Adjunctive ketamine in electroconvulsive therapy: updated systematic review and meta-analysis

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Background
Ketamine has emerged as a novel therapeutic agent for major depressive episodes, spurring interest in its potential to augment electroconvulsive therapy (ECT).

Aims
We sought to update our preliminary systematic review and meta-analysis, focusing on randomised controlled trials (RCTs) involving an index course of ECT, and testing the hypothesis that lack of efficacy is due to barbiturate anaesthetic co-administration.

Method
We searched EMBASE, CENTRAL and Medline to identify RCTs examining the efficacy of ketamine during a course of ECT. Data were synthesised from ten trials (ketamine group n = 333, comparator group n = 269) using pooled random effects models.

Results
Electroconvulsive therapy with ketamine was not associated with greater improvements in depressive symptoms or higher rates of clinical response or remission, nor did it result in pro-cognitive effects. This held true when limiting analysis to trials without barbiturate anaesthetic co-administration. Increased rates of confusion were reported.

Conclusions
Overall, our analyses do not support using ketamine over other induction agents in ECT.

Declaration of interest
D.J.B. has received speaking fees or acted as a consultant for the Canadian Network for Mood and Anxiety Treatments (CANMAT), the Canadian Psychiatric Association, Pfizer, Sunovion, BMS, Otsuka, Astra-Zeneca, Janssen-Ortho and Myriad, and has received research support from the Canadian Institutes of Health Research (CIHR), the UBC Institute of Mental Health/Costal Capital Depression Research Fund, and Pfizer. L.N.Y. has received research grants from, or is on speaking/advisory boards for, AstraZeneca, Bristol-Myers Squibb, CIHR CANMAT, Eli Lilly, GlaxoSmithKline, Janssen, Michael Smith Foundation for Health Research, Novartis, Pfizer, Ranbaxy, Servier, and the Stanley Foundation. R.W.L. is on ad hoc speaking/advisory boards for, or has received research funds from, Asia-Pacific Economic Cooperation, AstraZeneca, BC Leading Edge Foundation, Brain Canada, Bristol-Myers Squibb, CIHR, Canadian Depression Research and Intervention Network, CANMAT, Canadian Psychiatric Association, Janssen, Lundbeck Institute, Medscape, Pfizer, St. Jude Medical, Takeda, University Health Network Foundation, Vancouver Coastal Health Research Institute, and VGH Foundation.

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Studies were excluded if they comprised a single ECT session, or if summary data were not reported and raw data or summary data could not be obtained from the investigators.

Data extraction

Data were recorded by two independent observers, with subsequent review and consensus. The primary outcome was change in clinician-rated depressive symptoms pre- and post-intervention, assessed with the Hamilton Rating Scale for Depression (HRSD) or the Montgomery–Åsberg Depression Rating Scale (MADRS). Secondary outcomes were clinical response (> 50% reduction in depressive symptoms) and cognitive testing. Adverse events were extracted as described in the trials.

Statistical analysis

Analyses were performed using Comprehensive Meta-Analysis version 2.0. Given that true treatment effects were likely to vary between studies given different methodological characteristics, we used a random effects model. Intention-to-treat data were analysed. We used standardised mean differences (SMD) to quantify changes in depression scores and conservatively assumed a pre–post correlation of 0.7. We used risk difference for primary analyses, an absolute measure of the difference in proportions of individuals achieving the pre-specified outcome, to quantify clinical response and remission. Although absolute measures are less consistent than relative effect measures, our preliminary meta-analysis indicated consistent effects. Moreover, risk difference was chosen over relative effect measures such as odds ratios not only for its ease of clinical interpretability, but also because our preliminary meta-analyses revealed the absence of clinical response or remission in some studies, in which case relative statistics are inapplicable. We did, however, use odds ratios for adverse events, given the low incidence of such events. Pre-planned subgroup analyses were performed for studies involving co-administration of ketamine with a barbiturate anaesthetic agent (thiopental), and studies that co-administered ketamine with propofol or in isolation.

Heterogeneity was assessed using Q statistics and $I^2$. Values of $P < 0.1$ for the former and $P > 35\%$ for the latter were deemed as indicative of study heterogeneity. Finally, we used funnel plots and Egger’s regression intercept to test for publication bias. Funnel plots are a graphical representation of effect size and study precision (standard error) with an inverted funnel boundary depicted representing the 95% confidence region expected in the absence of publication bias and heterogeneity. This permits qualitative evaluation of publication bias, with a symmetric relationship implying dissociation of study precision and effect size, whereas an asymmetric relationship suggests possible publication bias. Egger’s regression intercept employs a qualitative estimation of the relationship between effect size and study precision using regression, with an intercept statistically different from zero suggesting publication bias. Study quality was evaluated using the Cochrane Collaboration’s tool for assessing risk of bias concomitant to eligibility.

Results

Our literature search resulted in ten RCTs considered suitable for our meta-analysis (Fig. 1, Table 1).3–18 These trials comprised 602 participants with a major depressive episode (ketamine group $n = 333$, comparator group $n = 269$). One study was retained despite important methodological concerns, including contradictory statements as to whether the trial was a single- or double-blind RCT,14 and therefore analyses were repeated excluding this trial. Other excluded studies are listed in online Table DS1 and study quality is summarised in online Table DS2. Five studies had diagnostically mixed samples comprising people with bipolar disorder as well as those with major depressive disorder.9,12,13,17,18 None of the trials focused on patients who did not respond to ECT, and no trial compared ketamine with another augmentation strategy. One study involved two subgroups in which ketamine was co-administered with thiopental;15 in the first subgroup patients received ketamine on the second and third ECT, whereas the second subgroup received ketamine on the second, fourth, eighth and tenth sessions.15 As ketamine exposure was uneven after five ECT sessions in this study, we extracted data after the fifth session. In all studies ketamine was administered intravenously. Three studies used ketamine at a dose of 0.5 mg/kg,9,12,18 one study gave subgroups doses of 0.5 mg/kg or 0.8 mg/kg,17 whereas the remaining studies used doses of 0.3 mg/kg,15 0.4 mg/kg,10 0.8 mg/kg,14 1 mg/kg,11 1.5 mg/kg,13 and 1–2 mg/kg.16

Depressive symptoms

Clinician-rated depressive symptoms were available for all ten RCTs. A non-significant SMD of 0.18 in favour of ketamine (95% CI −0.25 to 0.61, $P = 0.41$; Fig. 2) was observed, with significant statistical heterogeneity ($Q = 55.9$, $I^2 = 83.9$, $P < 0.001$). Sensitivity analyses revealed that excluding the trial by Zhong et al17 decreased heterogeneity ($Q = 24.8$, $I^2 = 67.7$, $P < 0.01$); however, exclusion of no other trial reduced $I^2$ by 5% or more. Examination of the funnel plot revealed a symmetrical distribution with outliers (online Fig. DS1). Egger’s intercept

![Flowchart of study selection process](https://example.com/flowchart)
was not statistically significant ($t(8) = 0.87, P = 0.40$). We repeated the analysis excluding the trial with major methodological issues,\textsuperscript{14} which similarly revealed a non-significant SMD of 0.14 in favour of ketamine (95% CI $-0.37$ to 0.66, $P=0.59$). A second sensitivity analysis was performed excluding the trial in which ketamine was alternately applied with thiopental.\textsuperscript{13} This again revealed a non-significant SMD in favour of ketamine (SMD = 0.17, 95% CI $0.30$ to $0.66$, $P=0.47$). A leading hypothesis for ketamine’s ineffectiveness in ECT relates to concomitant barbiturate use.\textsuperscript{13} This again revealed a non-significant SMD in favour of ketamine (SMD = 0.17, 95% CI $0.30$ to $0.66$, $P=0.47$). A leading hypothesis for ketamine’s ineffectiveness in ECT relates to concomitant barbiturate use. Therefore, we performed a separate analysis excluding trials (or subgroups within trials) in which ketamine was co-administered with a barbiturate anaesthetic agent (7 RCTs; ketamine group $n = 247$, comparator group $n = 219$). Again, we observed a non-significant SMD in favour of ketamine (SMD = 0.24, 95% CI $-0.33$ to 0.83, $P=0.40$) and significant statistical heterogeneity ($Q = 51.71, I^2 = 88.39, P < 0.001$). Egger’s intercept did not reveal statistical evidence of publication bias ($t(5) = 0.42, P = 0.68$).

**Clinical response**

Clinical response rates were available for seven RCTs (ketamine group $n = 191$, comparator group $n = 148$). No difference in clinical response was observed between patients receiving ketamine vs. comparator (ketamine $n = 103$, 53.9%; comparator $n = 79$, 53.4%; risk difference (RD) = 0.010, 95% CI $-0.06$ to $0.08$, $P=0.78$; Fig. 3). Qualitative inspection of the funnel plot revealed a broadly symmetrical distribution with some asymmetry at lower precision (online Fig. DS2); however, Egger’s intercept did not reveal statistical evidence of publication bias ($t(5) = 1.00, P = 0.35$).

**Clinical remission**

Rates of clinical remission were available for seven RCTs (ketamine group $n = 191$, comparator group $n = 148$). No difference in remission was observed between patients receiving ketamine vs. comparator (ketamine $n = 103$, 53.9%; comparator $n = 79$, 53.4%; risk difference (RD) = 0.010, 95% CI $-0.06$ to $0.08$, $P=0.78$; Fig. 3). Qualitative inspection of the funnel plot revealed a broadly symmetrical distribution with some asymmetry at lower precision (online Fig. DS2); however, Egger’s intercept did not reveal statistical evidence of publication bias ($t(5) = 1.00, P = 0.35$).

**Cognitive testing**

Several studies examined cognitive indices; however, few had overlapping instruments, preventing quantitative synthesis. Two

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**Table 1** Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Sample size, n</th>
<th>Rating scale</th>
<th>Design</th>
<th>Electrode placement</th>
<th>ECT system; seizure threshold</th>
<th>Number of ECTs</th>
<th>Age, mean (s.e.)</th>
<th>Gender, n(^{4})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdalhaf et al (2012)^{7}</td>
<td>MDD, BD</td>
<td>18 (2 withdrawn)</td>
<td>HRSD</td>
<td>(a) Ketamine (0.5 mg/kg) + thiopental (3.5 mg/kg) (b) Thiopental (3.5 mg/kg)</td>
<td>Right unilateral and bitemporal</td>
<td>MECTA; titration method</td>
<td>6</td>
<td>47.1 (0.9)</td>
<td>7F/9M</td>
</tr>
<tr>
<td>Anderson et al (in press)^{18}</td>
<td>MDD, BD</td>
<td>70</td>
<td>MADRS</td>
<td>(a) Ketamine (0.5 mg/kg) + propofol (thiopental $n = 4$) (b) Saline + propofol</td>
<td>Right unilateral and bifrontal</td>
<td>Unspecified; titration method</td>
<td>Mean 11.3 (s.d. = 0.5)</td>
<td>54.2 (1.4)</td>
<td>44F/36M</td>
</tr>
<tr>
<td>Jarventausta et al (2013)^{10}</td>
<td>MDD</td>
<td>34 (2 withdrawn)</td>
<td>MADRS</td>
<td>(a) S-Ketamine (0.4 mg/kg) + propofol (b) Saline + propofol</td>
<td>Right unilateral and bitemporal</td>
<td>Thymatron; titration method</td>
<td>6</td>
<td>(a) 48.8</td>
<td>13F/19M</td>
</tr>
<tr>
<td>Kuscu et al (2015)^{11}</td>
<td>Major depression</td>
<td>61 (3 withdrawn)</td>
<td>HRSD</td>
<td>(a) Thiopental (4 mg/kg) (b) Ketamine (1 mg/kg) (c) Thiopental (4 mg/kg) + ketamine (1 mg/kg)</td>
<td>Bitemporal</td>
<td>Thymatron; unspecified</td>
<td>6</td>
<td>42.0 (12.1)</td>
<td>27F/30M(^{12}</td>
</tr>
<tr>
<td>Loo et al (2012)^{12}</td>
<td>MDD, BD</td>
<td>51 (5 withdrawn)</td>
<td>MADRS</td>
<td>(a) Thiopental (3–5 mg/kg) + ketamine (0.5 mg/kg) (b) Thiopental (3–5 mg/kg) + saline</td>
<td>Right unilateral</td>
<td>MECTA; titration method</td>
<td>Mean 9.1 (s.d. = 4.3)</td>
<td>43.3 (1.9)</td>
<td>28F/18M</td>
</tr>
<tr>
<td>Rybakowski et al (2016)^{13}</td>
<td>MDD, BD</td>
<td>45</td>
<td>HRSD</td>
<td>(a) Thiopental (2–3 mg/kg) (b) Thiopental (2–3 mg/kg) + ketamine (1–1.5 mg/kg) on sessions 2 &amp; 3 (c) Thiopental (2–3 mg/kg) + ketamine (1–1.5 mg/kg) on sessions 2, 4, &amp; 8</td>
<td>Bifrontal</td>
<td>Thymatron; age method $&gt; 8$</td>
<td>53.0 (12.0)</td>
<td>34F/11M</td>
<td></td>
</tr>
<tr>
<td>Salehi et al (2015)^{14}</td>
<td>Major depression</td>
<td>160</td>
<td>HRSD</td>
<td>(a) Ketamine (1–1.5 mg/kg) + propofol (0.8 mg/kg)</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>8</td>
<td>20–60</td>
<td>86F/74M</td>
</tr>
<tr>
<td>Shams Alizadeh et al (2019)^{15}</td>
<td>MDD</td>
<td>44</td>
<td>HRSD</td>
<td>(a) Propofol (1 mg/kg) (b) Propofol (1 mg/kg) + ketamine (0.3 mg/kg)</td>
<td>Bifrontal</td>
<td>IEC 601-1 type BF Class 1</td>
<td>6</td>
<td>34.6 (1.7)</td>
<td>29F/13M</td>
</tr>
<tr>
<td>Yoossefi et al (2014)^{16}</td>
<td>MDD</td>
<td>31</td>
<td>HRSD</td>
<td>(a) Ketamine (1–2 mg/kg) (b) Thiopental (2–3 mg/kg)</td>
<td>Bitemporal</td>
<td>Thymatron; age method</td>
<td>6</td>
<td>43.8 (2.1)</td>
<td>14F/17M</td>
</tr>
<tr>
<td>Zhong et al (2016)^{17}</td>
<td>MDD, BD</td>
<td>90</td>
<td></td>
<td>(a) Propofol (0.8 mg/kg) (b) Propofol (0.5 mg/kg) + ketamine (0.5 mg/kg) (c) Ketamine (0.8 mg/kg)</td>
<td>Bitemporal</td>
<td>Thymatron; age method</td>
<td>8</td>
<td>30.6 (9.1)</td>
<td>54F/36M</td>
</tr>
</tbody>
</table>

\(BD\), bipolar disorder; ECT, electroconvulsive therapy; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder.

\(a\). F female, M male.

\(b\). Not fully reported.
studies with extensive neuropsychological batteries, including the autobiographical memory interview, found no benefit associated with ketamine. 12,18 Rybakowski et al reported poorer performance associated with ketamine on the Rey Auditory Verbal Learning Task and the Verbal Fluency Test, but not on the Stroop test or Digit Span Test. 13 Zhong et al reported no difference on the Digit Span Test, Digit Symbol Test, Word Fluency Test and Visual Recognition Test; however, they did find evidence for poorer performance on the Wisconsin Card Sorting Task and the Tower of Hanoi test with ketamine, and better performance on the Trail Making Test. 17 Time to reorientation was slower in ketamine-treated patients in one RCT, 15 but similar in another. 18 One RCT used the Mini-Mental State Examination and found benefit in favour of ketamine. 16

Adverse events

Adverse events, as defined and reported by the trials, are presented in online Fig. DS4. We excluded one trial owing to unusually high rates (> 60%) of ‘prolonged delirium’ in both ketamine and comparator groups. 14 We found an increased risk of confusion (OR = 6.01, 95% CI 1.03 to 94.30, P = 0.046). One trial could not be pooled as adverse events were presented by affected organ
system; however, it reported an increased rate of mild and moderate adverse events among ketamine-treated patients.18

Discussion

This updated systematic review and meta-analysis confirms that ketamine is not more efficacious than other induction agents in ECT, even without co-administered barbiturate anaesthetic compounds. Moreover, the literature does not support pro-cognitive effects, and adverse events – notably confusion – are more common with ketamine. The potential for temporising relief should not be discounted,14,17 especially among those who are highly suicidal or medically compromised by poor fluid and/or nutrient intake. Although three trials supported early efficacy,14,16,17 several features of these trials overshadow this conclusion: one trial had minimal benefit in either condition;18 another had a 100% response rate within eight sessions,17 in a treatment-resistant sample where a 60% response rate would be expected;19 and the third had quality concerns.14 Overall, the randomised, controlled research does not support accelerated clinical improvement with ketamine.

Limitations

Several sources of potential bias were identified in the included trials, but there was no relationship between these methodological issues and outcomes reported. Moreover, high-quality trials consistently report null results, supporting the interpretation of results from our quantitative synthesis of data. Nevertheless, explicit quality issues were identified in one trial,14 and repeated analyses excluding these data also supported our conclusions. It is important to note that there was tremendous variability in the rates of response identified in the included trials. Although the cause of this variability is unclear, possibilities include an overly brief course of ECT. Although a short index course is the preferred methodological approach to avoid ceiling effects when testing an augmenting agent, in the absence of treatment response in the comparison group, a larger issue with trial design or patient selection cannot be excluded. Clinical heterogeneity was evident, with differences in ketamine dose, comparison induction agent, co-administered agents and stimulation parameters, as well as in rating scales. We also observed statistical heterogeneity. As with our preliminary report, a major limitation is the applicability to patients for whom therapeutic seizures cannot be obtained in the absence of adjunctive agents. Clinical equipoise in that context might justify the use of ketamine in those for whom adequate seizures cannot otherwise be obtained. Additional questions deserving of investigation relate to potential dose response and long-term safety.

Clinical implications

Our meta-analysis of randomised controlled trials does not support the use of ketamine over other induction agents in ECT.

References