HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2015; **30**: 152–163
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.2475

REVIEW ARTICLE

The use of ketamine as an antidepressant: a systematic review and meta-analysis

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Objective The current meta-analysis examines the effects of ketamine infusion on depressive symptoms over time in major depressive disorder (MDD) and bipolar disorder (BD).
Methods Following a systematic review of the literature, data were extracted from 21 studies ($n = 437$ receiving ketamine) and analysed at four post-infusion time points (4 h, 24 h, 7 days and 12–14 days). The moderating effects of several factors were assessed including: repeat/single infusion, diagnosis, open-label/participant-blind infusion, pre–post/placebo-controlled design and the sex of patients.
Results Effect sizes were significantly larger for repeat than single infusion at 4 h, 24 h and 7 days. For single infusion studies, effect sizes were large and significant at 4 h, 24 h and 7 days. The percentage of males was a predictor of antidepressant response at 7 days. Effect sizes for open-label and participant-blind infusions were not significantly different at any time point.
Conclusions Single ketamine infusions elicit a significant antidepressant effect from 4 h to 7 days; the small number of studies at 12–14 days post infusion failed to reach significance. Results suggest a discrepancy in peak response time depending upon primary diagnosis — 24 h for MDD and 7 days for BD. The majority of published studies have used pre–post comparison; further placebo-controlled studies would help to clarify the effect of ketamine over time. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—ketamine; depression; major depressive disorder; bipolar disorder

INTRODUCTION

Most current antidepressants act on the monoamine systems of the brain and, crucially, are slow to elicit antidepressant effects. By contrast, ketamine is an N-methyl-D-aspartate antagonist with purported rapid antidepressant properties that are sustained beyond ketamine's 3 h half-life (Young, 2013; Salvadore and Singh, 2013). Ketamine is known to block N-methyl-D-aspartate receptors thereby affecting the action of glutamate, a major excitatory neurotransmitter in the brain (aan het Rot *et al*., 2012). Unlike traditional antidepressants, ketamine is administered intravenously. The first placebo-controlled study investigating ketamine for the treatment of depression was conducted by Berman *et al*. (2000). Antidepressant response to ketamine was maintained in four of the seven completers at the end of the 72-h follow-up period.

The prospect of using ketamine as an antidepressant is a fascinating and exciting one, particularly in terms of its potential for alleviating depressive symptoms in individuals with treatment-resistant depression (Zarate *et al*., 2006; Kollmar *et al*., 2008; Murrough *et al*., 2013; Liebrenz *et al*., 2007; Liebrenz *et al*., 2009; aan het Rot *et al*., 2010; Ibrahim *et al*., 2011; Ibrahim *et al*., 2012) and in reducing suicidal ideation, at least temporarily or in emergency situations (Price *et al*., 2009; Diazgranados *et al*., 2010a; Larkin and Beautrais 2011; Price *et al*., 2014).

Use of ketamine to treat depression in bipolar disorder

Ketamine has also been reported to alleviate depressive symptoms in treatment-resistant bipolar depression. Diazgranados *et al*. (2010b) conducted a double-blind, randomised, crossover, placebo-controlled study using a single ketamine infusion combined with lithium or valproate therapy for individuals diagnosed with bipolar I or II depression. The results indicated significantly fewer depressive symptoms within 40 min post infusion and for up to 3 days in those receiving ketamine compared with placebo; after this time, depression

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Received 12 January 2014
Accepted 12 February 2015

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scores began to increase, but remained below baseline level at day 14. Zarate *et al*. (2012a) replicated the study conducted by Diazgranados *et al*. (2010b). Analysis of the intent-to-treat sample showed a significant drug-by-time interaction for depression scores; participants receiving ketamine had significantly fewer depressive symptoms from 40 min to 3 days post infusion when compared with placebo. However, depression scores for placebo and ketamine did not significantly differ at days 7, 10 or 14. These findings are consistent with those of Berman *et al*. (2000), wherein depression scores returned to baseline levels within 1–2 weeks post infusion.

Safety, efficacy and durability of repeated ketamine infusions

Because the effects of ketamine appear to be relatively short lived, repeated ketamine infusions may potentially increase the duration of antidepressant response. The tolerability and safety of repeated ketamine infusions in treatment-resistant depression was investigated by aan het Rot *et al*. (2010) alongside the efficacy and clinical benefit of ketamine in treating depression. Depression scores were assessed at baseline and up to 24 h post infusion. At 24 h following a single intravenous ketamine (0.5 mg/kg) infusion, 90% of the participants met the response criterion [≥50% reduction in Montgomery–Åsberg Depression Rating Scale (MADRS) score] and were eligible for the second phase. These participants received five additional infusions of ketamine. The majority of the participants (89%) who had received multiple ketamine infusions were found to relapse within an average of 30 days after the first infusion (an average of 19 days after the sixth infusion). Notably, one participant who had received six infusions demonstrated reduced depressive symptoms for more than 4 weeks and another for almost 7 weeks; another continued to have decreased depressive symptoms for over 3 months.

The durability of response in individuals with treatment-resistant depression following repeated ketamine infusions was recently investigated in a larger treatment group ($n = 24$) by Murrough *et al*. (2012). It should be noted that the results for ten of the 24 participants in the study of Murrough *et al*. (2012) were previously reported by aan het Rot *et al*. (2010). The participants received up to six infusions of ketamine (0.5 mg/kg) on a Monday-Wednesday-Friday schedule over 12 days. The participants meeting response criteria (≥50% reduction in MADRS score) following multiple infusions were tracked for a maximum of 83 days or until relapse (<50% improvement in MADRS score compared with the baseline for two consecutive assessments). Overall, approximately 71% of the participants responded to ketamine. The median time to relapse after the last ketamine infusion was 18 days and so the duration of antidepressant effect for repeat infusions may not extend much beyond that of a single infusion as identified by Diazgranados *et al*. (2010a).

Rasmussen *et al*. (2013) conducted an open-label study to determine whether serial infusions of ketamine elicited better response and remission rates than single infusions. The participants received up to four ketamine infusions twice weekly (for up to 2 weeks). If a participant met remission criteria (MADRS score <9) on the morning after an infusion or on the morning of the next scheduled infusion, they received no further infusions. Half of the participants met remission criteria during the study. Rasmussen *et al*. (2013) inferred that serial infusions may be more successful than a single infusion in reducing depressive symptoms. Despite taking antidepressant medication throughout a 4-week follow-up period, however, symptom remission was maintained in only 20% of the participants at the end of the follow-up period. The advantage of repeated over single ketamine infusion is questionable because the seemingly prolonged antidepressant effect of repeated infusions is minimal in duration. Furthermore, and crucially, none of these studies (aan het Rot *et al*., 2010; Murrough *et al*., 2012 or Rasmussen *et al*., 2013) employed a control group with which to compare relapse times.

Objectives of the current study

To the authors' knowledge, no meta-analysis has synthesised the published clinical trial data on ketamine as an antidepressant. The key questions are the following: Does ketamine have an immediate effect in reducing depressive symptoms?; Are the antidepressant effects of ketamine sustained over time?; Are repeat infusions more effective in reducing depressive symptoms?; Do primary diagnosis and experimental design moderate the impact of ketamine on depressive symptoms? Finally, some evidence from studies on rats suggests a higher sensitivity of female rats to a low dose of ketamine (Carrier and Kabbaj, 2013). Thus, we will also examine for differences in the antidepressant effect of ketamine depending upon the sex of the patient.

METHOD

Identification and selection of studies

The review was conducted in accordance with preferred reporting items for systematic reviews and

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DOI: 10.1002/hup

meta-analyses (PRISMA) guidelines (Moher *et al*., 2009). A systematic search was conducted in *Web of Science*, *Science Direct*, *and PubMed* using the terms 'ketamine' AND 'depression'. In *Web of Science* and *Science Direct*, abstracts, title and keywords were searched; in *PubMed*, all fields were searched. The subject areas in *Science Direct* to which the search was restricted were: Arts and Humanities; Biochemistry, Genetics and Molecular Biology; Pharmacology, Toxicology and Pharmaceutical Science; Psychology and Social Science. As the first clinical trial of ketamine for the treatment of depression was conducted in 2000, all years from 2000 up to January 2015 were included in the search.

Criteria for inclusion of studies

Studies were included in the meta-analysis if at least one infusion of ketamine was administered for the treatment of depression; and primary diagnosis could include major depressive disorder (MDD) or bipolar disorder (BD). Included studies were also required to report on depressive symptoms using a standardised measure of depression, such as the MADRS or the Hamilton Depression Rating Scale (HDRS) and to include eight or more participants. A summary of the selection process is given in Figure 1.

Data extraction

Data were extracted from studies meeting the criteria outlined earlier. Where data were incomplete or unclear, we contacted authors for clarification or additional data. In some cases, additional data could not be obtained after enquiring with authors and such studies were consequently excluded from the meta-analysis. Meta-analysis was conducted for four post-infusion time points (4 h, 24 h, 7 days and 12–14 days). Where studies used a control group, the effect sizes were calculated for placebo *versus* ketamine; where no control group was used, the effect sizes were calculated for baseline depression scores *versus* scores at each time point. All data analysis was conducted using Comprehensive Meta-Analysis Version 2.0 (http://www.meta-analysis.com/). Effect sizes were calculated using Hedge's g, that is, the standardised difference between means, corrected for the tendency towards over estimation in small studies using a random effects model. Effect sizes were described using Cohen's convention wherein an effect size of 0.20 was considered small, 0.50 moderate and 0.80 large.

Statistical heterogeneity

We assessed heterogeneity using the I^2 value, which estimates the amount of total variation that is attributable to heterogeneity. An I^2 value of 0–40% suggests that heterogeneity may not be important, 30–60% may represent moderate heterogeneity, 50–90% may represent substantial heterogeneity and 75–100% may represent considerable heterogeneity (Higgins & Green, 2011).

Risk of bias

Studies involved in the meta-analysis were assessed for possible bias. A study was considered to have a low risk of bias if a control group was employed, if the allocation of participants to control and experimental groups was adequately randomised and if there was no evidence of conflict of interest. Medium risk of bias was assigned if a control condition was employed within an ABBA design (blindness may have been compromised by the 'high' associated with ketamine infusions), if there was evidence of an adequate randomisation of participants to control and experimental groups (where a control group was employed), if selection of the participants was randomised and if there was a potential conflict of interest. High risk of bias was assigned if a study did not employ a control group, demonstrated little evidence of random selection of the participants and a potential conflict of interest was identified.

Effects of moderators

The effects of several factors were examined, namely, experimental design (pre–post and placebo-controlled), diagnosis (MDD, BD and mixed/unknown), number of infusions (single or repeated), and infusion delivery (open-label or participant-blind). A meta-regression was also conducted to examine whether the percentage of males (% males) was a predictor of effect size.

Publication bias

Publication bias was examined using Fail Safe N, Duval and Tweedie's trim and fill (Duval and Tweedie, 2000), Begg and Mazumdar's Rank Correlation Test (Begg and Mazumdar, 1994) and Egger's test of the intercept (Egger *et al*., 1997).

RESULTS

Identification and selection of studies

The total number of studies (K) selected was 21 of which 17 were single infusion studies. The majority of studies collected and reported data at 4 h (K = 11) and 24 h (K = 13); a smaller number of studies reported data at 7 days (K = 6) and at 12–14 days (K = 4). For single infusion studies, results were reported for 9

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DOI: 10.1002/hup

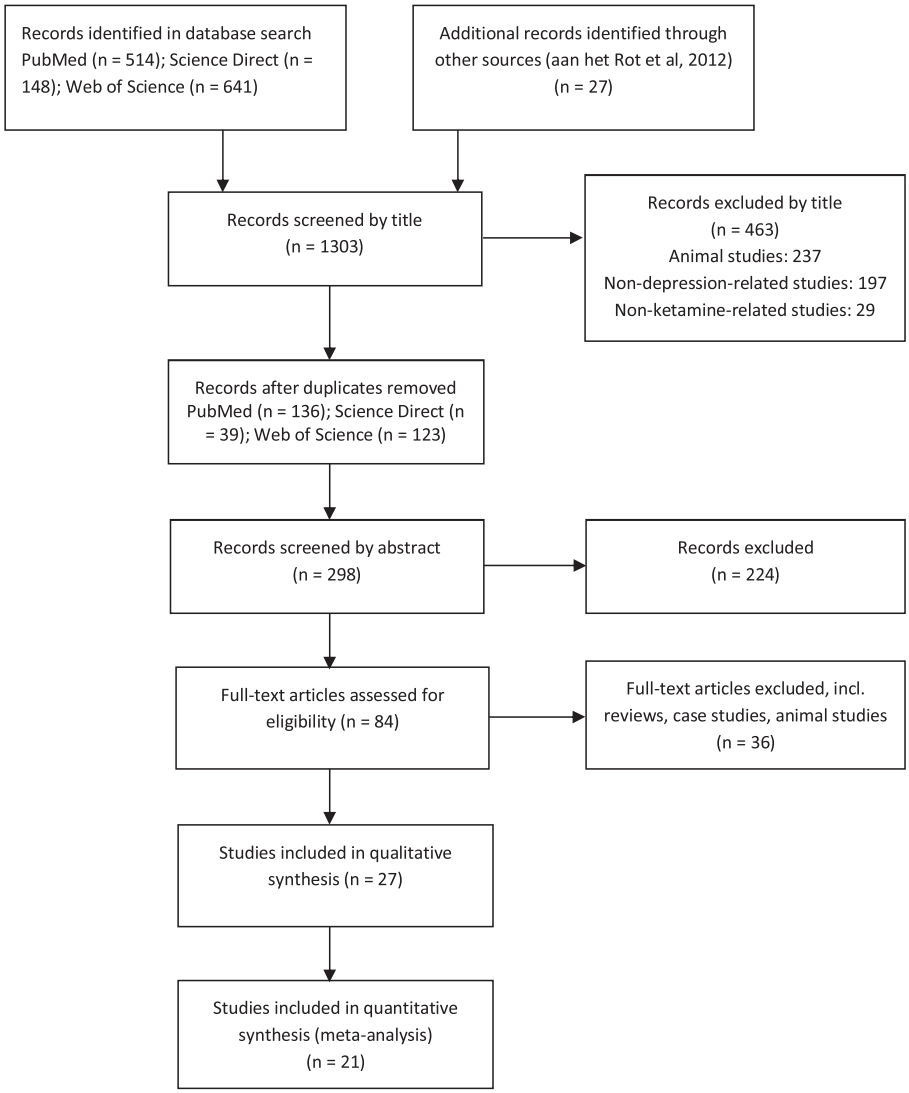

Figure 1. Flow diagram of the study selection process

studies at 4 h, for 11 studies at 24 h, for 5 studies at 7 days and for 2 studies at 12–14 days post infusion.

Risk of bias

Table 1

Overall pooled effect sizes

Overall pooled Hedge's g values were large and significant at all time points (Table 2). No significant differences in effect sizes emerged between any time points (4 h *vs* 24 h: $p=0.36$; 4 h *vs* 7 days: $p=0.47$; 4 h *vs* 12–14 days: $p=0.55$; 24 h *vs* 7 days: $p=0.45$; 24 h *vs* 12–14 days: $p=0.73$; 7 days *vs* 12–14 days: $p=0.31$). The heterogeneity across studies was large and significant at all time points (Table 2). The forest plot for all time points is given in Figure 2.

Moderating effect of single and repeat infusions

At all time points the effect sizes for repeat infusions were larger than for single infusions, and significant at 4 h (-3.34 *vs* -1.11, $p=0.001$), 24 h (-4.16 *vs* -1.11, $p=0.000$) and at 12–14 days (-2.95 *vs* -0.85, $p=0.012$) post infusion, but not at 7 days (-1.96 *vs* -0.88, $p>0.05$); however, the number of repeat infusions studies is limited at each of these time points (K = 2, 2, 1 and 2, respectively). Single infusion studies were significant at 4 h, 24 h, and at 7 days. A large effect size was determined at 12–14 days, but did not reach significance (possibly because of

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DOI: 10.1002/hup

Table 1. Table of analysis of risk of bias in studies used in the meta-analysis

Study	*n*	% Males	4 h	24 h	7 days	12–14 days	Control group	Randomised	Rater blind	ITT sample	Conflict of interest	Risk of bias
Zarate *et al.* (2006)	18	33	N	Y	Y	N	Control condition	Yes	Yes	No	None	Low
Salvadore *et al.* (2009)	11	64	Y	N	N	N	No	N/A	No	No	Yes	Medium
Price *et al.* (2009)	26 (S); 10 (R)	61.5 (S); 50 (R)	N	Y	N	N	No	N/A	Unknown	No	Yes	Low
aan het Rot *et al.* (2010)	9	50	Y	Y	N	N	No	N/A	Unknown	No	Yes	High
Salvadore *et al.* (2010)	15	Unknown	Y	N	N	N	No	N/A	No	No	Yes	Medium
Mathew *et al.* (2010)	26	61.5	N	Y	N	N	Yes	Yes	No	No	Yes	Medium
Diazgranados *et al.* (2010a, 2010b)	18	33	N	Y	N	Y	Yes	Yes	Yes	Yes	Yes	Low
Ibrahim *et al.* (2011)	17 (E); 23 (NE)	59 (E); 61 (NE)	Y	N	N	N	ECT-resist *versus* no-ECT	No	No	No	None	Medium
Larkin *et al.* (2011)	14	Unknown	Y	N	N	N	No	N/A	Unknown	No	Unknown	Medium
Salvadore *et al.* (2012)	14	64	Y	N	N	N	No	N/A	No	No	None	Medium
Zarate *et al.* (2012a)	15	47	Y	Y	N	N	Yes	Yes	Yes	Yes	Yes	Medium
Thakurta *et al.* (2012)	20	Unknown	Y	N	Y	N	No	N/A	No	No	None	Medium
Abdallah *et al.* (2012)	8	56	N	Y	N	N	Yes	Yes	Yes	No	Unknown	Low
Loo *et al.* (2012)	22	50	N	N	Y	Y	Yes	Yes	Yes	No	None	Low
Murrough *et al.* (2012)	24	62.5	Y	Y	N	N	No	N/A	No	No	Yes	High
Carlson *et al.* (2013)	20	70	Y	Y	N	N	No	N/A	No	No	Yes	Medium
Rybakowski *et al.* (2013)	25	16	N	Y	Y	Y	No	N/A	Unknown	No	None	Medium
Permoda-Osip *et al.* (2011)	10	0	N	N	Y	N	No	N/A	Unknown	No	Unknown	Medium
Murrough *et al.* (2013)	47 (K)	45 (K)	N	Y	N	N	Yes	Yes	Yes	Yes	Yes	Medium
Sos *et al.* (2013)	27	50	N	Y	Y	N	CO	Yes	Yes	Yes	None	Low
Lapidus *et al.* (2014)	18	50	—	Y	Y	N	CO	Yes	Yes	Yes	Yes	Medium

ECT, electroconvulsive therapy; ITT, intention-to-treat; E, ECT; NE, no ECT; S, single infusion; R, repeat infusion; K, ketamine; O, overall; CO, crossover design.

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DOI: 10.1002/hup

Table 2. Effect sizes and heterogeneity values (I^2) for all studies

Time	K	Hedge's g	CI lower	CI upper	*p*-value	I^2
4 h	11	−1.29	−1.66	−0.92	<0.001	81.73
24 h	13	−1.24	−1.56	−0.93	<0.001	79.81
7 days	6	−1.06	−1.57	−0.55	<0.001	81.02
12–14 days	4	−1.67	−2.85	−0.49	0.006	93.65

K, number of studies; CI, 95% confidence interval.

insufficient available studies; see Table 3). Comparison of single infusion studies revealed no significant differences in effect sizes between time points (4 h *vs* 24 h: $p=0.59$; 4 h *vs* 7 days: $p=0.43$; 4 h *vs* 12–14 days: $p=0.71$; 24 h *vs* 7 days: $p=0.16$; 24 h *vs* 12–14 days: $p=0.55$; 7 days *vs* 12–14 days: $p=0.85$).

Single infusion: moderating effect of diagnosis

We examined the impact of moderators for single infusion studies but insufficient data were available for repeat infusion studies to permit similar analyses (Cochrane, 2011).

For MDD, effect sizes ranged from moderate at 7 days (−0.53) to large at 4 h (−1.03) and 24 h (−1.35). For BD, effect sizes ranged from moderate at 24 h (−0.64) to large at 4 h (−0.80) and at 7 days (−1.51) post infusion; a large but not significant effect size was determined at 12–14 days post infusion (Table 4). The effect sizes for MDD and BD did not significantly differ at 4 h post infusion ($p=0.30$), but were significant at 24 h ($p<0.001$) and 7 days ($p<0.001$) post infusion. The effect size for MDD was largest at 24 h, whereas the effect size for BD was largest at 7 days. Comparison of MDD and BD at 12–14 days was not possible because no MDD studies measured depression scores at this time point.

Single infusion: moderating effect of experimental design

For pre–post design, the effect sizes were large and significant at all post-infusion time points (Table 5). For placebo-controlled design, effect sizes ranged from small to large; the effect sizes were significant at 4 h, 24 h and 7 days post infusion, but not at 12–14 days post infusion; however, only one placebo-controlled study was available at 4 h and at 12–14 days post infusion so the results must be interpreted with caution. The difference between effect sizes for pre–post and placebo-controlled design was not significant at 4 h ($p=0.10$), 24 h ($p=0.26$) or 7 days ($p=0.41$) post infusion, but was significant at 12–14 days ($p<0.001$); however, only one study was available for each design at 12–14 days post infusion.

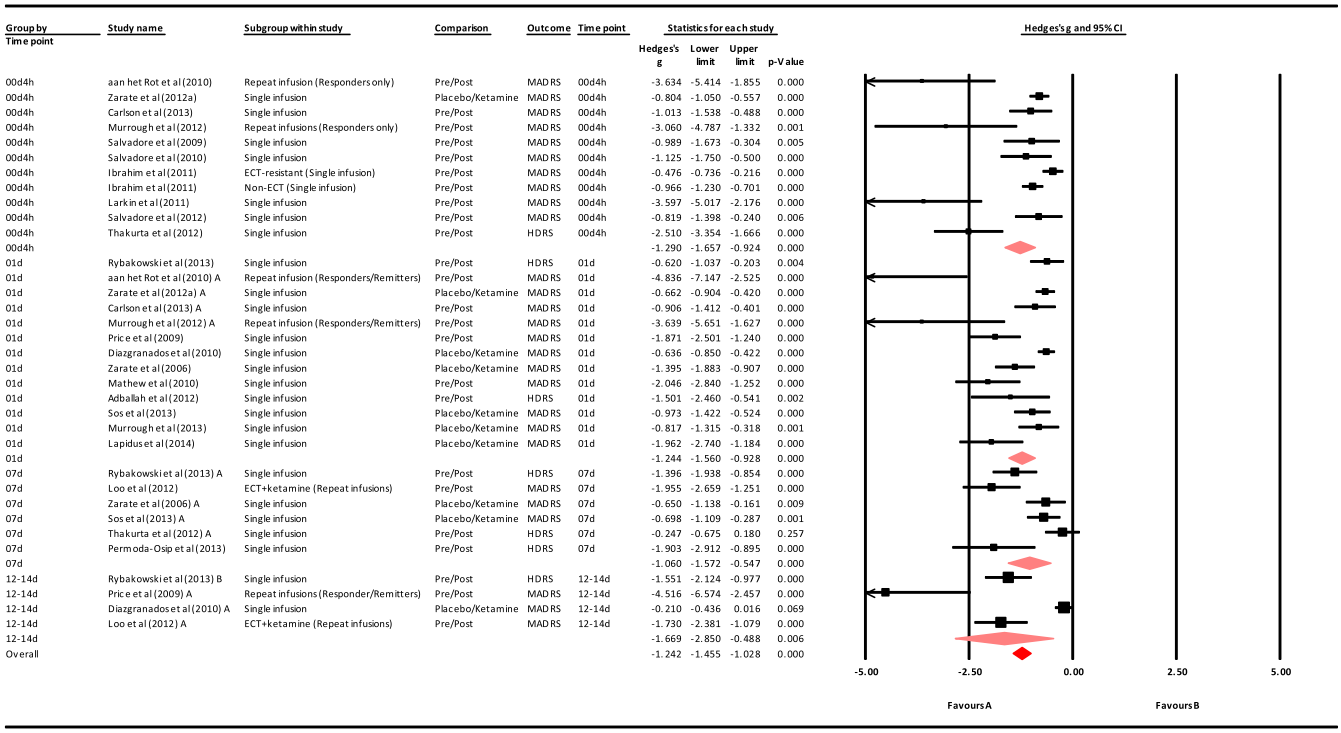

Figure 2. Forest plot for moderating effect of time point for all studies. MADRS, Montgomery–Åsberg Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; ECT, electroconvulsive therapy

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DOI: 10.1002/hup

Table 3. Effect sizes for single and repeated infusions

	Single						Repeated					
Time	K	Hedge's g	CI lower	CI upper	*p*-value	I^2	K	Hedge's g	CI lower	CI upper	*p*-value	I^2
4 h	9	−1.11	−1.44	−0.78	<0.001	79.65	2	−3.34	−4.58	−2.10	<0.001	0
24 h	11	−1.11	−1.38	−0.83	<0.001	75.53	2	−4.16	−5.67	−2.64	<0.001	0
7 days	5	−0.88	−1.35	−0.41	<0.001	75.00	1	−1.96	−2.66	−1.25	<0.001	0
12–14 days	2	−0.85	−2.17	0.46	0.203	94.50	2	−2.95	−5.65	−0.24	0.033	84.36

K, number of studies; CI, 95% confidence interval.

Table 4. Single infusion: moderating effect of diagnosis

	MDD					BD				
Time	K	Hedge's g	CI lower	CI upper	*p*-value	K	Hedge's g	CI lower	CI upper	*p*-value
4 h	7	−1.03	−1.39	−0.68	<0.001	1	−0.80	−1.05	−0.56	<0.001
24 h	7	−1.35	−1.72	−0.99	<0.001	3	−0.64	−0.79	−0.49	<0.001
7 days	3	−0.53	−0.82	−0.24	<0.001	2	−1.51	−1.99	−1.03	<0.001
12–14 days	0	—	—	—	—	2	−0.85	−2.17	0.46	0.20

MDD, major depressive disorder; BD, bipolar disorder; K, number of studies; CI, 95% confidence interval.

Table 5. Moderating effects of pre–post comparison and placebo-controlled single infusion studies

	Pre–post					Placebo *versus* ketamine				
Time	K	Hedge's g	CI lower	CI upper	*p*-value	K	Hedge's g	CI lower	CI upper	*p*-value
4 h	8	−1.21	−1.63	−0.79	<0.001	1	−0.80	−1.05	−0.56	<0.001
24 h	5	−1.33	−1.91	−0.75	<0.001	6	−0.96	−1.26	−0.66	<0.001
7 days	3	−1.12	−2.10	−0.13	0.03	2	−0.68	−0.99	−0.36	<0.001
12–14 days	1	−1.55	−2.12	−0.98	<0.001	1	−0.21	−0.44	0.02	0.07

K, number of studies; CI, 95% confidence interval.

Table 6. Table of publication bias for single infusion studies

	K	Unadjusted ES (95% CI)	Trim and fill adjusted ES (95% CI)	Begg and Mazumdar's test	Egger's test
4 h	9	−1.11 (−1.44, −0.78)	−1.27 (−1.69, −0.86)	$z = 1.77$ $p = 0.04$	$t = 3.05$ $p = 0.02$
24 h	11	−1.11 (−1.38, −0.83)	−0.97 (−1.25, −0.70)	$z = 2.65$ $p = 0.004$	$t = 4.81$ $p = 0.0005$
7 days	5	−0.88 (−1.35, −0.41)	−0.88 (−1.35, −0.40)	$z = 0.73$ $p = 0.23$	$t = 2.05$ $p = 0.07$

K, number of studies; CI, confidence interval; ES, effect size (Hedge's g).
No bias analyses were calculated for 12–14 days as only two studies exist.

Single infusion: moderating effect of open-label and blind infusions

For open-label infusions, the effect sizes ranged from small to large and, with the exception of 7 days post infusion, all effect sizes were significant [4 h: −1.03, 95% confidence interval (CI) = −1.39, −0.68, K = 7; 24 h: −1.57, 95% CI = −2.32, −0.82, K = 3; 7 days: −0.25, 95% CI = −0.66, 0.16, K = 1]. No open-label single infusion studies were available at 12–14 days. For participant-blind infusions, the effect sizes ranged from small to large (4 h: −0.80, 95% CI = −1.05, −0.56, K = 1; 24 h: −1.00, 95% CI = −1.29, −0.71, K = 7; 7 days: −0.68, 95% CI = −0.99, −0.36, K = 2; 12–14 days: −0.21, 95% CI = −0.44, 0.02, K = 1). The effect size at 12–14 days was not significant; effect sizes at all other time points were significant. The difference between effect sizes for open-label and participant-

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DOI: 10.1002/hup

blind infusions was not significant at any time point (4 h: $p = 0.30$; 24 h: $p = 0.17$; 7 days: $p = 0.11$).

Single infusion: effect of sex

A meta-regression was conducted with a percentage of males as a predictor of effect size, with no significant effects determined at 4 h ($p = 0.60$) or 24 h ($p = 0.08$). However, a significant positive relationship between percentage males and effect size was determined at 7 days ($p = 0.008$); however, only four data points were available at this time point. Meta-regression could not be conducted at 12–14 days post single ketamine infusion because of an insufficient number of studies.

Single infusion: publication bias

Publication bias (Table 6) was examined using Fail Safe N, Duval and Tweedie's trim and fill (Duval and Tweedie, 2000), Begg and Mazumdar's Rank Correlation Test (Begg and Mazumdar, 1994), and Egger's test of the intercept (Egger *et al*., 1997). The results across all the tests indicate publication bias at 4 h and 24 h for single infusion studies.

DISCUSSION

The results of the meta-analysis suggest that ketamine reduces depressive symptoms with large effect sizes at every time point analysed (4 h, 24 h, 7 days and 12–14 days). The relative stability of the effect size across time points suggests a sustained antidepressant response to ketamine at least up to 2 weeks post infusion as examined in clinical trials to date.

Turning to single infusion studies, large effects emerged at 4 h and at 24 h, confirming the reported rapid reduction in depressive symptoms, and also at 7 days; a large effect at 12–14 days failed to reach significance. The lack of longer term effect is consistent with reports of relapse within 1–2 weeks for a single infusion (Zarate *et al*., 2006); however, few single infusion studies have assessed up to 12–14 days post infusion (K = 2). No significant difference in effect size emerged between any time points for single infusions. As expected, effect sizes for repeat infusions were larger than for single infusions and differed significantly at 4 h, at 24 h and at 7 days. It must be noted that the number of repeat infusion studies was limited and further studies are required.

Moderating effects of diagnosis

Although effect sizes for MDD and BD were moderate to large, some differences emerged in responsiveness. Following a single infusion, the effect for MDD at 24 h was significantly larger than for BD; at 7 days, BD showed a significantly larger effect size than MDD. These findings hint that the antidepressant effect of a single ketamine infusion may vary according to the primary diagnosis, although this interpretation is limited by the small number of studies available, particularly at 7 days (K = 3 and K = 2 for MDD and BD, respectively).

Moderating effects of experimental design

Single infusion pre–post comparisons resulted in larger effect sizes than placebo-controlled designs, although the difference was significant only at 12–14 days. Interpretations are somewhat limited by the small number of placebo-controlled studies at each time point. Furthermore, all studies employing pre–post designs also used open-label infusions and this may have affected the outcome owing to the potential of an expectancy bias. Further blind placebo-controlled studies, such as that carried out by Murrough *et al.* (2013), are required to confirm the findings.

Moderating effects of open-label and participant-blind infusions

Firstly, as might be expected, effect sizes in open-label trials were larger than for participant-blind trials. The difference reached significance at 12–14 days with a large effect size for open-label infusions, although it consisted of comparing just two studies. Indeed, the lack of significant differences at other time points may reflect the small numbers of studies being compared (with just one blind trial at 4 h, 7 days and 12–14 days). Consideration of further interpretations is, however, required. In particular, the larger effect sizes for open-label infusion may arise as a result of expectancy bias, with knowledge of having received ketamine impacting the participants' reported decrease in depressive symptoms. Similarly, those assessing symptoms may also have an expectancy bias for open-label infusions, which may affect how they make MADRS and HDRS ratings. Conversely, and noted by Berman *et al*. (2000) in the first published trial, blinding itself is likely to be compromised given the psychotomimetic effects of ketamine, especially with the lack of any active controls in the studies. Indeed, at doses comparable with those used in depression studies reported here, subanaesthetic ketamine does generate self-reported 'mystical-type phenomena' (Dakwar *et al*., 2014). These authors remark that 'An intriguing but unexplored question is whether the psychoactive effects of ketamine influence its efficacy through psychological mechanisms.' (p. 153). Apart from needing more placebo-controlled studies *per se*, future studies need to explore potential active controls

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DOI: 10.1002/hup

to ensure that blindness to a ketamine infusion is preserved and thus provide more accurate conclusions regarding ketamine's specific effect on depressive symptoms. Secondly, confounding occurs as all open-label trials have utilised a pre–post design whereas placebo-controlled design was employed in all participant-blind studies. Therefore, we cannot eliminate experimental design differences as the cause of the discrepancy in effect sizes. As it is not possible to extricate the moderating effects of experimental design from the nature of the administration of ketamine, we cannot currently determine if one or both factors have a moderating effect on depression scores.

Effect of sex

A significant effect of sex was found at 7 days post infusion, but not at any other time point, indicating that the percentage of men is a predictor of response. This finding hints at a bigger symptom reduction perhaps in men, but the finding is for only a few studies (K = 4) and only at that one time point — a finding that needs to be examined in future studies. This finding is not consistent with the higher sensitivity of female rats to a low dose of ketamine (Carrier and Kabbaj, 2013). Additional studies are required to confirm whether there is an effect of sex on the outcome of ketamine infusion and what exactly that effect is, as the current meta-analysis and the effect of ketamine in rats appear to contradict each other.

Limitations of the current meta-analysis

The main limitation of this meta-analysis is the relatively small number of studies with useable data (K = 21), particularly for repeated ketamine infusion (K = 4). Although most studies reported results at 4 h (K = 11) and 24 h (K = 13) post infusion, the results suggest an antidepressant effect of ketamine may last for up to 14 days.

What happens beyond 14 days is unknown. The reported relapse rates have varied across studies. Ibrahim *et al*. (2012) reported an average time to relapse of 13.2 days. Mathew *et al*. (2010) reported that for participants prescribed with post-infusion placebo, the average time to relapse, as indicated by MADRS scores, was 22 days. Of the participants who received post-infusion riluzole (a glutamate-modulating agent expected to maintain the antidepressant effects of ketamine) in the study of Mathew *et al*. (2010), 80% relapsed compared with 50% of those taking post-infusion placebo. Furthermore, 17% of those taking riluzole and 50% of those taking placebo continued to meet response criteria at 32 days post infusion. Thus, riluzole appears to be less effective at maintaining antidepressant response when compared with placebo. The results of Mathew *et al*. (2010) imply that an antidepressant response of up to 32 days post ketamine is possible. It must be noted, however, that those assigned to the placebo/riluzole trial had maintained a post-infusion antidepressant response for 72 h. As this group is highly selective, it is not representative of all individuals receiving ketamine infusion and thus the likelihood is that an antidepressant effect of 32 days duration is more likely to be the exception rather than the rule.

It is plausible that the duration of the antidepressant effect of ketamine may extend beyond 14 days, but with most studies reporting ketamine's antidepressant effects only up to 24 h, we cannot currently determine if this is the case. The results of the meta-analysis show that repeat infusions elicit larger effect sizes when compared with a single infusion in the three published repeat infusion studies we examined. The larger effect sizes for repeat infusions are consistent with the exacerbated effects of ketamine with repeated exposure found in rats (Trujillo *et al.*, 2008). Nonetheless, two of the repeat infusion studies used in this meta-analysis selected participants who had previously responded to ketamine. Specifically, the participants who had responded to two prior infusions of ketamine in the study of aan het Rot *et al*. (2010) were selected to receive additional infusions. Although eight of the nine participants in this study continued to respond for an average of 30 days from the first infusion, such an effect might not be found outside of this highly selective group. Furthermore, Price *et al*. (2009) reported repeat infusion data for the participants who had responded to a single ketamine infusion and subsequently received multiple infusions. Additional repeat infusion studies are required to ascertain the effect of multiple ketamine infusions in a larger and less-selective population.

The results of the current meta-analysis indicate that the antidepressant effects of ketamine last up to 14 days after a single infusion. For repeat infusions, the median time to relapse has been reported as 18 days (Murrough *et al*., 2012) and 19 days (aan het Rot *et al*., 2010) after the last in a series of six infusions. In both cases, the duration of response for repeat infusion studies is only slightly longer than the apparent 14-day duration for single infusion studies as assessed by this meta-analysis. Further investigation is required to see if repeat infusions, administered over a short period of time, have any significant long-term benefit over a single infusion.

Although previous experience of ketamine was used as an exclusion criterion in some trials (e.g. Zarate *et al*., 2012a), others included patients who had

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DOI: 10.1002/hup

participated in previous ketamine trials. Salvadore *et al*. (2012) included 4/14 patients tested by Salvadore *et al.* (2009 and 2010); and Salvadore *et al*. (2010) included 7/15 patients previously assessed by Salvadore *et al*. (2009). More notably perhaps, aan het Rot *et al*. (2010) assessed the same 10 patients as in the trial by Mathew *et al*. (2010). Although both studies tested the same participants using a ketamine infusion of 0.5 mg/kg over 40 min, the two studies revealed quite different effect sizes at 24 h, an effect size of −4.8 for aan het Rot *et al*.(2010) and −2.05 for Mathew *et al*. (2010). The use of known ketamine responders by aan het Rot *et al*. (2010) may well have inflated the ketamine effect, especially as the study was also non-blind. Studies assessing those who have had prior exposure to ketamine have also employed pre–post designs and, so, are not using randomised samples or controls *per se*. Rather, those studies are selecting participants who have already been shown to exhibit large, albeit temporary, symptomatic reduction, for example, in aan het Rot *et al*. (2010) patients had previously (Mathew *et al*., 2010) shown a 50% reduction in the severity of their depressive symptoms for at least 24 h. Given the larger response to repeated administration of ketamine, this is an important limitation of non-randomised open trials. Moreover, studies using known responders are, of course, primed to produce significant effects.

The future of ketamine as a treatment for depression

Our meta-analysis reveals peak time differences in elicited response according to primary diagnosis; this requires further investigation. If primary diagnosis affects the antidepressant outcome of ketamine infusion, this may have an impact on how ketamine is used in the treatment of depressive symptoms and the groups for whom it will be effective. For example, Niciu *et al*. (2013) reported two cases of suicidal ideation, dysphoria and anxiety within 24 h of a single ketamine infusion in two patients with a diagnosis of obsessive–compulsive disorder and a history of, but not current, MDD. These findings indicate the importance of considering potential comorbid diagnoses that may occur alongside depression. The meta-analysis also highlighted a need for randomised control trials to establish the safety, efficacy and durability of response of single and of repeated ketamine infusions. Placebo-controlled studies where the 'blindness' of the infusion is maintained, such as Murrough *et al*. (2013) where midazolam was employed as a control, are particularly important to understanding ketamine's antidepressant effects.

Although ketamine has been employed as an anaesthetic since the 1960s (Salvadore and Singh, 2013), repeated ketamine infusions in rats have elicited an escalated response consistent with sensitisation (Trujillo *et al*., 2008). Sensitisation to ketamine was greater when rats were exposed to distinct environmental cues and this suggests that repeated exposure to ketamine could result in addiction. A 1-year longitudinal study of recreational users found that frequent users were more likely to demonstrate dissociative and delusional symptoms, along with cognitive impairments affecting spatial working memory and pattern recognition memory tasks (Morgan *et al*., 2010). Interestingly, elevated depression scores were also reported in both frequent and abstinent ketamine users across the 12-month period (Morgan *et al*., 2010). A more recent study found that ketamine users showed elevated delusional, schizotypal and depressive symptoms when compared with controls (Freeman *et al*., 2013). The addictive potential of repeated ketamine exposure must be addressed (Morgan and Curran, 2012; Trujillo *et al*., 2008; Hillemacher *et al*., 2007), as should any long-term adverse effects extending beyond the infusion period (Freeman *et al*., 2013). None of the studies included in the current meta-analysis documented major adverse effects, but side effects such as transient headache, dizziness and nausea were commonly reported; such side effects reportedly dissipated fairly quickly, usually once the infusion was complete (aan het Rot *et al*., 2010; Abdallah *et al*., 2012; Thakurta *et al*., 2012; Murrough *et al*., 2013). Many studies also documented the dissociative effects of ketamine in participants (Diazgranados *et al*., 2010a 2010b; Ibrahim *et al*., 2011; Larkin *et al*., 2011; Zarate *et al*., 2012a; Loo *et al*., 2012; Murrough *et al*., 2012, 2013; Carlson *et al*., 2013; Sos *et al*., 2013; Lapidus *et al*., 2014) and increased, if somewhat mild, psychotomimetic experiences (Salvadore *et al*., 2009, 2010; Mathew *et al*., 2010; Larkin *et al*., 2011; Loo *et al*., 2012; Murrough *et al*., 2012, 2013; Sos *et al*., 2013; Lapidus *et al*., 2014). As most studies have not followed the participants beyond 24 h post infusion, any long-term side effects and addictive potential of ketamine infusion in the treatment of depression are difficult to determine. Future studies should address this key issue.

The reported rapid antidepressant effects of ketamine may be well placed in situations where an immediate alleviation of depressive symptoms is required; however, it does not have a significant antidepressant effect on everyone. Murrough *et al*. (2012) found that MADRS score at 4 h post infusion was an indicator of response or non-response; lack of a response to a

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DOI: 10.1002/hup

single ketamine infusion was an adequate predictor of lack of response to subsequent infusions. Several studies have reported a response rate of around 40% at 4 h post infusion (Ibrahim *et al*., 2012; Phelps *et al*., 2009; Zarate *et al*., 2012b; Cornwell *et al.*, 2012; Sos *et al*., 2013; Lapidus *et al*., 2014) while some studies have reported response rates of approximately 60–70% between 4 h and 24 h following ketamine infusion (Zarate *et al*., 2012b; Duncan *et al.*, 2013; Mathew *et al*., 2010; Zarate *et al*., 2006; Murrough *et al*., 2012). Conversely, Rybakowski *et al*. (2013)) determined response rates of only 4% at 6 h post infusion and 24% at 24 h post infusion in participants with a primary diagnosis of BD. The disparity in response rates highlights the need for future studies incorporating larger samples to determine the average response rate for the target population; primary diagnosis must also be considered. Furthermore, certain groups have shown stronger antidepressant response to ketamine than others and this also requires consideration. For example, Phelps *et al*. (2009) and Luckenbaugh *et al*. (2012) reported that ketamine infusion elicited a significantly greater reduction in MADRS scores for the participants with a family history of alcoholism, compared with the participants without a family history of alcoholism.

CONCLUSION

The present meta-analysis has established ketamine as an effective and rapid treatment for depression in the short term, impacting depressive symptoms from 4 h and, as far as we know, for up to 2 weeks post infusion in participants with a primary diagnosis of MDD or BD. When time to relapse is taken into account, repeat infusion does not appear to extend the duration of antidepressant effect. Thus, single and repeat ketamine infusions appear to be equally effective in reducing depressive symptoms; however, the small number of repeat infusion studies available hinders the interpretation of this finding. More adequately controlled studies are necessary, especially randomised control trials with a control group and, preferably, some kind of active control. The extent to which ketamine can be used as an emergency treatment and, indeed, as a longer-term treatment for depression, requires much greater investigation.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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*Studies included in meta-analysis

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