

# A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes

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**Background.** There is growing interest in glutamatergic agents in depression, particularly ketamine, a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist. We aimed to assess the efficacy of ketamine in major depressive episodes.

**Method.** We searched EMBASE, PsycINFO, CENTRAL, and Medline from 1962 to January 2014 to identify double-blind, randomized controlled trials with allocation concealment evaluating ketamine in major depressive episodes. Clinical remission, response and depressive symptoms were extracted by two independent raters. The primary outcome measure was clinical remission at 24 h, 3 days and 7 days post-treatment. Analyses employed a random-effects model.

**Results.** Data were synthesized from seven RCTs employing an intravenous infusion and one RCT employing intranasal ketamine, representing 73 subjects in parallel arms and 110 subjects in cross-over designs [ $n=34$  with bipolar disorder (BD),  $n=149$  with major depressive disorder (MDD)]. Ketamine was associated with higher rates of clinical remission relative to comparator (saline or midazolam) at 24 h [OR 7.06, number needed to treat (NNT)=5], 3 days (OR 3.86, NNT=6), and 7 days (OR 4.00, NNT=6), as well as higher rates of clinical response at 24 h (OR 9.10, NNT=3), 3 days (OR 6.77, NNT=3), and 7 days (OR 4.87, NNT=4). A standardized mean difference of 0.90 in favor of ketamine was observed at 24 h based on depression rating scale scores, with group comparisons revealing greater efficacy in unipolar depression compared to bipolar depression (1.07 *v.* 0.68). Ketamine was associated with transient psychotomimetic effects, but no persistent psychosis or affective switches.

**Conclusion.** Our meta-analysis suggests that single administrations ketamine are efficacious in the rapid treatment of unipolar and bipolar depression. Additional research is required to determine optimal dosing schedules, route, treatment schedules, and the potential efficacy of other glutamatergic agents.

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**Key words:** Bipolar disorder, ketamine, major depressive disorder, meta-analysis, RCT.

## Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) are major sources of global disability (WHO, 2008). These disorders are usually chronic, characterized by relapsing remitting courses and significant impairment persisting even during periods of remission (Fagiolini *et al.* 2005; Conradi *et al.* 2011).

Despite effective treatments, some patients will not experience symptomatic relief despite several adequate trials of medication and psychotherapy (Rush *et al.* 2006).

The search for novel targets has stimulated interest in the glutamatergic system (Skolnick *et al.* 1996; Sanacora *et al.* 2008; Skolnick *et al.* 2009). Post-mortem characterizations support the notion of dysfunctional glutamatergic signaling in MDD and BD (Knable *et al.* 2002; Sequeira *et al.* 2009; Deschwanden *et al.* 2011). Indeed, there is evidence for the efficacy of agents that directly target glutamatergic system such as lamotrigine (Geddes *et al.* 2009) in bipolar

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depression and riluzole in major depression (Zarate *et al.* 2004). Moreover, animal data suggests that antagonism of *N*-methyl-D-aspartate (NMDA) receptors, an ionotropic subpopulation of glutamate receptors, is associated with antidepressant effects (Trullas & Skolnick, 1990; Przegalinski *et al.* 1997).

Ketamine is an NMDA receptor antagonist that has been the focus of significant clinical, research, and media interest. Since the initial report by Berman *et al.* (2000) that ketamine produces a rapid and marked antidepressant effect, there have been several efforts to replicate and extend this finding (aan het Rot *et al.* 2012). Indeed, there have been several trials in both MDD and BD, yet this literature is disparate, predominantly characterized by small sample sizes and has involved several methodological variations.

The purpose of our systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials was to assess the efficacy of ketamine in the treatment of major depressive episodes. In order to maximize the clinical relevance of our findings, we focused on clinical remission and response, but we also examined changes in clinician-rated depression scores to allow meaningful comparison of the efficacy in MDD and BD.

## Methodology of the literature review

### Search strategy

We identified articles for inclusion in this meta-analysis by:

Searching Medline, EMBASE, PsycINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL) until 14 January 2014, and reviewing the bibliography of retained studies for additional unidentified studies. The search procedures are described in detail in the Supplementary online material.

### Study selection

Studies were included if they satisfied all of the following criteria (Higgins & Green, 2008):

- *Study validity*: Random allocation; allocation concealment; double-blind; placebo-controlled; parallel or cross-over design;  $\geq 5$  subjects per study arm; clinician-rated primary outcome measure.
- *Sample characteristics*: Subjects aged 18–75 years with a diagnosis of primary major depressive episode (unipolar or bipolar) according to DSM-IV (APA, 1994) or ICD (WHO, 1992) criteria.
- *Treatment characteristics*: Treatment with ketamine as a single administration (oral, intranasal or parenteral).
- *Publication-related*: Written in English.

Exclusion criteria:

- ‘Narrow’ diagnoses (e.g. postpartum depression) or secondary depression (e.g. vascular depression).
- Absence of response and/or remission rates.
- Ketamine as an ECT adjunct.

In cases where potentially eligible studies were missing key data, their corresponding authors were contacted by e-mail. All cross-over trial corresponding authors were contacted in order to obtain data relating to the first arm of the study.

### Data extraction

Data were recorded by two independent observers with subsequent review and consensus in a structured fashion as follows:

*Sample characteristics*: Mean age, sex, and primary diagnosis.

*Ketamine related*: Route, dose, duration of infusion, and frequency.

*Control condition*: Substance, route, dose, duration and frequency.

*Primary outcome measure*: Clinical remission, defined as a Hamilton Depression Rating Scale (HAMD; Hamilton, 1960) score of  $< 7$  or a Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) score of  $< 10$ . Clinical response, defined as a  $\geq 50\%$  reduction in post-treatment clinician-rated depression scores.

*Secondary outcome measures*: Depressive symptoms as assessed by clinician-rated depression instruments (i.e. HAMD or MADRS). Psychotomimetic and dissociative symptoms as measured by the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) and the Clinician Administered Dissociative States Scale (CADSS; Bremner *et al.* 1998).

*Acceptability of Treatment*: Adverse events and drop-out rates.

### Data synthesis and analyses

Analyses were performed using Comprehensive Meta-Analyses Version 2.0 (Biostat, USA).

Given that true treatment effects likely vary between studies given methodological differences, we used a random-effects model (Riley *et al.* 2011). Analyses were restricted to intention-to-treat data (Fergusson *et al.* 2002). The efficacy of ketamine was investigated by odds ratios (ORs) (Deeks, 2002), number needed to treat (NNT), and standardized mean differences (SMD). With respect to SMDs, we followed the recommendation by Rosenthal (1993) and assumed a conservative estimation of  $r=0.7$ . Subgroup analyses were conducted to determine the potential impact of

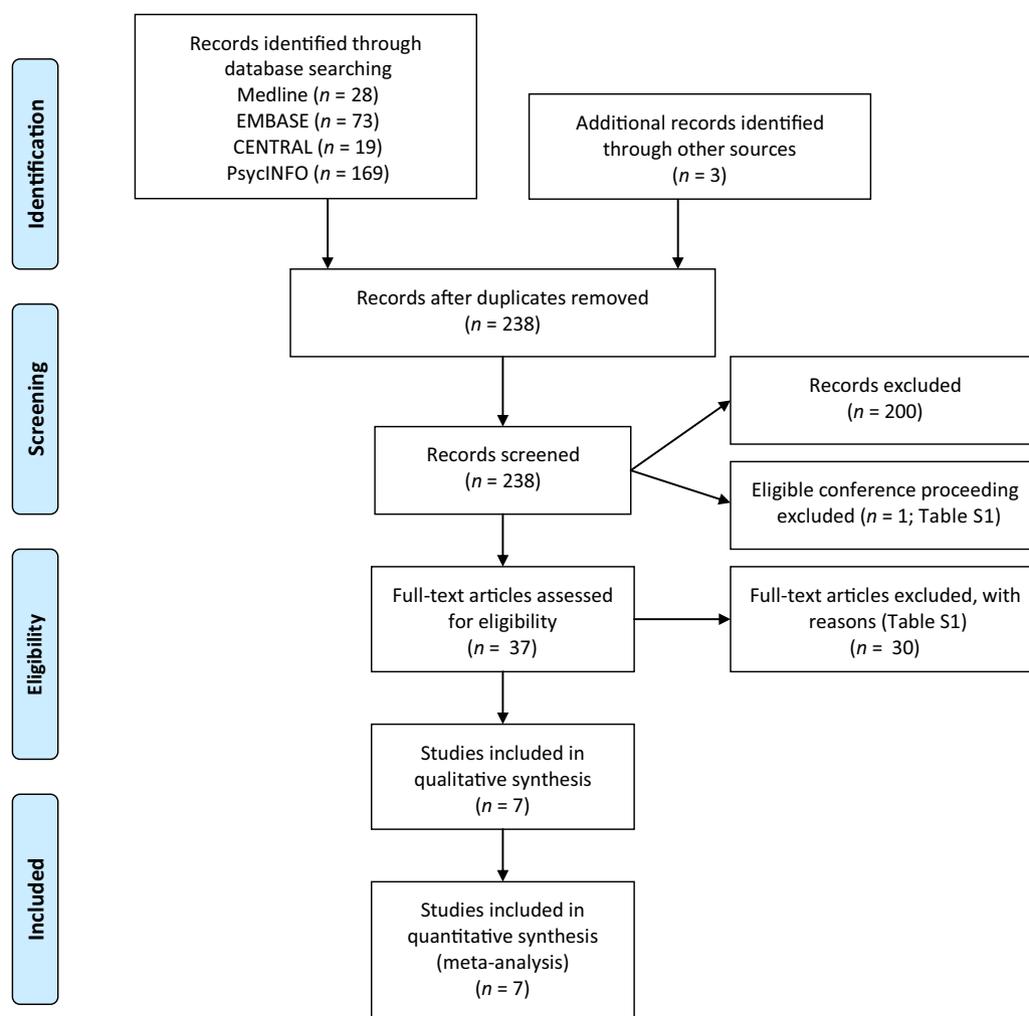


Fig. 1. Study selection PRISMA flowchart.

primary diagnosis (MDD *v.* BD) and placebo condition (saline *v.* midazolam) on effect-size estimates.

Heterogeneity was assessed using  $Q$  statistics and  $I^2$  (Cooper *et al.* 2009) and two-tailed  $p$  values reported. Values of  $p < 0.1$  for the former and  $> 35\%$  for the latter were deemed as indicative of study heterogeneity (Borenstein *et al.* 2009). Finally, we used funnel plots, Rosenthal's fail-safe  $N$  (Rosenthal, 1979), and Egger's regression intercept (Egger *et al.* 1997) to test for the presence of publication bias (Borenstein *et al.* 2009; Cooper *et al.* 2009).

## Results

### Literature search

Our literature search is detailed in Fig. 1 and the Supplementary material (Supplementary Figs S1–S4). We identified six double-blind randomized controlled trials (RCTs) (Berman *et al.* 2000; Zarate *et al.* 2006, 2012; Diazgranados *et al.* 2010; Murrough *et al.* 2013a;

Sos *et al.* 2013) through our systematic review, all of which met inclusion criteria. An additional double-blind RCT was published during manuscript preparation and included in our analyses (Lapidus *et al.* 2014). Study quality was assessed using the Cochrane Collaboration's Tool for Assessing Risk of Bias (Higgins *et al.* 2011) (Supplementary Table S2).

A double-blind RCT in a surgical setting was identified, but could not be assessed as it was available in abstract form (Bastos *et al.* 2012) and correspondence with the authors did not successfully yield the required information to assure quality or data for analyses.

### Included RCTs: main characteristics

Overall, seven RCTs (Berman *et al.* 2000; Zarate *et al.* 2006, 2012; Diazgranados *et al.* 2010; Murrough *et al.* 2013a; Sos *et al.* 2013; Lapidus *et al.* 2014) were included in our meta-analysis, totaling 183 subjects with a major depressive episode ( $n = 34$  with BD,  $n = 149$  with MDD; Table 1). Six of the studies were

**Table 1.** Characteristics of included studies

Study	Design	Diagnosis	Sample size	Instrument	Depression score	Placebo comparator	Ketamine dose	Follow-up period	Age (mean±s.d.)	Sex
Berman <i>et al.</i> (2000)	Cross-over RCT Double-blind	MDD(8)+BD(1)	9	HAMD-25	29.61±2.21	Saline	0.5 mg/kg 40 min infusion	3 days	37±10	5F/4M
Zarate <i>et al.</i> (2006)	Cross-over RCT Double-blind	MDD	18	HAMD-21	24.90±1.57	Saline	0.5 mg/kg 40 min infusion	7 days	45.86±11.80	12F/6M
Diazgranados <i>et al.</i> (2010)	Cross-over RCT Double-blind	BD	18	MADRS	32.60±1.09	Saline	0.5 mg/kg 40 min infusion	14 days	47.90±13.10	12F/6M
Zarate <i>et al.</i> (2012)	Cross-over RCT Double-blind	BD	15	MADRS	34.00±1.99	Saline	0.5 mg/kg 40 min infusion	14 days	53.90±3.27	8F/7M
Sos <i>et al.</i> (2013)	Cross-over RCT	MDD	30	MADRS	23.06±0.93	Saline	0.54 mg/kg; 0.27 mg/kg bolus and 0.27 mg/kg 20 min infusion	7 days	43.72±2.26	15F/15M
Murrough <i>et al.</i> (2013)	Double-blind RCT Double-blind	MDD	73	MADRS	32.07±0.69	Midazolam	0.5 mg/kg 40 min infusion	7 days (with additional 4 weeks in responders)	45.44±1.47	37F/36M
Lapidus <i>et al.</i> (2014)	Cross-over RCT Double-blind	MDD	20	MADRS	IDS-C 42.7±8.5	Saline	50 mg intranasal	7 days	48.0±12.8	10F/10M

RCT, Randomized controlled trial; MDD, major depressive disorder; BD, bipolar disorder; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; IDS-C, Inventory of Depressive Symptoms – Clinician rated; F, Female; M, Male.

double-blind cross-over RCTs (Berman *et al.* 2000; Zarate *et al.* 2006, 2012; Diazgranados *et al.* 2010; Sos *et al.* 2013; Lapidus *et al.* 2014) ( $n=110$ ), while one was a parallel arm RCT (Murrough *et al.* 2013a) ( $n=73$ ). When our efforts to obtain data relating to the initial arm of cross-over studies were unsuccessful, remission and response rates as presented in the published manuscripts were analyzed. Only one study had a mixed MDD and BD sample (MDD,  $n=8$ ; BD,  $n=1$ ) (Berman *et al.* 2000) and was pooled with MDD studies in analyses.

Ketamine was administered intravenously in all but one study, which employed intranasal ketamine at a dose of 50 mg (Lapidus *et al.* 2014). Intravenous infusion protocols most commonly used 0.5 mg/kg over 40 min (Berman *et al.* 2000; Zarate *et al.* 2006, 2012; Diazgranados *et al.* 2010; Murrough *et al.* 2013a). One study involved an intravenous bolus of 0.27 mg/kg and an additional 0.27 mg/kg infused over 20 min (Sos *et al.* 2013).

Five of the studies used a saline infusion as a placebo condition (Berman *et al.* 2000; Zarate *et al.* 2006, 2012; Diazgranados *et al.* 2010; Sos *et al.* 2013), while one used midazolam (0.045 mg/kg) (Murrough *et al.* 2013a). Saline was employed as an intranasal placebo (Lapidus *et al.* 2014).

Participants' mean age was 46.5 (s.d.=12.3) years, with 84 males and 99 females. Primary outcome measures were as follows: one study (Zarate *et al.* 2006) utilized the 21-item HAMD, one study used the 25-item HAMD (Berman *et al.* 2000), and five studies used the MADRS (Diazgranados *et al.* 2010; Zarate *et al.* 2012; Murrough *et al.* 2013a; Sos *et al.* 2013; Lapidus *et al.* 2014). Baseline mean scores are presented in Table 1.

In three studies (Berman *et al.* 2000; Zarate *et al.* 2006; Murrough *et al.* 2013a) involving MDD patients, patients were medication free after a washout period that ranged from 1–4 weeks, and in the remaining study involving MDD patients, patients maintained a stable pharmacological regimen for 4 weeks prior to entering the study (Sos *et al.* 2013). One study required stable medication for an unknown time period prior to entering and then during the study (Lapidus *et al.* 2014). Both studies in BD involved concomitant lithium or valproate (Diazgranados *et al.* 2010; Zarate *et al.* 2012).

### Remission and response rates

Rates of clinical remission were available for five RCTs (Zarate *et al.* 2006, 2012; Diazgranados *et al.* 2010; Murrough *et al.* 2013a; Sos *et al.* 2013) while response rates were available for all seven RCTs (Berman *et al.* 2000; Zarate *et al.* 2006, 2012; Diazgranados *et al.*

2010; Murrough *et al.* 2013a; Sos *et al.* 2013; Lapidus *et al.* 2014). Analyses are presented at 24 h, 3 days (Sos *et al.* 2013 – 4 days), and 7 days post-infusion (Fig. 2a, b).

After 24 h, the pooled OR was 7.06 (95% CI 2.50–19.95,  $z=3.69$ ,  $p<0.001$ ) for clinical remission and 9.10 (95% CI 4.28–19.34,  $z=5.74$ ,  $p<0.001$ ) for clinical response, indicating a significant difference in outcome favoring ketamine. This translated into NNTs=5 with respect to clinical remission and NNTs=3 with respect to clinical response. There was no evidence of heterogeneity in clinical remission ( $Q=0.25$ ,  $df=1$ ,  $p=0.61$ ) or response ( $Q=1.27$ ,  $df=1$ ,  $p=0.25$ ) between MDD and BD samples.

After 3 days, the pooled OR was 3.86 (95% CI 1.53–9.74,  $z=2.87$ ,  $p<0.01$ ) for clinical remission and 6.77 (95% CI 3.40–13.50,  $z=5.44$ ,  $p<0.001$ ) for clinical response, indicating a significant difference in outcome favoring ketamine. This translated into NNTs=6 for clinical remission and NNTs=3 for clinical response. There was no evidence of heterogeneity with respect to clinical remission ( $Q=0.36$ ,  $df=1$ ,  $p=0.54$ ) or response ( $Q=0.62$ ,  $df=1$ ,  $p=0.42$ ) between MDD and BD samples.

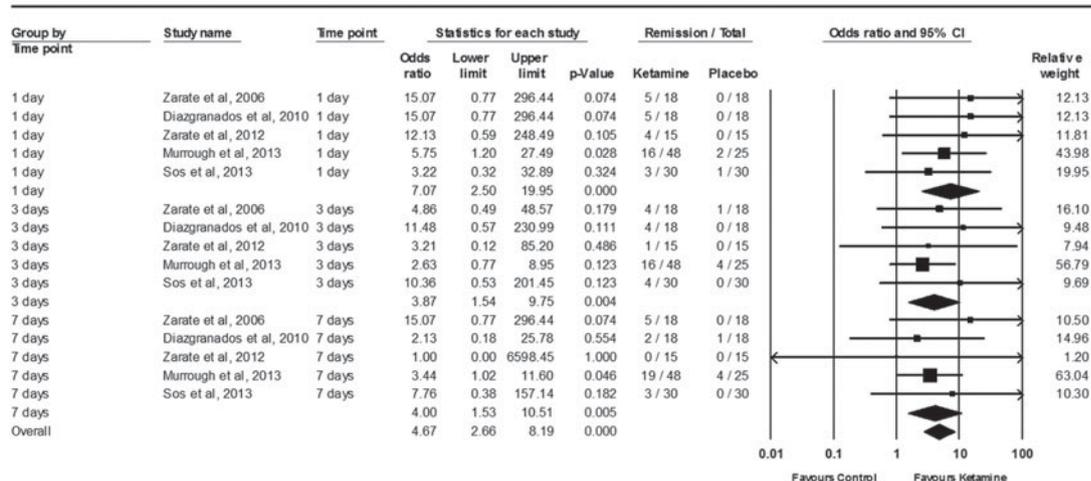
After 7 days, the pooled OR was 4.00 (95% CI 1.52–10.51,  $z=2.81$ ,  $p<0.01$ ) for clinical remission and 4.87 (95% CI 2.24–10.55,  $z=4.01$ ,  $p<0.001$ ) for clinical response, indicating a significant difference in outcome favoring ketamine. This translated into NNTs=6 for clinical remission and NNTs=5 for clinical response. There was no evidence of heterogeneity with respect to clinical remission ( $Q=0.30$ ,  $df=1$ ,  $p=0.58$ ) or response ( $Q=0.00$ ,  $df=1$ ,  $p=0.94$ ) between MDD and BD samples.

### Cross-over studies and control interventions

Saline as a placebo was compared to midazolam to assess the influence of the placebo condition.

After 24 h (Fig. 3a), no difference was noted between saline and midazolam with respect to clinical remission ( $Q=0.56$ ,  $df=1$ ,  $p=0.45$ ); however, a trend towards lower response in midazolam-placebo conditions was observed for clinical response ( $Q=3.39$ ,  $df=1$ ,  $p=0.06$ ) with sensitivity analyses limited to studies employing intravenous administration showing a significant difference ( $Q=4.06$ ,  $df=1$ ,  $p<0.05$ ). Nevertheless, ketamine was superior to both midazolam (OR 4.53, 95% CI 1.57–12.05,  $z=2.80$ ,  $p\leq 0.01$ , NNT=3) and saline placebo conditions (OR 18.73, 95% CI 6.39–54.87,  $z=5.34$ ,  $p\leq 0.001$ , NNT=3). However, at 3 and 7 days (Fig. 3b, c) a significant difference was no longer observed ( $Q\leq 0.43$ ,  $p\leq 0.51$ ), nor when performing sensitivity analyses limited

(a)



(b)

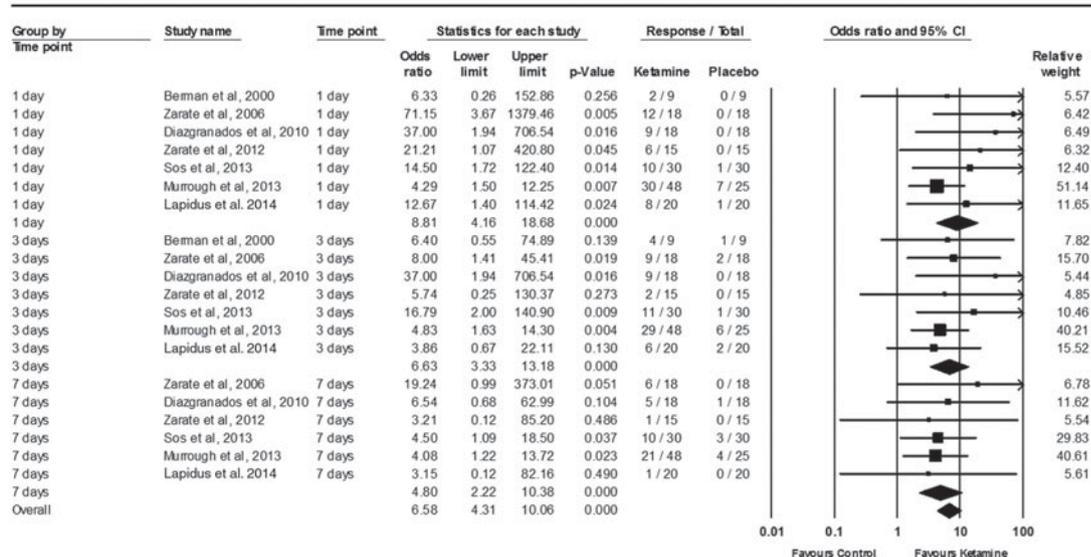


Fig. 2. Meta-analysis of (a) rates of clinical remission and (b) rates of clinical response for ketamine v. placebo in major depression.

to trials utilizing intravenous ketamine ( $Q \leq 0.96$ ,  $p \geq 0.33$ ).

**Depression scores**

Data relating to continuous scores for outcome measures were available at 24 h for all seven RCTs.

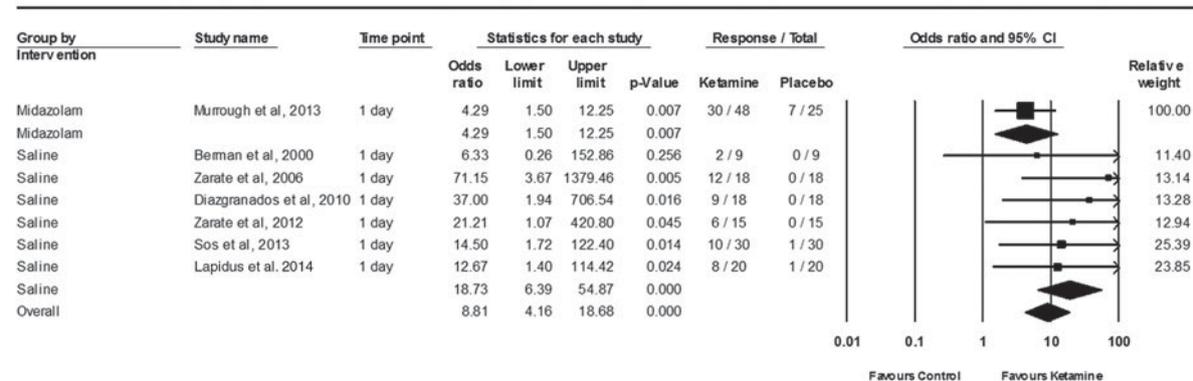
Overall, a SMD of 0.90 (95% CI 0.66–1.13,  $z=7.59$ ,  $p \leq 0.001$ ) was observed, indicating a significant difference in outcome favoring ketamine (Fig. 4). Comparison of MDD and BD samples revealed a marginally significant difference favoring MDD (MDD=1.07, 95% CI 0.72–1.42 v. BD=0.68, 95% CI 0.50–0.86;  $Q=3.73$ ,  $p=0.053$ ; Fig. 4a), and sensitivity analyses limited to intravenous ketamine demonstrated a strong significant difference in outcome favoring MDD. Specifically, MDD was associated with a SMD of 1.21

(95% CI 0.93–1.49,  $z=8.47$ ,  $p \leq 0.001$ ) while BD was associated with a SMD of 0.68 (95% CI 0.50–0.86,  $z=7.54$ ,  $p \leq 0.001$ ,  $Q=9.81$ ,  $df=1$ ,  $p \leq 0.01$ ; Fig. 4b).

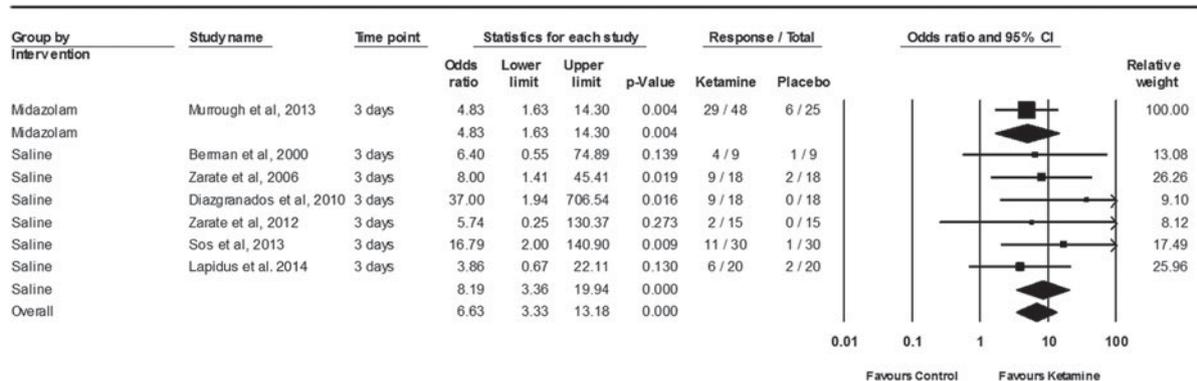
**Potential carry-over in cross-over studies**

To address the possibility of cross-over effects, we were able to obtain data from the first arm of the majority of cross-over design studies ( $N=81$ , Zarate et al. 2006, 2012; Diazgranados et al. 2010; Sos et al. 2013). Pooled effects were calculated including the parallel study (Murrough et al. 2013a). With respect to response rates, at 24 h there was a significant benefit for ketamine (OR 6.18, 95% CI 2.61–14.62,  $p < 0.001$ , NNT=3), with similar benefit at 3 days (OR 6.30, 95% CI 2.56–15.52,  $p < 0.001$ , NNT=3) and 7 days (OR 5.53, 95% CI 1.98–15.41,  $p < 0.001$ , NNT=4).

(a)



(b)



(c)

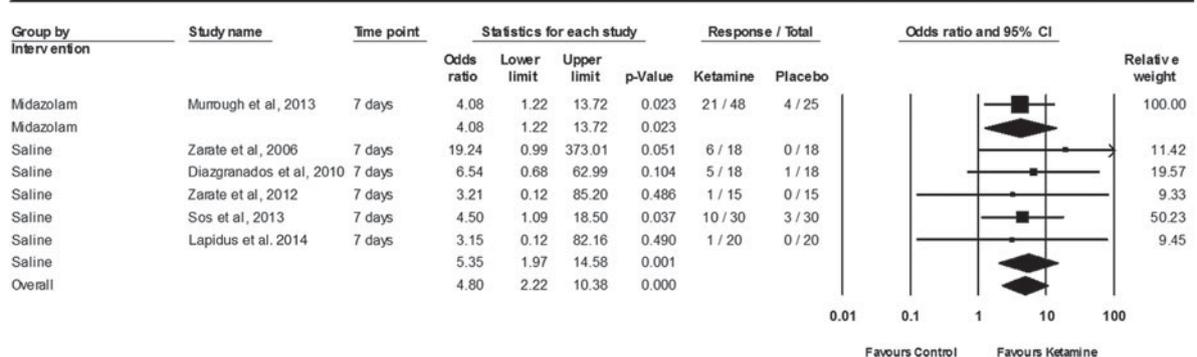


Fig. 3. Subgroup analyses of ketamine in cross-over v. parallel arm designs and saline placebo v. psychoactive placebo. (a) 24 h, (b) 3 days, (c) 7 days.

When considering depression scores for first arm and parallel design studies, there was evidence of a significant benefit in favor of ketamine (SMD=1.53, 95% CI 0.85–2.21,  $p < 0.001$ ).

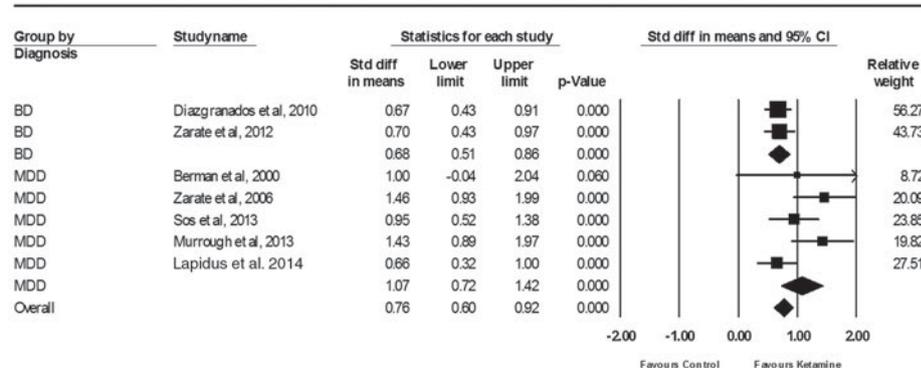
Although we were unable to obtain data relating to the first arm of all cross-over studies, null analyses relating to order effects were reported in all cross-over studies for which data pertaining to the first arm was not available. Examining study withdrawal after clinical response as a proxy for this potential limitation

revealed that 7/17 (7.7%) patients in ketamine arms and 1/6 (1.1%) patients in placebo arms who withdrew from cross-over studies did so after a clinical response.

**Psychotomimetic and dissociative symptoms – blinding efficacy**

Blinding efficacy was not reported; however, all studies assessed psychotomimetic symptoms as measured by the BPRS, and therefore this was analyzed as a

(a)



(b)

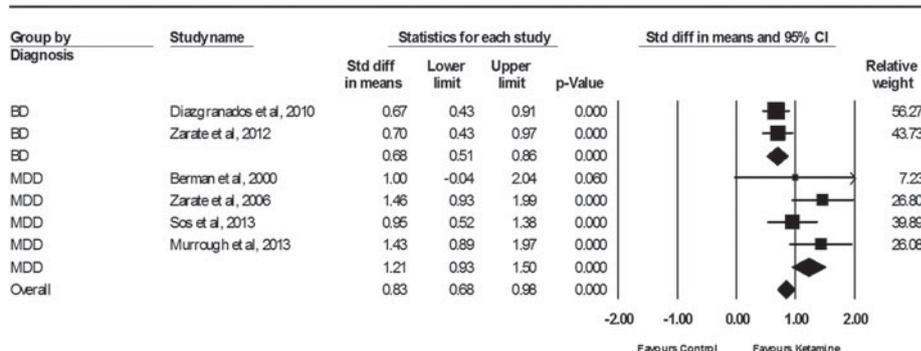


Fig. 4. (a) Standardized mean difference in depression scores at 24 h and subgroup analysis of ketamine in bipolar *v.* unipolar depression and (b) sensitivity analysis limited to intravenous administration studies.

proxy. In some cases, the study reported the full positive subscale (Zarate *et al.* 2006, 2012; Diazgranados *et al.* 2010; Sos *et al.* 2013) while three studies reported a reduced item positive BPRS (Berman *et al.* 2000; Murrough *et al.* 2013a; Lapidus *et al.* 2014). Overall, a maximal SMD occurred at 30–60 min post-infusion of 1.43 (95% CI 0.80–2.07,  $z=4.45$ ,  $p<0.001$ ; Supplementary Fig. S5A) before returning to baseline. There was no evidence of heterogeneity between studies employing the full- and reduced-item BPRS ( $Q=0.02$ ,  $df=1$ ,  $p=87$ ). Three studies reported data with respect to the CADSS, with an overall maximal SMD at 40 min post-infusion of 3.70 (95% CI 1.27–5.91,  $z=3.28$ ,  $p<0.001$ ; Supplementary Fig. S5B).

#### Adverse events and dropout rates

The majority of studies reported no serious adverse events (Zarate *et al.* 2006, 2012; Diazgranados *et al.* 2010; Sos *et al.* 2013; Lapidus *et al.* 2014). One study did not comment on adverse events (Berman *et al.* 2000). One study reported cardiovascular side-effects in 2/47 patients ( $n=1$  refractory hypertension,  $n=1$  hypotension and bradycardia) who received ketamine and no such side-effects among control patients (Murrough *et al.* 2013a).

The only recorded induction of mania/hypomania occurred in a patient with BD who was receiving saline placebo infusion (Diazgranados *et al.* 2010). No severe psychotic symptoms occurred in any patient.

Study completion and drop-out rates were used as a proxy for tolerability. Of the 158 patients who were to receive ketamine, 21 (13.3%) dropped out (in crossover studies, they dropped out of the arm they had just received), compared to 10/135 (7.4%) of patients who were to receive control interventions (OR 1.95, 95% CI 0.86–4.42,  $z=1.59$ ,  $p=0.11$ ).

#### Publication bias and heterogeneity

With respect to clinical remission, the fail-safe  $N$  was 14 at 24 h, 7 at 3 days, and 4 at 7 days. For response rates, the fail-safe  $N$  was 59 at 24 h, 47 at 3 days, and 17 at 7 days post-infusion. This suggests that 15–43 unpublished or missing null-finding studies would be needed to render the difference in clinical response statistically non-significant, and 1–11 studies for clinical remission. The risk of publication bias was also assessed with Egger's regression intercept, which for clinical remission was 1.12 ( $t_3=1.49$ ,  $p=0.23$ ) at 24 h, 1.06 ( $t_3=2.31$ ,  $p=0.10$ ) at 3 days, and 0.20 ( $t_3=0.34$ ,  $p=0.75$ ), and for response data was 1.70 ( $t_5=3.37$ ,

$p \leq 0.05$ ) at 24 h, 1.02 ( $t_5=1.56$ ,  $p=0.17$ ) at 3 days, and 0.35 ( $t_4=0.67$ ,  $p=0.53$ ) at 7 days. Additionally, the associated funnel plots revealed broadly symmetrical distributions (Supplementary Figs S6 and S7), indicating a marginal risk of publication bias.

For continuous data, the fail-safe  $N$  was 247, while Egger's regression intercept was 2.72 ( $t_5=2.39$ , two-tailed  $p=0.06$ ) and the funnel plot revealed an asymmetrical distribution (Supplementary Fig. S8). These findings suggest relatively low potential for publication bias.

With respect to continuous data at 24 h, heterogeneity between RCTs exceeded that expected by chance ( $df=6$ ,  $Q=14.16$ ,  $p \leq 0.05$ ,  $I^2=57.63$ ). Yet, this appeared to be related to the effect of diagnosis and method of ketamine administration, as heterogeneity did not exceed that expected by chance in infusion studies with MDD samples ( $df=3$ ,  $Q=3.11$ ,  $p=0.37$ ,  $I^2=3.78$ ) or BD samples ( $df=1$ ,  $Q=0.02$ ,  $p=0.86$ ,  $I^2=0.0$ ).

## Discussion

To our knowledge, this is the first meta-analysis of RCTs to assess whether intravenous ketamine is an efficacious and acceptable treatment in MDD and BD. Our analyses suggest that this NMDA receptor antagonist is superior to placebo interventions and well tolerated, yet is accompanied by transient psychotomimetic and dissociative symptoms. After 24 h, 3 days, and 7 days, we observed significantly higher rates of clinical remission (ORs  $\geq 3.86$ , NNTs  $\leq 6$ ) and response (ORs  $\geq 4.87$ , NNTs  $\leq 4$ ) associated with ketamine. Though a psychoactive placebo intervention evidenced a lower pooled OR at 24 h than saline placebo, the difference from saline studies no longer held by 3 days post-intervention. Finally, we found evidence for higher effect sizes in MDD compared to BD (SMD of 1.07 *v.* 0.68).

We excluded two RCTs from our analyses as they were not double-blind placebo-controlled trials. The first of these involved randomizing MDD patients ( $n=70$ ) to ketamine or propofol in a surgical setting (Kudoh *et al.* 2002), and the second involved randomizing MDD patients ( $n=18$ ) to repeated ketamine infusions or a similar number of electroconvulsive therapy treatments (Ghasemi *et al.* 2013). In support of the generalizability of our findings, these studies revealed a pooled SMD of 1.24 after 24 h (95% CI 0.78–1.70,  $z=5.34$ ,  $p<0.001$ ) in favor of ketamine.

One critique of the clinical applicability of ketamine trials is the conclusion that treatment response is short-lived. Nevertheless, Murrough *et al.* (2013a) present the longest treatment follow-up reported in an RCT to date, in which 9/48 of ketamine-treated patients compared to 0/25 midazolam-treated patients with

treatment-refractory MDD demonstrated sustained response 5 weeks after a single infusion.

Nevertheless, early clinical adoption of ketamine as a treatment for depression is likely to occur in areas of medicine undeterred by the potential for early relapse and where the potential for misuse is negligible. Indeed, the palliative field has shown great interest in the potential for the use of ketamine in the management of depressive symptoms at the end of life (Irwin *et al.* 2013).

While controlled clinical trials to date have examined the efficacy of single dose of ketamine, few treatments in psychiatry or medicine are deemed sufficient after a single dose. Indeed, given the substantial efficacy of single infusion, research groups are now turning their attention to administering repeated infusions in order to maximize and sustain clinical response. These efforts, while still involving open label designs, suggest that higher and sustained rates of response and remission can be achieved with repeated doses (aan het Rot *et al.* 2010; Murrough *et al.* 2013b; Rasmussen *et al.* 2013; Shiroma *et al.* 2014); however, comparison to single dose is still lacking. Similarly, from a clinical standpoint, additional research is required to elucidate appropriate follow-up and maintenance protocols in ketamine, in addition to its role as an adjunct to existing treatments.

Currently, all but one RCT have employed intravenous administration (Lapidus *et al.* 2014), which is constrained by medical and infrastructure requirements. There is currently open-label evidence to suggest benefit of oral ketamine (Irwin *et al.* 2013; Lara *et al.* 2013), including sublingual administration (Lara *et al.* 2013); however, efficacy data is lacking. Oral ketamine, however, has limited bioavailability, and therefore other methods of administration are being investigated, including intramuscular and intranasal routes (Mathew *et al.* 2012; Lapidus *et al.* 2014).

An additional concern that has been the psychotomimetic side effects experienced during ketamine infusions and the ensuing safety concerns; however, there is some evidence to suggest that such side-effects may be related to ketamine's antidepressant effectiveness (Luckenbaugh *et al.* 2014). A growing area of research is the exploration of NMDA antagonists without the psychotomimetic effects of ketamine, and there are already positive trials with such agents [AZD6765 (Sanacora *et al.* 2013; Zarate *et al.* 2013)], albeit with a lower level of efficacy.

Ketamine's mechanism of action in depression remains elusive (Murrough, 2012). In clinically depressed samples, peripheral brain-derived neurotrophic factor increases with NMDA antagonism (Haile *et al.* 2014). Yet, agonism of the NMDA receptors also induces synaptic plasticity, and several trials

support the antidepressant effects of NMDA agonists, for example a recent report of oral sarcosine in depressed patients (Huang *et al.* 2013) and D-cycloserine administered chronically in treatment-resistant depression (Heresco-Levy *et al.* 2013). It is likely that NMDA-dependent cellular mechanisms are exquisitely finely tuned, and additional research is needed in order to identify individuals whose major depressive episodes may be improved by NMDA antagonism or agonism.

### Limitations

The first limitation is the predominance of small samples and crossover designs. A second limitation is the adequacy of saline placebo, as our analyses clearly demonstrate a marked psychotomimetic effect in ketamine conditions compared to placebo conditions that was least pronounced in the intranasal trial. While efficacy is nevertheless observed using psychoactive placebo such as midazolam, an adequate control for ketamine's psychotomimetic effects has not been evaluated. A third limitation is the limited duration of follow-up, and therefore it is not possible to estimate the long-term benefit or cost-effectiveness. The safety and potential for long-term consequences has not been addressed, and will require additional attention from researchers. To date, all of the placebo-controlled trials have involved single administrations, and therefore the efficacy of repeated administrations is unknown. Further, a minimal effective dose in treating depression has yet to be identified.

A limitation levied against the meta-analytical method is the combination of heterogeneous studies, poor-quality or unrepresentative studies, or the potential of publication bias. While we cannot definitively rule out these influences, we have attempted to temper these by using a comprehensive systematic review of the literature, assessing the quality of studies, and by examining both publication bias and heterogeneity.

### Conclusion

Our meta-analysis of RCTs demonstrates that ketamine, whether intravenously or intranasally administered, in the treatment of depression is well tolerated, and associated with rapid and persistent clinical remission (NNTs  $\leq 6$ ) and response (NNTs  $\leq 4$ ) for up to 7 days following a single dose. While effective in both MDD and BD, ketamine appears to be less effective in BD.

Areas requiring additional research and clarification include the specificity of effect to NMDA antagonism, the minimal effective dose and the potential benefit of repeated ketamine infusions, optimizing

non-parenteral administration, long-term safety and the identification of other NMDA agents with fewer psychotomimetic effects, reduced potential for abuse, and agents with fewer systemic effects.

### Supplementary material

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0033291714001603>

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### Declaration of Interest

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### References

- aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, Mathew SJ (2010). Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biological Psychiatry* **67**, 139–145.
- aan het Rot M, Zarate CA Jr., Charney DS, Mathew SJ (2012). Ketamine for depression: where do we go from here? *Biological Psychiatry* **72**, 537–547.

- APA (1994). *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. American Psychiatric Association: Washington, DC.
- Bastos M, Pereira M, Pereira E (2012). Effects of intra-operative sedation with low-doses of s-ketamine on depression: randomized double-blind controlled trial. 15th WFA World Congress of Anaesthesiologists, Predio Ferial de Buenos Aires, Argentina. *British Journal of Anaesthesia*. Oxford University Press, 2012, 108 pp.
- Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000). Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry* 47, 351–354.
- Borenstein M, Hedges LV, Higgins JPT, Rothstein HR (2009). *Introduction to Meta-Analysis*. Wiley & Sons Ltd: West Sussex, England.
- Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM (1998). Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *Journal of Traumatic Stress* 11, 125–136.
- Conradi HJ, Ormel J, de Jonge P (2011). Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. *Psychological Medicine* 41, 1165–1174.
- Cooper H, Hedges LV, Valentine JC (2009). *The Handbook of Research Synthesis and Meta-Analysis*. Russell Sage Foundation Publications: New York, US.
- Deeks JJ (2002). Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Statistics in Medicine* 21, 1575–1600.
- Deschwenden A, Karolewicz B, Feyissa AM, Treyer V, Ametamey SM, Johayem A, Burger C, Auberson YP, Sovago J, Stockmeier CA, Buck A, Hasler G (2011). Reduced metabotropic glutamate receptor 5 density in major depression determined by [(11)C]ABP688 PET and postmortem study. *American Journal of Psychiatry* 168, 727–734.
- Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, Kammerer WA, Quezado Z, Luckenbaugh DA, Salvatore G, Machado-Vieira R, Manji HK, Zarate CA Jr. (2010). A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Archives of General Psychiatry* 67, 793–802.
- Egger M, Davey Smith G, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal* 315, 629–634.
- Fagiolini A, Kupfer DJ, Masalehdan A, Scott JA, Houck PR, Frank E (2005). Functional impairment in the remission phase of bipolar disorder. *Bipolar Disorders* 7, 281–285.
- Fergusson D, Aaron SD, Guyatt G, Hebert P (2002). Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *British Medical Journal* 325, 652–654.
- Geddes JR, Calabrese JR, Goodwin GM (2009). Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *British Journal of Psychiatry* 194, 4–9.
- Ghasemi M, Kazemi MH, Yoosefi A, Ghasemi A, Paragomi P, Amini H, Afzali MH (2013). Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. *Psychiatry Research* 28, 355–361.
- Haile CN, Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Foulkes A, Iqbal S, Mahoney JJ, De La Garza R, Charney DS, Newton TF, Mathew SJ (2014). Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. *International Journal of Neuropsychopharmacology* 17, 331–336.
- Hamilton M (1960). A rating scale for depression. *Journal of Neurology Neurosurgery and Psychiatry* 23, 56–62.
- Heresco-Levy U, Gelfin G, Bloch B, Levin R, Edelman S, Javitt DC, Kremer I (2013). A randomized add-on trial of high-dose d-cycloserine for treatment-resistant depression. *International Journal of Neuropsychopharmacology* 16, 501–506.
- Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *British Medical Journal* 343, d5928.
- Higgins JPT, Green S (2008). *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons Ltd: West Sussex, England.
- Huang CC, Wei IH, Huang CL, Chen KT, Tsai MH, Tsai P, Tun R, Huang KH, Chang YC, Lane HY, Tsai GE (2013). Inhibition of glycine transporter-I as a novel mechanism for the treatment of depression. *Biological Psychiatry* 74, 734–741.
- Irwin SA, Iglewicz A, Nelesen RA, Lo JY, Carr CH, Romero SD, Lloyd LS (2013). Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial. *Journal of Palliative Medicine* 16, 958–65.
- Knable MB, Barci BM, Bartko JJ, Webster MJ, Torrey EF (2002). Molecular abnormalities in the major psychiatric illnesses: classification and regression tree (CRT) analysis of post-mortem prefrontal markers. *Molecular Psychiatry* 7, 392–404.
- Kudoh A, Takahira Y, Katagai H, Takazawa T (2002). Small-dose ketamine improves the postoperative state of depressed patients. *Anesthesia and Analgesia* 95, 114–118.
- Lapidus K, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, Feder A, Iosifescu DV, Charney DS, Murrough JW (2014). A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biological Psychiatry*. Published online: 3 April 2014. doi:10.1016/j.biopsych.2014.03.026.
- Lara DR, Bisol LW, Munari LR (2013). Antidepressant, mood stabilizing and recognitive effects of very low dose sublingual ketamine in refractory unipolar and bipolar depression. *International Journal of Neuropsychopharmacology* 16, 2111–2117.
- Luckenbaugh D, Niciu MJ, Ionescu DE, Nolan NM, Richards EM, Brutsche NE, Guevara S, Zarate CA (2014).

- Do the dissociative effects of ketamine mediate its antidepressant effects? *Journal of Affective Disorders* **159**, 58–61.
- Mathew SJ, Shah A, Lapidus K, Clark C, Jarun N, Ostermeyer B, Murrough JW** (2012). Ketamine for treatment-resistant unipolar depression: current evidence. *CNS Drugs* **26**, 189–204.
- Montgomery SA, Asberg M** (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* **134**, 382–389.
- Murrough JW** (2012). Ketamine as a novel antidepressant: from synapse to behavior. *Clinical Pharmacology and Therapeutics* **91**, 303–309.
- Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, Charney DS, Mathew SJ** (2013a). Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *American Journal of Psychiatry* **170**, 1134–1142.
- Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, van der Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV** (2013b). Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biological Psychiatry* **74**, 250–256.
- Overall JE, Gorham DR** (1962). The brief psychiatric rating scale. *Psychological Reports* **10**, 799–812.
- Przegalinski E, Tatarczynska E, Deren-Wesolek A, Chojnacka-Wojcik E** (1997). Antidepressant-like effects of a partial agonist at strychnine-insensitive glycine receptors and a competitive NMDA receptor antagonist. *Neuropharmacology* **36**, 31–37.
- Rasmussen KG, Lineberry TW, Galardy CW, Kung S, Lapid MI, Palmer BA, Ritter MJ, Schak KM, Sola CL, Hanson AJ, Frye MA** (2013). Serial infusions of low-dose ketamine for major depression. *Journal of Psychopharmacology* **27**, 444–450.
- Riley RD, Higgins JP, Deeks JJ** (2011). Interpretation of random effects meta-analyses. *British Medical Journal* **342**, d549.
- Rosenthal R** (1979). The file drawer problem and tolerance for null results. *Psychological Bulletin* **86**, 638–641.
- Rosenthal R** (1993). *Meta-Analytic Procedures for Social Research*. Sage Publications: Newbury Park, CA.
- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M** (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR\*D report. *American Journal of Psychiatry* **163**, 1905–1917.
- Sanacora G, Smith MA, Pathak S, Su HL, Boeijinga PH, McCarthy DJ, Quirk MC** (2013). Lanicemine: a low-trapping NMDA channel blocker produces sustained antidepressant efficacy with minimal psychotomimetic adverse effects. *Molecular Psychiatry*. Published online: 15 October 2013. doi:10.1038/mp.2013.130.
- Sanacora G, Zarate CA, Krystal JH, Manji HK** (2008). Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nature Reviews Drug Discovery* **7**, 426–437.
- Sequeira A, Mamdani F, Ernst C, Vawter MP, Bunney WE, Lebel V, Rehal S, Klempan T, Gratton A, Benkelfat C, Rouleau GA, Mechawar N, Turecki G** (2009). Global brain gene expression analysis links glutamatergic and GABAergic alterations to suicide and major depression. *PLoS One* **4**, e6585.
- Shiroma PR, Johns B, Kuskowski M, Wels J, Thuras P, Albott CS, Lim KO** (2014). Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. *Journal of Affective Disorders* **155**, 123–129.
- Skolnick P, Layer RT, Popik P, Nowak G, Paul IA, Trullas R** (1996). Adaptation of N-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. *Pharmacopsychiatry* **29**, 23–26.
- Skolnick P, Popik P, Trullas R** (2009). Glutamate-based antidepressants: 20 years on. *Trends in Pharmacological Science* **30**, 563–569.
- Sos P, Klirova M, Novak T, Kohutova B, Horacek J, Palenicek T** (2013). Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. *Neuroendocrinology Letters* **34**, 287–293.
- Trullas R, Skolnick P** (1990). Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. *European Journal of Pharmacology* **185**, 1–10.
- WHO** (1992). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. World Health Organization: Geneva, Switzerland.
- WHO** (2008). *The Global Burden of Disease: 2004 Update*. WHO Press: Geneva.
- Zarate CA Jr., Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, Selter J, Marquardt CA, Liberty V, Luckenbaugh DA** (2012). Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biological Psychiatry* **71**, 939–946.
- Zarate CA Jr., Mathews D, Ibrahim L, Chaves JF, Marquardt C, Ukoh I, Jolkovsky L, Brutsche NE, Smith MA, Luckenbaugh DA** (2013). A randomized trial of a low-trapping nonselective N-methyl-D-aspartate channel blocker in major depression. *Biological Psychiatry* **74**, 257–264.
- Zarate CA Jr., Payne JL, Quiroz J, Sporn J, Denicoff KK, Luckenbaugh D, Charney DS, Manji HK** (2004). An open-label trial of riluzole in patients with treatment-resistant major depression. *American Journal of Psychiatry* **161**, 171–174.
- Zarate CA Jr., Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK** (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry* **63**, 856–864.