Review article

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.

Electroconvulsive therapy (ECT) remains one of the most effective treatments for refractory depression. Ketamine has gained increasing attention for use during ECT in the light of evidence supporting subanaesthetic ketamine's antidepressant properties. Ketamine is a prototype rapid-acting antidepressant for which preclinical data suggest both *N*-methyl-ᴅ-aspartate (NMDA) receptor and non-NMDA receptor-dependent mechanisms.[1,2] In depressed humans, meta-analyses of randomised placebo-controlled trials employing intravenous ketamine provide strong evidence of antidepressant efficacy,[3,4] and other routes of administration have also garnered randomised controlled evidence of efficacy.[5] Moreover, ketamine results in widespread increases in brain-derived neurotrophic factor,[1] which is a putative mechanism underlying ECT's effects, despite conflicting evidence.[6] We previously reported a preliminary systematic review and meta-analysis of randomised controlled trials (RCTs) using ketamine in ECT, which found increased seizure duration, but not efficacy for ketamine as an adjunct.[7] However, our report involved a small number of trials and patients, and furthermore considered trials employing either a course of ECT or a single session. Few trials examined cognitive function. Moreover, a clinically important source of heterogeneity was concomitant anaesthetic administration, an important consideration as barbiturate anaesthetic compounds may counteract ketamine's antidepressant effects.[8] In light of these limitations, and given that several studies have since been published, we sought

to update our systematic review and meta-analysis, focusing on RCTs involving an index course of ECT.

Method

The study was conducted following the Preferred Reporting Items for Systematic Meta-Analyses (PRISMA) guidelines, and the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42016043909).

Search strategy

We searched Medline, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception until 30 July 2016. The search procedures are described in online supplement DS1. We also reviewed the references of included studies for unidentified RCTs.

Study selection

Inclusion criteria were as follows:

(a) study validity: random allocation, double-blind, controlled, parallel arm design;

(b) sample characteristics: a diagnosis of primary major depressive episode according to DSM-IV or ICD criteria;

(c) treatment characteristics: ketamine given as an adjunct to ECT.

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 incalculable. 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 quantitative 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 assessed 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).[9–18] 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:[13] 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.[13] 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 al*[17] 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

Fig. 1 Study selection.

(Flow diagram)
- Records identified through database search — Medline 73, EMBASE 399, CENTRAL 11, Additional references 4
- Records after duplicates removed — 390
- Records screened — 390
- Records excluded — 372
- Full-text articles assessed for eligibility — 18
- Full-text articles excluded (see online Table DS1 for reasons) — 8
- Studies included in qualitative synthesis — 10
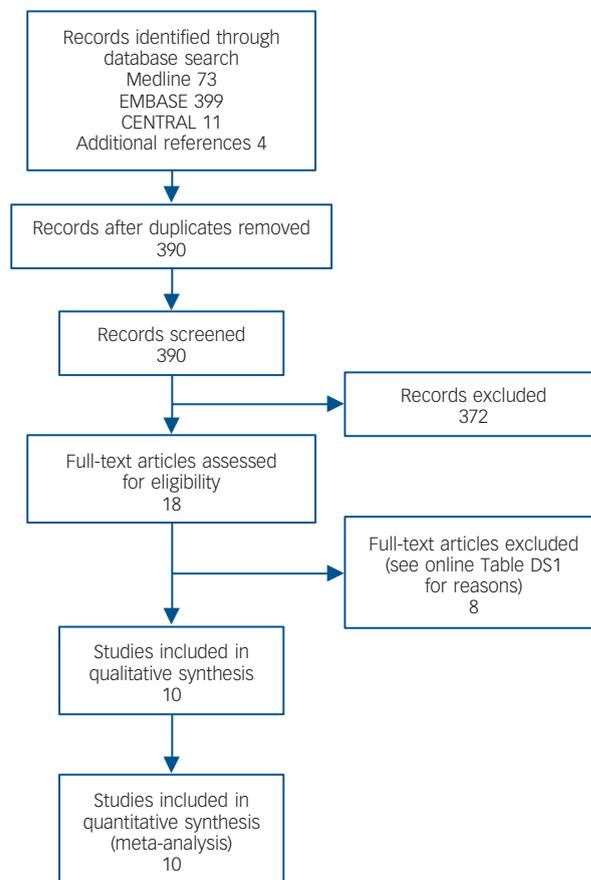- Studies included in quantitative synthesis (meta-analysis) — 10

Table 1 Characteristics of included studies

Study	Diagnosis	Sample size, n	Rating scale	Design	Electrode placement	ECT system; seizure threshold	Number of ECTs	Age, years: mean (s.e.)	Gender, n[a]
Abdallah et al (2012)[9]	MDD, BD	18 (2 withdrawn)	HRSD	(a) Ketamine (0.5 mg/kg) + thiopental (3.5 mg/kg) (b) Thiopental (3.5 mg/kg)	Right unilateral and bitemporal	MECTA; titration method	6	47.1 (0.9)	7F/9M
Anderson et al (in press)[18]	MDD, BD	70	MADRS	(a) Ketamine (0.5 mg/kg) + propofol (thiopental n = 4) (b) Saline + propofol (thiopental n = 1)	Right unilateral and bifrontal	Unspecified; titration method	Mean 11.3 (s.d. = 0.5)	54.2 (1.4)	44F/36M
Jarventausta et al (2013)[10]	MDD	34 (2 withdrawn)	MADRS	(a) S-Ketamine (0.4 mg/kg) + propofol (b) Saline + propofol	Right unilateral and bitemporal	Thymatron; titration method	6	(a) 48.8 (b) 53.7	13F/19M
Kuscu et al (2015)[11]	Major depression	61 (3 withdrawn)	HRSD	(a) Thiopental (4 mg/kg) (b) Ketamine (1 mg/kg) (c) Thiopental (4 mg/kg) + ketamine (1 mg/kg)	Bitemporal	Thymatron; unspecified	6	42.0 (12.1)	27F/30M[b]
Loo et al (2012)[12]	MDD, BD	51 (5 withdrawn)	MADRS	(a) Thiopental (3–5 mg/kg) + ketamine (0.5mg/kg) (b) Thiopental (3–5 mg/kg) + saline	Right unilateral	MECTA; titration method	Mean 9.1 (s.d. = 4.3)	43.3 (1.9)	28F/18M
Rybakowski et al (2016)[13]	MDD, BD	45	HRSD	(a) Thiopental (2–3 mg/kg) (b) Thiopental (2-3 mg/kg) + ketamine (1–1.5 mg/kg) on sessions 2 & 3 (c) Thiopental (2–3 mg/kg) + ketamine (1–1.5 mg/kg) on sessions 2, 4, 6 & 8	Bifrontal	Thymatron; age method	>8	53.0 (12.0)	34F/11M
Salehi et al (2015)[14]	Major depression	160	HRSD	(a) Thiopental (1–1.5 mg/kg) (b) Ketamine (0.8 mg/kg)	Unspecified	Unspecified	8	20–60	86F/74M
Shams Alizadeh et al (2015)[15]	MDD	44	HRSD	(a) Propofol (1 mg/kg) (b) Propofol (1 mg/kg) + ketamine (0.3 mg/kg)	Bifrontal	IEC 601-1 type BF Class 1	6	34.6 (1.7)	29F/13M
Yoosefi et al (2014)[16]	MDD	31	HRSD	(a) Ketamine (1–2 mg/kg) (b) Thiopental (2–3 mg/kg)	Bitemporal	Thymatron; age method	6	43.8 (2.1)	14F/17M
Zhong et al (2016)[17]	MDD, BD	90		(a) Propofol (0.8 mg/kg) (b) Propofol (0.5 mg/kg) + ketamine (0.5 mg/kg) (c) Ketamine (0.8 mg/kg)	Bitemporal	Thymatron; age method	8	30.6 (9.1)	54F/36M

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.

was not statistically significant ($t(8) = 0.87$, $P = 0.40$). We repeated the analysis excluding the trial with major methodological issues,[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.[13] This again revealed a non-significant SMD in favour of ketamine (SMD = 0.17, 95% CI −0.30 to 0.65, $P = 0.47$). 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 v. 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 v. comparator (ketamine $n = 32$, 16.7%; comparator $n = 28$, 18.9%; RD = 0.026, 95% CI −0.02 to 0.07, $P = 0.30$; Fig. 4). The funnel plot revealed minimal spread around a risk difference of zero (online Fig. DS3) and Egger's intercept did not reveal statistical evidence of publication bias ($t(5) = 0.56$, $P = 0.59$).

Cognitive testing

Several studies examined cognitive indices; however, few had overlapping instruments, preventing quantitative synthesis. Two
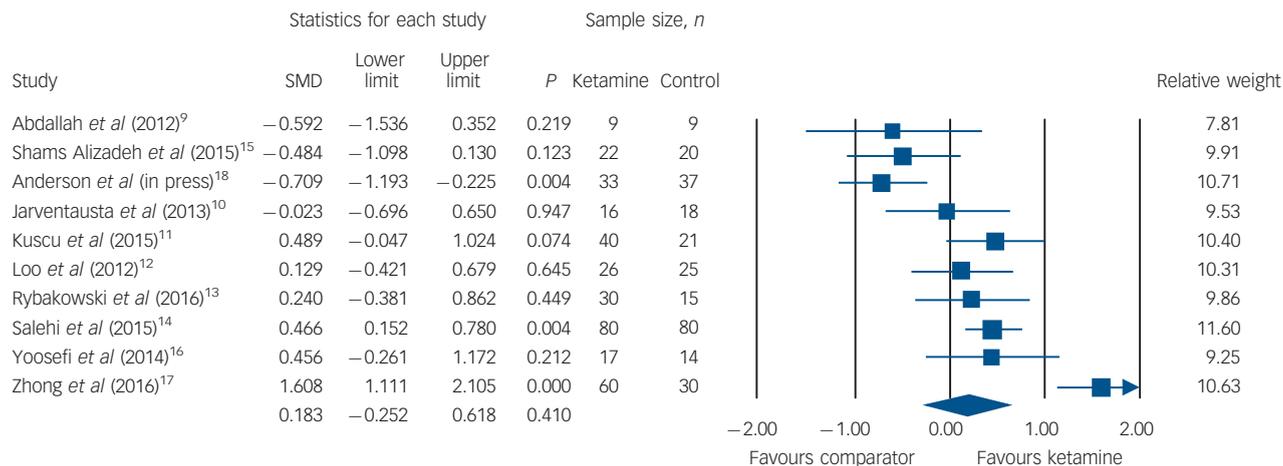
Study	Statistics for each study				Sample size, n			Relative weight
	SMD	Lower limit	Upper limit	P	Ketamine	Control		
Abdallah et al (2012)[9]	−0.592	−1.536	0.352	0.219	9	9		7.81
Shams Alizadeh et al (2015)[15]	−0.484	−1.098	0.130	0.123	22	20		9.91
Anderson et al (in press)[18]	−0.709	−1.193	−0.225	0.004	33	37		10.71
Jarventausta et al (2013)[10]	−0.023	−0.696	0.650	0.947	16	18		9.53
Kuscu et al (2015)[11]	0.489	−0.047	1.024	0.074	40	21		10.40
Loo et al (2012)[12]	0.129	−0.421	0.679	0.645	26	25		10.31
Rybakowski et al (2016)[13]	0.240	−0.381	0.862	0.449	30	15		9.86
Salehi et al (2015)[14]	0.466	0.152	0.780	0.004	80	80		11.60
Yoosefi et al (2014)[16]	0.456	−0.261	1.172	0.212	17	14		9.25
Zhong et al (2016)[17]	1.608	1.111	2.105	0.000	60	30		10.63
	0.183	−0.252	0.618	0.410				

Favours comparator — Favours ketamine

Fig. 2 Change in clinician-administered depression rating scores. SMD, standardised mean difference.

Study	Statistics for each study				Response/total, n/n			Relative weight
	Risk difference	Lower limit	Upper limit	P	Ketamine	Control		
Abdallah et al (2012)[9]	−0.222	−0.592	0.148	0.239	1/9	3/9		3.86
Anderson et al (in press)[18]	−0.110	−0.342	0.123	0.355	16/33	22/37		9.40
Jarventausta et al (2013)[10]	0.201	−0.094	0.497	0.182	13/16	11/18		5.97
Loo et al (2012)[12]	−0.140	−0.409	0.129	0.308	13/26	16/25		7.14
Rybakowski et al (2016)[13]	0.033	−0.132	0.199	0.693	3/30	1/15		17.47
Yoosefi et al (2014)[16]	0.000	−0.118	0.118	1.000	0/17	0/14		30.84
Zhong et al (2016)[17]	0.083	−0.050	0.217	0.221	57/60	26/30		25.33
	0.010	−0.064	0.084	0.789				

Favours comparator — Favours ketamine

Fig. 3 Rates of clinical response.

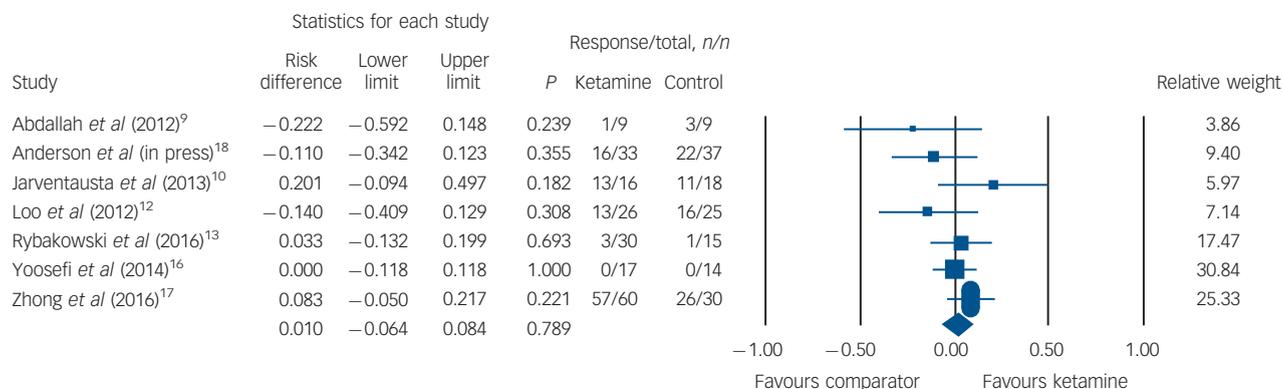| Study	Statistics for each study				Remission/total, n/n			Relative weight
	Risk difference	Lower limit	Upper limit	P	Ketamine	Control		
Abdallah et al (2012)[9]	0.000	−0.290	0.290	1.000	1/9	3/9		2.81
Anderson et al (in press)[18]	0.043	−0.184	0.269	0.713	13/33	13/37		4.61
Jarventausta et al (2013)[10]	−0.021	−0.335	0.294	0.897	5/16	6/18		2.39
Loo et al (2012)[12]	0.065	−0.197	0.326	0.628	10/26	8/25		3.47
Rybakowski et al (2016)[13]	0.000	−0.096	0.096	1.000	0/30	0/15		25.67
Yoosefi et al (2014)[16]	0.000	−0.118	0.118	1.000	0/17	0/14		16.92
Zhong et al (2016)[17]	0.050	−0.023	0.123	0.181	3/60	0/30		44.13
	0.026	−0.023	0.074	0.300				

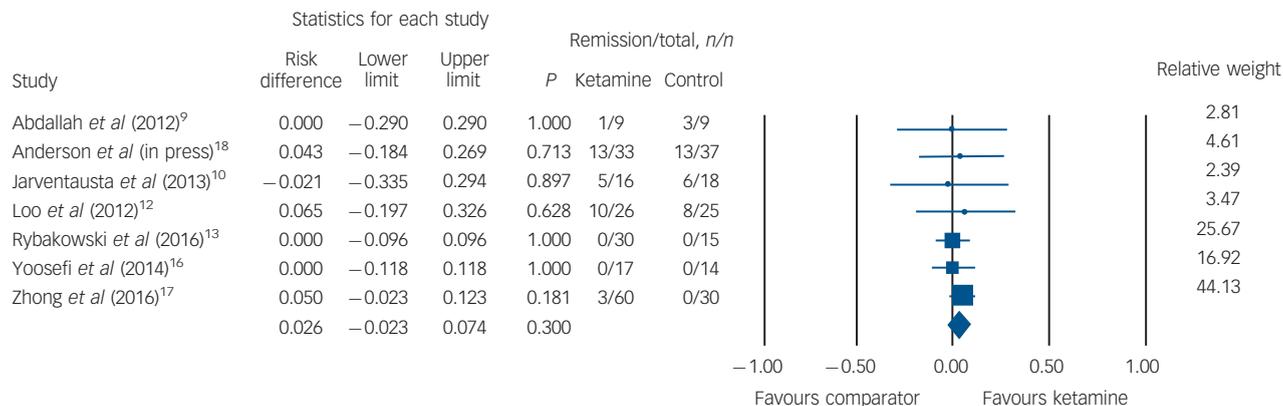Favours comparator — Favours ketamine

Fig. 4 Rates of clinical remission.

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,[7,17] 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;[16] 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.

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EXTRA CONTENT ONLINE