propofol group: forest plot for depressive symptoms at days 1, 3 and 7 after a single electroconvulsive therapy session.

Publication bias

Publication bias was not evaluated for all outcomes because a minimum of 10 RCTs are needed to perform funnel plot or Egger's test.[59]
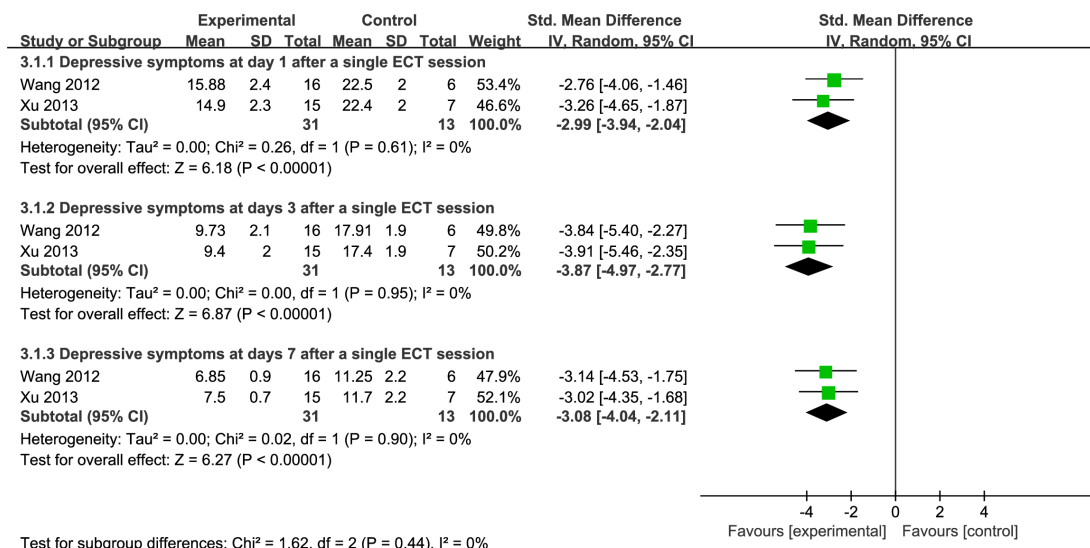
DISCUSSION
Main findings

This is the first meta-analysis to examine the effectiveness and safety of ketamine alone or ketamine combined with propofol in patients with MDD undergoing a single ECT session. Ketamine alone and ketamine combined with propofol were more efficacious than propofol alone as an ECT anaesthesia in treating depressive symptoms at days 1, 3 and 7 after a single ECT session with large effect size.[51] However, the significant superiority of ketamine to propofol alone in improving depressive symptoms was driven by an outlying study.[17] Compared with propofol,

ketamine alone and the combination of ketamine and propofol significantly increased the seizure duration and seizure energy index. Furthermore, ketamine alone, but not ketamine combined with propofol, could significantly increase opening-eye time compared with propofol. However, a recent study found that ketamine as an anaesthetic did not enhance the antidepressant effects of six ECT treatments.[45]

Limitations

This study has several limitations. Firstly, the number of included RCTs and sample size of each included RCT were relatively small, which impeded more comprehensive analyses, including subgroup and meta-regression analyses. Secondly, the significant heterogeneity in the meta-analytic findings for the primary outcome could be partly attributed to each included study with differences

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.1 Depressive symptoms at day 1 after a single ECT session								
Wang 2012	15.88	2.4	16	22.5	2	6	53.4%	-2.76 [-4.06, -1.46]
Xu 2013	14.9	2.3	15	22.4	2	7	46.6%	-3.26 [-4.65, -1.87]
Subtotal (95% CI)			31			13	100.0%	-2.99 [-3.94, -2.04]
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%								
Test for overall effect: Z = 6.18 (P < 0.00001)								
3.1.2 Depressive symptoms at days 3 after a single ECT session								
Wang 2012	9.73	2.1	16	17.91	1.9	6	49.8%	-3.84 [-5.40, -2.27]
Xu 2013	9.4	2	15	17.4	1.9	7	50.2%	-3.91 [-5.46, -2.35]
Subtotal (95% CI)			31			13	100.0%	-3.87 [-4.97, -2.77]
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%								
Test for overall effect: Z = 6.87 (P < 0.00001)								
3.1.3 Depressive symptoms at days 7 after a single ECT session								
Wang 2012	6.85	0.9	16	11.25	2.2	6	47.9%	-3.14 [-4.53, -1.75]
Xu 2013	7.5	0.7	15	11.7	2.2	7	52.1%	-3.02 [-4.35, -1.68]
Subtotal (95% CI)			31			13	100.0%	-3.08 [-4.04, -2.11]
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%								
Test for overall effect: Z = 6.27 (P < 0.00001)								

Test for subgroup differences: Chi² = 1.62. df = 2 (P = 0.44). I² = 0%

Figure 3 Combination of the ketamine and propofol group versus the propofol group: forest plot for depressive symptoms at days 1, 3 and 7 after a single electroconvulsive therapy session.

Table 2 Secondary outcomes

Secondary outcomes	Subjects (active treatment arms)	SMDs or RRs (95% CI)	I^2 (%)	P value
Ketamine versus propofol				
Seizure duration (s)	86 (3)	-2.11 (1.54 to 2.67)	0	**<0.001**
Seizure energy index (uv2)	41 (2)	-1.74 (0.97 to 2.51)	0	**<0.001**
Open eyes (min)	68 (2)	2.73 (1.53 to 3.94)	64	**<0.001**
Hypertension	92 (3)	1.31 (0.58 to 2.93)	0	0.51
Nausea and vomiting	92 (3)	1.19 (0.34 to 4.20)	0	0.78
Ketamine plus propofol versus propofol				
Seizure duration (s)	89 (3)	-2.11 (0.55 to 3.67)	84	**0.008**
Seizure energy index (uv2)	44 (2)	-1.71 (0.95 to 2.47)	0	**<0.001**
Open eyes (min)	67 (2)	1.78 (-0.31 to 3.86)	88	0.09
Hypertension	91 (3)	0.81 (0.33 to 2.00)	0	0.65

Boldfaced values: data was considered to have significant differences when p < 0.05.
RR, risk ratio; SMD, standardised mean difference.

in methodological characteristics, including the dosage of propofol and ketamine, electrode placements and patient property. Further, future studies should compare between single and multiple ECT sessions for MDD. Finally, none of the RCTs reported randomisation methods with a specific description as measured by the Cochrane risk of bias; moreover, three RCTs (75%, 3/4) were rated as low quality as measured by the Jadad scale. Furthermore, quality of evidence for all meta-analytic outcomes was considered as 'very low' or low according to the GRADE approach. However, as suggested by Guyatt *et al.*,[60] low-quality evidence could still lead to strong recommendations.

Implications

We found that ECT-treated patients with MDD receiving ketamine plus propofol or ketamine alone had more significant improvements in depressive symptoms compared with patients receiving propofol alone. This suggests that ketamine alone or the combination of ketamine and propofol as an ECT anaesthesia has an early and rapid antidepressant effect superior to that of propofol anaesthesia, which was consistent with the findings of previous meta-analyses indicating that ketamine has rapid antidepressant effects.[9]

Two previous meta-analyses[20 21] reported that ketamine used in ECT did not reduce the depressive symptoms at the end of the treatment; however, it could accelerate the antidepressive effects in depressive patients undergoing ECT. Thus, ketamine use in ECT has considerable clinical significance because the delayed onset of antidepressant effects is closely associated with prolonged severe morbidity suicide risk.[61] However, none of the included RCTs assessed the antisuicidal effects of ketamine used in ECT. The incidence of hypertension was similar in the ketamine group and ketamine combined with the propofol group compared with the propofol group.

Thus, the use of ketamine and ketamine combined with propofol is safe and tolerable.

As expected, there were significant difference regarding the seizure activity duration and the seizure energy index between propofol and ketamine alone, and ketamine combined with propofol. Interestingly, the combination of ketamine and propofol group was not associated with longer mean eye-opening time compared with the propofol group. Thus, the use of ketamine plus propofol as an ECT anaesthesia might be advantageous for analgesia and haemodynamic stability.[12] Notably, ketamine-related nauseant and psychomimetic effects could be counterbalanced by the sedative and antiemetic effects of propofol. Given the potential balance of effects, the combination of ketamine and propofol as an ECT anaesthesia is superior to either agent alone.[12]

CONCLUSION

According to very low or low evidence level, compared with propofol alone, ketamine alone and the combination of ketamine and propofol have an advantage in rapidly improving depressive symptoms of patients with MDD undergoing a single ECT session. Due to significant heterogeneity and small sample size, high-quality RCTs are required to confirm and extend these findings.

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REFERENCES

1. Petrides G, Fink M, Husain MM, *et al*. Ect remission rates in psychotic versus nonpsychotic depressed patients: a report from core. *J Ect* 2001;17:244–53.
2. Green SM, Andolfatto G, Krauss B. Ketofol for procedural sedation? pro and con. *Ann Emerg Med* 2011;57:444–8.
3. Hooten WM, Rasmussen KG. Effects of general anesthetic agents in adults receiving electroconvulsive therapy: a systematic review. *J Ect* 2008;24:208–23.
4. McGirr A, Berlim MT, Bond DJ, *et al*. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol Med* 2015;45:693–704.
5. Zheng W, Zhou Y-L, Liu W-J, *et al*. Investigation of medical effect of multiple ketamine infusions on patients with major depressive disorder. *J Psychopharmacol* 2019;33:494–501.
6. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med* 2008;26:985–1028.
7. Parsaik AK, Singh B, Khosh-Chashm D, *et al*. Efficacy of ketamine in bipolar depression: systematic review and meta-analysis. *J Psychiatr Pract* 2015;21:427–35.
8. Han Y, Chen J, Zou D, *et al*. Efficacy of ketamine in the rapid treatment of major depressive disorder: a meta-analysis of randomized, double-blind, placebo-controlled studies. *Neuropsychiatr Dis Treat* 2016;12:2859–67.
9. Kishimoto T, Chawla JM, Hagi K, *et al*. Single-Dose infusion ketamine and non-ketamine N-methyl-D-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. *Psychol Med* 2016;46:1459–72.
10. Xu Y, Hackett M, Carter G, *et al*. Effects of low-dose and very low-dose ketamine among patients with major depression: a systematic review and meta-analysis. *Int J Neuropsychopharmacol* 2016;19:pyv124.
11. Wilkinson ST, Ballard ED, Bloch MH, *et al*. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry* 2018;175:150–8.
12. Yalcin S, Aydoğan H, Selek S, *et al*. Ketofol in electroconvulsive therapy anesthesia: two stones for one bird. *J Anesth* 2012;26:562–7.
13. Finnegan M, Galligan T, Ryan K, *et al*. Ketamine versus midazolam for depression relapse prevention following successful electroconvulsive therapy: a randomized controlled pilot trial. *J Ect* 2019;35:115–21.
14. Rasmussen KG, Jarvis MR, Zorumski CF. Ketamine anesthesia in electroconvulsive therapy. *Convuls Ther* 1996;12:217–23.
15. Patel AS, Gorst-Unsworth C, Venn RM, *et al*. Anesthesia and electroconvulsive therapy: a retrospective study comparing etomidate and propofol. *J Ect* 2006;22:179–83.
16. Mitchell P, Torda T, Hickie I, *et al*. Propofol as an anaesthetic agent for ECT: effect on outcome and length of course. *Aust N Z J Psychiatry* 1991;25:255–61.
17. Wang X, Chen Y, Zhou X, *et al*. Effects of propofol and ketamine as combined anesthesia for electroconvulsive therapy in patients with depressive disorder. *J Ect* 2012;28:128–32.
18. XM X, JB H, Chen Y, *et al*. Effects of propofol and ketamine administration in electroconvulsive therapy for patients with major depressive disorder (in Chinese). *China health care & nutrition* 2013;23:7597–8.
19. Zhao HZ, Li H, Cui EL. A comparative study of intraocular pressure and depression reducing score in depression patients undergoing MECT with different anesthetics (in Chinese). *Chinese Journal of Practical Medicine* 2016;43:61–3.
20. Zheng W, Li X-H, Zhu X-M, *et al*. Adjunctive ketamine and electroconvulsive therapy for major depressive disorder: a meta-analysis of randomized controlled trials. *J Affect Disord* 2019;250:123–31.
21. Ren L, Deng J, Min S, *et al*. Ketamine in electroconvulsive therapy for depressive disorder: a systematic review and meta-analysis. *J Psychiatr Res* 2018;104:144–56.
22. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.. In: *BMJ (Clinical research ed).* , 2009: 339, b2535.
23. Zheng W, Cai D-B, Yang X-H, *et al*. Adjunctive aripiprazole for antipsychotic-related hyperprolactinaemia in patients with first-episode schizophrenia: a meta-analysis. *Gen Psychiatr* 2019;32:e100091.
24. Zheng W, Zhu X-M, Zhang Q-E, *et al*. Adjunctive minocycline for major mental disorders: a systematic review. *J Psychopharmacol* 2019;33:1215–26.
25. McGirr A, Berlim MT, Bond DJ, *et al*. A systematic review and meta-analysis of randomized controlled trials of adjunctive ketamine in electroconvulsive therapy: efficacy and tolerability. *J Psychiatr Res* 2015;62:23–30.
26. Fond G, Bennabi D, Haffen E, *et al*. A Bayesian framework systematic review and meta-analysis of anesthetic agents effectiveness/tolerability profile in electroconvulsive therapy for major depression. *Sci Rep* 2016;6:19847.
27. Li D-J, Wang F-C, Chu C-S, *et al*. Significant treatment effect of add-on ketamine anesthesia in electroconvulsive therapy in depressive patients: a meta-analysis. *Eur Neuropsychopharmacol* 2017;27:29–41.
28. McGirr A, Berlim MT, Bond DJ, *et al*. Adjunctive ketamine in electroconvulsive therapy: updated systematic review and meta-analysis. *Br J Psychiatry* 2017;210:403–7.
29. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9.
30. Zhong BL, Wang Y, Chen HH, *et al*. Reliability, validity and sensitivity of Montgomery-Åsberg Depression Rating Scale for patients with current major depressive disorder [in Chinese]. *Chinese Journal of Behavioural Medicine and Brain Sciences* 2011;20:85–7.
31. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62.
32. G. R X, Shen QJ. Use of the Chinese version of the Hamilton rating scale for depression in general population and patients with major depression (in Chinese). *Chinese Journal of Nervous and Mental Diseases* 1984;10:364.
33. Abdallah CG, Fasula M, Kelmendi B, *et al*. Rapid antidepressant effect of ketamine in the electroconvulsive therapy setting. *J Ect* 2012;28:157–61.
34. Loo CK, Katalinic N, Garfield JBB, *et al*. Neuropsychological and mood effects of ketamine in electroconvulsive therapy: a randomised controlled trial. *J Affect Disord* 2012;142:233–40.
35. Yoosefi A, Sepehri AS, Kargar M, *et al*. Comparing effects of ketamine and thiopental administration during electroconvulsive therapy in patients with major depressive disorder: a randomized, double-blind study. *J Ect* 2014;30:15–21.
36. Erdil F, Begeç Z, Kayhan GE, *et al*. Effects of sevoflurane or ketamine on the QTc interval during electroconvulsive therapy. *J Anesth* 2015;29:180–5.
37. Erdil F, Ozgul U, Çolak C, *et al*. Effect of the addition of ketamine to sevoflurane anesthesia on seizure duration in electroconvulsive therapy. *J Ect* 2015;31:182–5.
38. Kuşçu Özlem Özkan, Karacaer F, Biricik E, *et al*. Effect of ketamine, thiopental and ketamine-thiopental combination during electroconvulsive therapy for depression. *Turk J Anaesthesiol Reanim* 2015;43:313–7.
39. Salehi B, Mohammadbeigi A, Kamali AR, *et al*. Impact comparison of ketamine and sodium thiopental on anesthesia during electroconvulsive therapy in major depression patients with drug-resistant; a double-blind randomized clinical trial. *Ann Card Anaesth* 2015;18:486–90.
40. Shams Alizadeh N, Maroufi A, Nasseri K, *et al*. Antidepressant effect of combined ketamine and electroconvulsive therapy on patients with major depressive disorder: a randomized trial. *Iran J Psychiatry Behav Sci* 2015;9:e1578.
41. Rybakowski JK, Bodnar A, Krzywotulski M, *et al*. Ketamine anesthesia, efficacy of electroconvulsive therapy, and cognitive functions in treatment-resistant depression. *J Ect* 2016;32:164–8.
42. Zhong X, He H, Zhang C, *et al*. Mood and neuropsychological effects of different doses of ketamine in electroconvulsive therapy for treatment-resistant depression. Available: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/791/CN-01158791/frame.html;
43. Anderson IM, Blamire A, Branton T, *et al*. Ketamine augmentation of electroconvulsive therapy to improve neuropsychological and clinical outcomes in depression (Ketamine-ECT): a multicentre, double-

blind, randomised, parallel-group, superiority trial. *Lancet Psychiatry* 2017;4:365–77.

44 Chen Q, Min S, Hao X, *et al*. Effect of low dose of ketamine on learning memory function in patients undergoing electroconvulsive therapy-a randomized, double-blind, controlled clinical study. *J Ect* 2017;33:89–95.

45 Fernie G, Currie J, Perrin JS, *et al*. Ketamine as the anaesthetic for electroconvulsive therapy: the KANECT randomised controlled trial. *Br J Psychiatry* 2017;210:422–8.

46 Ray-Griffith SL, Eads LA, Han X, *et al*. A randomized pilot study comparing ketamine and methohexital anesthesia for electroconvulsive therapy in patients with depression. *J Ect* 2017;33:268–71.

47 Zheng W, Cai D-B, Zheng W, *et al*. Brexanolone for postpartum depression: a meta-analysis of randomized controlled studies. *Psychiatry Res* 2019;279:83–9.

48 Furukawa TA, Barbui C, Cipriani A, *et al*. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006;59:7–10.

49 Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available: www.cochrane-handbook.org

50 Zheng W, Cai D-B, Li H-Y, *et al*. Adjunctive Peony-Glycyrrhiza decoction for antipsychotic-induced hyperprolactinaemia: a meta-analysis of randomised controlled trials. *Gen Psychiatr* 2018;31:e100003.

51 Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd edn. Hillsdale: Lawrence Erlbaum Associates, 1988.

52 DerSimonian R, Laird N. Meta-Analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.

53 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.

54 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.

55 Higgins J, Higgins J P. *Cochrane Handbook for systematic reviews of interventions*. John Wiley & Sons, 2008.

56 Jadad AR, Moore RA, Carroll D, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.

57 Balshem H, Helfand M, Schünemann HJ, *et al*. Grade guidelines: 3. rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–6.

58 Atkins D, Best D, Briss PA, *et al*. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.

59 ed)Sterne JAC, Sutton AJ, Ioannidis JPA, *et al*. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials.. In: *Bmj (clinical research*. , 2011: 343, d4002.

60 Guyatt GH, Oxman AD, Vist GE, *et al*. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.

61 Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA* 2004;292:338–43.

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