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Single-dose infusion ketamine and non-ketamine *N*-methyl-D-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories

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Supplementary material

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0033291716000064>

Declaration of Interest

T.K. has received consultant fees from Sumitomo Dainippon, Novartis, Otsuka and Taisho and has received speaker's honoraria from Abbvie, Banyu, Eli Lilly, Dainippon Sumitomo, Janssen, Mochida, Novartis, Otsuka Pfizer and Shionogi. He has received grant support from the Byoutaitaisyakenkyukai Fellowship (Fellowship of Astellas Foundation of Research on Metabolic Disorders), Eli Lilly Fellowship for Clinical Psychopharmacology, Research Group for Schizophrenia Japan, Dainippon-Sumitomo, Mochida and Otsuka.

J.M.C. has nothing to disclose.

K.H. is an employee of Sumitomo Dainippon Pharma, Japan.

C.A.Z. is listed as a co-inventor on a patent application for the use of ketamine and its metabolites in major depression. C.A.Z. has assigned his rights in the patent to the US government but will share a percentage of any royalties that may be received by the government.

J.M.K. has been a consultant to Alkermes, Amgen, Astra-Zeneca, Janssen, Pfizer, Eli Lilly, Bristol-Myers Squibb, Dainippon Sumitomo/Sepracor/Sunovion, Johnson & Johnson, Otsuka, Pierre Fabre, Vanda, Proteus, Takeda, Targacept, IntraCellular Therapies, Merck, Lundbeck, Novartis, Roche, Rules Based Medicine, Sunovion and has received honoraria for lectures from Otsuka, Eli Lilly, Esai, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck and Janssen. He is a shareholder of Vanguard Research Group and MedAvante. He has received grant support from the NIMH.

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Abstract

Background—Ketamine and non-ketamine *N*-methyl-D-aspartate receptor antagonists (NMDAR antagonists) recently demonstrated antidepressant efficacy for the treatment of refractory depression, but effect sizes, trajectories and possible class effects are unclear.

Method—We searched PubMed/PsycINFO/Web of Science/clinicaltrials.gov until 25 August 2015. Parallel-group or cross-over randomized controlled trials (RCTs) comparing single intravenous infusion of ketamine or a non-ketamine NMDAR antagonist *v.* placebo/pseudo-placebo in patients with major depressive disorder (MDD) and/or bipolar depression (BD) were included in the analyses. Hedges' *g* and risk ratios and their 95% confidence intervals (CIs) were calculated using a random-effects model. The primary outcome was depressive symptom change. Secondary outcomes included response, remission, all-cause discontinuation and adverse effects.

Results—A total of 14 RCTs (nine ketamine studies: $n = 234$; five non-ketamine NMDAR antagonist studies: $n = 354$; MDD = 554, BD = 34), lasting 10.0 ± 8.8 days, were meta-analysed. Ketamine reduced depression significantly more than placebo/pseudo-placebo beginning at 40 min, peaking at day 1 (Hedges' $g = -1.00$, 95% CI -1.28 to -0.73 , $p < 0.001$), and losing superiority by days 10–12. Non-ketamine NMDAR antagonists were superior to placebo only on days 5–8 (Hedges' $g = -0.37$, 95% CI -0.66 to -0.09 , $p = 0.01$). Compared with placebo/pseudo-placebo, ketamine led to significantly greater response (40 min to day 7) and remission (80 min to days 3–5). Non-ketamine NMDAR antagonists achieved greater response at day 2 and days 3–5. All-cause discontinuation was similar between ketamine ($p = 0.34$) or non-ketamine NMDAR antagonists ($p = 0.94$) and placebo. Although some adverse effects were more common with ketamine/NMDAR antagonists than placebo, these were transient and clinically insignificant.

Conclusions—A single infusion of ketamine, but less so of non-ketamine NMDAR antagonists, has ultra-rapid efficacy for MDD and BD, lasting for up to 1 week. Development of easy-to-administer, repeatedly given NMDAR antagonists without risk of brain toxicity is of critical importance.

Keywords

Bipolar depression; depression; ketamine; meta-analyses; *N*-methyl-D-aspartate receptor antagonists; trajectories

Introduction

Mood disorders and accompanying suicidality result in great personal suffering and public expenditure. In 2010, major depressive disorder (MDD) rose from 15th to 11th rank in its contribution to disability-adjusted life years (Murray *et al.* 2012). Although for decades antidepressants that act via monoamine pathways have dominated the treatment of depression, efficacy is often unsatisfactory. For example, in the large, randomized, multi-step National Institute of Mental Health (NIMH)-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, only 47% of patients responded to standard

antidepressant treatment and only 33% achieved remission (Warden *et al.* 2007). Moreover, the onset of clinically noticeable efficacy usually takes 2 weeks (Kasper *et al.* 2006). Further, the efficacy of antidepressants in bipolar depression (BD) has been challenged (Sachs *et al.* 2007; Pacchiarotti *et al.* 2013) and fewer treatment options are available than for MDD (Vieta *et al.* 2010). Thus, interventions with fast efficacy and efficacy for patients not responding to available antidepressants are sorely needed.

Recent studies demonstrated the role of glutamate-mediated neuroplasticity in the pathophysiology of mood disorders and antidepressant effects of glutamatergic agents (Tardito *et al.* 2006; Pittenger & Duman, 2008; Sanacora *et al.* 2008). Ketamine, a non-selective *N*-methyl-D-aspartic acid receptor (NMDAR) antagonist, used for decades as an anesthetic, has shown anti-depressant efficacy in subanesthetic doses within hours of administration in placebo-controlled crossover studies for MDD (Berman *et al.* 2000; Zarate *et al.* 2006; Sos *et al.* 2013) and BD (Diazgranados *et al.* 2010*a*; Zarate *et al.* 2012). In these trials, ketamine showed quick and dramatic antidepressant effects for refractory and non-refractory depression. Furthermore, ketamine reduced suicidal thoughts in both open (Price *et al.* 2009; Diazgranados *et al.* 2010*b*; Larkin & Beautrais, 2011) and controlled (Zarate *et al.* 2012; Price *et al.* 2014) trials.

Ketamine's primary mechanism of action is NMDAR blockade at the phencyclidine site within the ionotropic channel. Ketamine induces presynaptic glutamate release by activating GABAergic inputs leading to increased glutamatergic neuronal firing (Machado-Vieira *et al.* 2009). Thus, a relevant question is whether non-ketamine NMDAR antagonists could be similarly efficacious for depression. In this context, five randomized trials of non-ketamine NMDAR antagonists, Traxoprodil CP-101,606 (Preskorn *et al.* 2008), AZD6765 (Zarate *et al.* 2013; Sanacora *et al.* 2014) and GLYX-13 (Preskorn *et al.* 2015) have been conducted. Traxoprodil (CP-101,606) is a selective antagonist of the NR2B subunit of NMDARs. AZD6765 (lanicemine) is a non-selective NMDAR channel blocker like ketamine, but with lower trapping channel blockade (54% *v.* 86%) (Monaghan & Larsen, 1997). GLYX-13 is a NMDAR glycine site partial agonist, producing NMDA functional antagonism, with long-term efficacy without psychotomimetic effects after a single intravenous dose in animal models (Burch *et al.* 2010).

There are systematic and/or narrative reviews (Aan Het Rot *et al.* 2012; Covvey *et al.* 2012; Mathew *et al.* 2012; Caddy *et al.* 2014; Fond *et al.* 2014; Coyle & Laws, 2015; McGirr *et al.* 2015; Newport *et al.* 2015) including five meta-analyses to date that summarized the efficacy of ketamine and non-ketamine NMDAR antagonists. However these meta-analyses have some deficits, such as not assessing the efficacy change over time for all studies (Fond *et al.* 2014) or for some studies (Newport *et al.* 2015), including only ketamine studies (Caddy *et al.* 2014; Fond *et al.* 2014; Coyle & Laws, 2015), mixing pre-post data comparison with placebo-controlled studies (Coyle & Laws, 2015), mixing intranasal with injection studies (Newport *et al.* 2015), missing some relevant studies (McGirr *et al.* 2015; Newport *et al.* 2015), and/or mixing in electroconvulsive therapy studies (Fond *et al.* 2014). Here, we conducted a meta-analysis of ketamine and non-ketamine NMDAR antagonists in patients with depression. We included all studies conducted to date that examined the efficacy of

NMDAR antagonists compared with placebo in randomized trials and examined the time course of efficacy after a single NMDAR antagonist infusion.

Method

Search and inclusion criteria

Two investigators independently searched PubMed, PsycINFO, ISI Web of Science, and the US National Institutes of Health clinical trials registry (<http://www.clinicaltrials.gov>), from database inception until 25 August 2015, for, parallel-group or cross-over randomized controlled trials (RCTs), comparing single-dose, intravenous NMDAR antagonist infusion *v.* placebo (saline infusion) or pseudo-placebo (non-antidepressant anesthetic) for MDD and/or BD. We also included multiple injection studies, but only if data before the second injection were available. We excluded RCTs of NMDAR antagonists administered orally or intranasally. The following search string was used: (ketamine OR *N*-methyl-D-aspartic acid OR NMDA OR glutamat*) AND (depression OR depressive OR depressed OR bipolar OR suicidal) AND (random* OR placebo), supplementing the electronic search by hand-searching reference lists of identified studies, review articles and major meeting proceedings.

Data extraction and outcomes

The primary outcome was symptom change measured by the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) or the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) at study-defined time points post-infusion. When both the HAM-D and MADRS were reported, we used HAM-D scores. Secondary outcomes included response (> 50% reduction in HAM-D/MADRS score), study-defined remission, all-cause discontinuation, and adverse effects, including psychotic, manic and dissociative symptoms, assessed by the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), the Young Mania Rating Scale (YMRS; Young *et al.* 1978) and the Clinician Administered Dissociative States Scale (CADSS; Bremner *et al.* 1998), among others. When assessment time points were similar but not identical, we combined these (e.g. days 3–4). When 2 doses were examined in a single study, we combined multiple doses into one experimental arm, given that the ideal dose of such agents has not been established. However, in one phase 2, dose-finding study of GLYX-13 (Preskorn *et al.* 2015), the mean and S.D. of HAM-D were combined across the 1, 5 and 10 mg doses, but the 30 mg dose was excluded, being a clear outlier, suggesting an inverted U-shaped dose–response curve with an ineffective high GLYX-13 dose. Conversely, in the three-arm phase IIB study (Sanacora *et al.* 2014) of AZD6765, the mean and S.D. of the MADRS scores were combined for the 100 and 150 mg doses. Data were extracted independently by two or three reviewers (J.M.C., K.H. and T.K.), calculating results from graphs if needed and resolving inconsistencies by consensus.

Risk assessment including publication bias

Two reviewers independently assessed risk of bias for each study using the Cochrane Collaboration's risk-of-bias tool, rating studies as having low, high, or unclear risks of bias on seven predefined criteria (Higgins & Green, 2011; Higgins *et al.* 2011).

Publication bias was assessed inspecting funnel plots for depressive symptom change, response and remission.

Meta-analytic calculations

For continuous outcomes, standardized mean difference between the intervention and placebo/pseudo-placebo was calculated as Hedges' g with 95% confidence intervals (CIs), using random-effects models. For dichotomous outcomes, relative risk (RR) was calculated with 95% CIs, and with number-needed-to-treat/harm (NNT/NNH) when appropriate. Heterogeneity is expressed by τ^2 , I^2 , Q and p values. All-cause discontinuation was analysed both in the intent-to-treat sample and in a sensitivity analysis after excluding patients discontinuing due to significant improvement in the first phase of cross-over trials to avoid biasing against the more efficacious treatment. A second sensitivity analysis focused on the three AZD6765 studies.

Results

Search results

The search yielded 1574 hits. Altogether, 1548 articles were excluded based on abstract/title. Of the remaining 26 full-text articles, 14 articles were removed (for reasons, see online Supplementary Fig. S1), resulting in 12 articles reporting on 14 trials (ketamine = 9 trials, NMDAR antagonists = 5 trials) that were meta-analysed.

Study design, population, treatment and outcomes

Of 14 trials (Berman *et al.* 2000; Zarate *et al.* 2006, 2012, 2013; Diazgranados *et al.* 2010a; Murrough *et al.* 2013a; Sos *et al.* 2013; Lai *et al.* 2014; Sanacora *et al.* 2014; Singh *et al.* 2014; Preskorn *et al.* 2008, 2015), which lasted 10.0 ± 8.8 days, seven were placebo-controlled cross-over studies (duration = 8.4 ± 4.1 days, interval until crossover = 9.0 ± 3.4 days), and seven were parallel-group studies (duration = 11.6 ± 12.1 days) (online Supplementary Table S1). Participants were 45.8 ± 3.8 years old, $40.7 \pm 8.7\%$ were male, $77.1 \pm 9.2\%$ were white (studies = 7). The current episode duration was 45.1 ± 49.0 months (studies = 9), and patients had failed 6.0 ± 1.1 anti-depressant trials (studies = 3). Nine studies investigated single-dose intravenous ketamine ($n = 234$), five used intravenous non-ketamine NMDAR antagonists ($n = 354$), i.e. CP-101,606 (studies = 1, $n = 30$), AZD6765 (studies = 3 including one repeated infusion study, $n = 158$) and GLYX-13 ($n = 116$). Although technically not an NMDAR antagonist, we included GLYX-13, as it pharmacodynamically reduces NMDA transmission. Placebo was the comparator in all but one parallel-group ketamine study (Murrough *et al.* 2013a), which used midazolam, an anesthetic without known anti-depressant effect, as active pseudo-placebo.

Ketamine studies

Of nine ketamine studies ($n = 234$, range = 4–73/study), seven were independently funded, six were placebo-controlled cross-over studies (duration = 8.7 ± 4.4 days, interval before cross-over = 9.5 ± 3.5 days) (Berman *et al.* 2000; Zarate *et al.* 2006, 2012; Diazgranados *et al.* 2010a; Sos *et al.* 2013; Lai *et al.* 2014), and three were parallel-group studies (duration = 4.0 ± 2.6 days) (Murrough *et al.* 2013a; Lai *et al.* 2014; Singh *et al.* 2014) (online

Supplementary Table S1). There were three monotherapy studies and six add-on studies (to lithium or valproate = 2, to antidepressants = 3, to tranylcypromine and second-generation antipsychotics = 1). Of nine studies, five washed out antidepressants for 12.6 ± 3.1 days, while prior antidepressants were maintained throughout the study in the add-on ketamine studies (Sos *et al.* 2013; Lai *et al.* 2014; Singh *et al.* 2014).

Seven RCTs (Berman *et al.* 2000; Zarate *et al.* 2006; Murrough *et al.* 2013a; Sos *et al.* 2013; Lai *et al.* 2014; Singh *et al.* 2014) studied MDD patients ($n = 200$), two trials (Diazgranados *et al.* 2010a; Zarate *et al.* 2012) studied BD patients ($n = 25$), and one trial included both BD and MDD patients ($n = 9$) (Berman *et al.* 2000).

In five studies with information (Zarate *et al.* 2006, 2012; Diazgranados *et al.* 2010a; Sos *et al.* 2013; Singh *et al.* 2014), subjects were hospitalized for the duration of the study. In the Murrough *et al.* (2013a) study, subjects were hospitalized for the first 24 h after infusion only. In the remaining two studies, the treatment setting was either unclear (Berman *et al.* 2000) or subjects were out-patients treated in a day-hospital setting (Lai *et al.* 2014).

Co-morbid anxiety disorders were permitted if not requiring current treatment in three studies; no study permitted recent substance use, unstable medical illness, serious/imminent suicidal or homicidal risk. Five of seven MDD studies included patients with inadequate response to antidepressants (the number of prior failed trials varied) (Zarate *et al.* 2006; Murrough *et al.* 2013a; Lai *et al.* 2014; Singh *et al.* 2014); whereas in BD studies, patients had to have failed 1 adequate antidepressant trial plus one prospective open trial of either lithium or valproate for 4 weeks at therapeutic levels (lithium = 0.6–1.2 mEq/l; valproic acid = 50–125 $\mu\text{g/ml}$) (Diazgranados *et al.* 2010a; Zarate *et al.* 2012) (online Supplementary Table S1).

Seven studies randomized patients to ketamine single infusion at 0.1–0.5 mg/kg per h for 40 min or saline; in one study (Sos *et al.* 2013), patients received 0.27 mg/kg for the first 10 min using the same dose over next 20 min. Patients were crossed over after 7–14 days in six studies, except that five patients were not crossed over because of marked responses.

Response was defined as a 50% decrease in either HAM-D (Berman *et al.* 2000; Zarate *et al.* 2006; Diazgranados *et al.* 2010a) or MADRS score (Diazgranados *et al.* 2010a; Zarate *et al.* 2012; Murrough *et al.* 2013a; Sos *et al.* 2013; Lai *et al.* 2014; Singh *et al.* 2014). Three studies reported remission data, i.e. MADRS < 10 (Diazgranados *et al.* 2010a; Zarate *et al.* 2012) or HAM-D < 7 (Zarate *et al.* 2006).

Non-ketamine NMDAR antagonist

In five studies ($n = 354$, range = 22–168/study), three non-ketamine NMDAR antagonists ($n = 354$) were studied: CP-101,600 ($n = 30$) (Preskorn *et al.* 2008), GLYX-13 ($n = 116$) (Preskorn *et al.* 2015) and AZD6765 ($n = 208$) (Zarate *et al.* 2013; Sanacora *et al.* 2014) (online Supplementary Table S1). Four RCTs were parallel-group, industry-sponsored RCTs ($n = 332$) (Preskorn *et al.* 2008, 2015; Sanacora *et al.* 2014); one was a non-industry sponsored, 7-day cross-over study of AZD6765 (Zarate *et al.* 2013). There were three monotherapy studies and two add-on studies [paroxetine = 1 (Tardito *et al.* 2006), non-

tricyclic anti-depressants = 1 (Sanacora *et al.* 2014)]. All patients had MDD and had failed either 1 antidepressant in the current episode (Preskorn *et al.* 2015), 2 anti-depressant trials (Zarate *et al.* 2013; Sanacora *et al.* 2014); or 1 selective serotonin reuptake inhibitor trial, without non-responsiveness to adequate trials of 3 different antidepressant classes, plus failure to a 6-week prospective paroxetine lead-in treatment (Preskorn *et al.* 2008). In the three monotherapy studies, antidepressants were washed out for 11.7 ± 4.0 days (Zarate *et al.* 2013; Sanacora *et al.* 2014; Preskorn *et al.* 2015). One adjunctive study added CP-101,600 to paroxetine after a 6-week lead-in trial (Preskorn *et al.* 2008) and a second study added AZD6765 to anti-depressant, sedative and hypnotic treatment (study 9) (Sanacora *et al.* 2014).

Single CP-101,606 infusion was added to paroxetine at 0.75 mg/kg per h for 1.5 h followed by 0.15 mg/kg per h for 6.5 h for the first seven patients. Due to dissociative symptoms, the infusion dose and duration were lowered to 0.5 mg/kg per h for 1.5 h for the remaining 23 patients (online Supplementary Table S1). AZD6765 was given as a single fixed dose of 100 mg (Sanacora *et al.* 2014) and/or 150 mg (Zarate *et al.* 2013; Sanacora *et al.* 2014) over 60 min. In the one cross-over study (Zarate *et al.* 2013), one patient who responded to AZD6765 was not crossed over.

In one study, response was defined as a 50% decrease in HAM-D score from baseline at day 5 and remission was defined as an HAMD score of ≤ 7 (Preskorn *et al.* 2008). In the second study, response was defined as a 50% MADRS score decrease and remission was defined as a MADRS score of <10 (Zarate *et al.* 2013). Two studies did not report response or remission results (Sanacora *et al.* 2014; Preskorn *et al.* 2015) and data from the last study (Sanacora *et al.* 2014, study 9) could not be used, as information for the individual included study arms was not available.

Change in depressive symptoms

Ketamine—Pooled together, single ketamine infusion resulted in superior reduction of depressive symptoms compared with placebo/pseudo-placebo starting at 40–60 min (studies = 4, Hedges' $g = -0.50$, 95% CI -1.00 to -0.00 , $p = 0.05$; heterogeneity: $\tau^2 = 0.11$, $I^2 = 44.3$, $Q = 5.39$, $p = 0.15$), peaking at day 1 (studies = 7, Hedges' $g = -1.00$, 95% CI -1.28 to -0.73 , $p < 0.001$; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 2.14$, $p = 0.91$) and lasting until days 5–8 (studies = 5, Hedges' $g = -0.38$, 95% CI -0.73 to -0.03 , $p = 0.036$; heterogeneity: $\tau^2 = 0.02$, $I^2 = 9.38$, $Q = 4.41$, $p = 0.35$), with non-significant group differences on days 10–12 and days 14–15 (Fig. 1).

Non-ketamine NMDAR antagonist—Pooled together, non-ketamine NMDAR antagonists resulted in superior reduction of depressive symptoms compared with placebo on days 5–8 (studies = 4, Hedges' $g = -0.37$, 95% CI -0.66 to -0.09 , $p = 0.01$; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 2.28$, $p = 0.52$), without significant group differences at any other time point (Fig. 2). Repeating the analyses for the three AZD6765 studies yielded no significant group differences at any time points (data not shown).

Response and remission

Ketamine—Compared with placebo/pseudo-placebo, ketamine was associated with significantly greater response starting at 40–60 min (studies = 3, ketamine = 43.1% *v.* placebo = 0.00%; RR = 13.6, 95% CI 2.67–69.6, $p = 0.00$; NNT = 3; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 0.63$, $p = 0.73$), peaking at 230–240 min (studies = 3, ketamine = 58.8% *v.* placebo = 2.00%; RR = 14.7, 95% CI 3.72–58.3, $p < 0.001$; NNT = 2; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 0.20$, $p = 0.91$) and lasting until day 7 (studies = 5, ketamine = 34.4% *v.* placebo = 7.77%; RR = 3.43, 95% CI 1.77–6.63, $p < 0.001$; NNT = 5; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 1.19$, $p = 0.88$) (Fig. 3a).

Similarly, ketamine was associated with significantly greater remission starting at 80 min (studies = 3, ketamine = 17.6% *v.* placebo = 0.00%; RR = 6.63, 95% CI 1.23–35.7, $p = 0.03$; NNT = 7; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 0.19$, $p = 0.91$), peaking at day 1 (studies = 4, ketamine = 34.0% *v.* placebo = 0.00%; RR = 9.89, 95% CI 2.4–40.5, $p = 0.00$; NNT = 3; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 0.30$, $p = 0.96$) and lasting until days 3–5 (studies = 3, ketamine = 19.6% *v.* placebo = 1.96%; RR = 5.22, 95% CI 1.20–22.6, $p = 0.03$; NNT = 7; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 0.26$, $p = 0.88$) (Fig. 3b).

Non-ketamine NMDAR antagonists—Compared with placebo, non-ketamine NMDAR antagonists were associated with significantly greater response on day 2 and days 3–5 (studies = 2, non-ketamine NMDAR antagonists = 27.0%, placebo = 0.00%; RR = 8.52, 95% CI 1.07–67.9, $p = 0.04$; NNT = non-significant; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 0.75$, $p = 0.39$) (Fig. 4a). However, remission was not significantly different from placebo on days 3–5 (studies = 2, non-ketamine NMDAR antagonists = 16.2%, placebo = 0.00%; RR = 6.18, 95% CI 0.76–50.3, $p = 0.089$; NNT = non-significant; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 0.36$, $p = 0.55$) (Fig. 4b).

All-cause discontinuation

Ketamine—All-cause discontinuation was not significantly different between ketamine and placebo (studies = 6, ketamine = 12.1% *v.* placebo = 7.8%; RR = 1.52, 95% CI 0.64–3.58, $p = 0.34$; NNT = non-significant; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 4.38$, $p = 0.50$), remaining non-significant after removal of five patients ‘dropping out’ during the first cross-over phase for marked improvement to ketamine (studies = 6, ketamine = 8.66% *v.* placebo = 6.86%; RR = 1.14, 95% CI 0.42–3.10, $p = 0.81$; NNT = non-significant; heterogeneity: $\tau^2 = 0.14$, $I^2 = 8.83$, $Q = 5.48$, $p = 0.36$) (online Supplementary Fig. S2).

Non-ketamine NMDAR antagonists—All-cause discontinuation did not differ between placebo and non-ketamine NMDAR antagonists (studies = 2, non-ketamine NMDAR antagonists = 12.3% *v.* placebo = 20.0%; RR = 0.92, 95% CI 0.11–8.09, $p = 0.94$; NNT = non-significant; heterogeneity: $\tau^2 = 1.47$, $I^2 = 52.6$, $Q = 2.11$, $p = 0.15$). When one patient on AZD6765 ‘dropping out’ due to marked response to AZD6765 during the first cross-over phase was excluded, results did not change (studies = 2, non-ketamine NMDAR antagonists = 11.1% *v.* placebo = 20.0%; RR = 0.62, 95% CI 0.14–2.66, $p = 0.52$; NNT = non-significant; heterogeneity: $\tau^2 = 0.35$, $I^2 = 19.2$, $Q = 1.24$, $p = 0.27$) (online Supplementary Fig. S3).

Changes in psychopathology scales

Ketamine—The BPRS score was significantly higher in the keta-mine group than with placebo at 40–60 min (studies = 5, Hedges' $g = 0.90$, 95% CI 0.58–1.22, $p < 0.001$; heterogeneity: $\tau^2 = 0.02$, $I^2 = 10.8$, $Q = 4.48$, $p = 0.35$), becoming significantly lower on day 3 (studies = 3, Hedges' $g = -0.48$, 95% CI -0.86 to -0.09 , $p = 0.015$; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 0.23$, $p = 0.89$) (online Supplementary Fig. S4). The YMRS score was significantly lower in the ketamine group than placebo at all time points until day 14, except at 40–60 min (studies = 3, Hedges' $g = 0.29$, 95% CI -0.10 to 0.68 , $p = 0.15$; heterogeneity: $\tau^2 = 0.03$, $I^2 = 22.5$, $Q = 2.58$, $p = 0.28$), 80 min (studies = 2, Hedges' $g = -0.59$, 95% CI -1.24 to 0.06 , $p = 0.076$; heterogeneity: $\tau^2 = 0.10$, $I^2 = 44.1$, $Q = 1.79$, $p = 0.18$) and day 7 (studies = 2, Hedges' $g = -0.57$, 95% CI -1.43 to 0.30 , $p = 0.20$; heterogeneity: $\tau^2 = 0.27$, $I^2 = 68.3$, $Q = 3.15$, $p = 0.08$) (online Supplementary Fig. S5). The CADSS score was only significantly higher in the ketamine group than with placebo at 40–60 min post-ketamine infusion (studies = 5, Hedges' $g = 2.42$, 95% CI 1.13–3.73, $p < 0.001$; heterogeneity: $\tau^2 = 1.96$, $I^2 = 92.3$, $Q = 52.1$, $p < 0.001$) (online Supplementary Fig. S6).

Non-ketamine NMDAR antagonists—The BPRS score was significantly lower in the non-ketamine NMDAR antagonists than placebo at 110 min (studies = 2, Hedges' $g = -0.37$, 95% CI -0.72 to -0.03 , $p = 0.035$; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 0.38$, $p = 0.54$) and 230–240 min (studies = 3, Hedges' $g = -0.32$, 95% CI -0.63 to -0.02 , $p = 0.04$; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$, $Q = 1.40$, $p = 0.50$) (online Supplementary Fig. S7). Regarding YMRS scores, there was no difference between non-ketamine NMDAR antagonists and placebo at any post-baseline time points. The CADSS score was significantly higher in non-ketamine NMDAR antagonists than placebo at 230–240 min (studies = 1, Hedges' $g = -0.66$, 95% CI -1.26 to -0.07 , $p = 0.03$; heterogeneity: not applicable) and at day 1 (studies = 1, Hedges' $g = -0.69$, 95% CI -1.29 to -0.09 ; heterogeneity: not applicable), whereas the CADSS score was lower than placebo at day 3 (studies = 1, Hedges' $g = 0.67$, 95% CI 0.07 – 1.26 , $p = 0.03$; heterogeneity: not applicable) and day 7 (studies = 1, Hedges' $g = 0.68$, 95% CI 0.08 – 1.28 , $p = 0.03$; heterogeneity: not applicable).

Other adverse effects

Ketamine—Among adverse events reported by 2 studies, no significant differences emerged between ketamine and placebo: tiredness/fatigue ($p = 0.37$), feeling 'woozy/loopy' ($p = 0.95$), dizziness/faintness ($p = 0.22$), nausea ($p = 0.30$) and vivid dreams ($p = 0.23$) (online Supplementary Fig. S8).

Non-ketamine NMDAR antagonists—Adverse events were not significantly different between non-ketamine NMDAR antagonists and placebo: tiredness/fatigue ($p = 0.65$), dizziness/faintness ($p = 0.054$), anxiety ($p = 0.70$), nausea ($p = 0.12$), drowsiness/sedation ($p = 0.40$), irritability ($p = 0.36$), stomach/abdominal discomfort ($p = 0.65$), muscle/bone/joint pain ($p = 0.96$), tingling ($p = 0.96$), diarrhea ($p = 0.75$), headache ($p = 0.72$), insomnia/interrupted sleep ($p = 0.38$) and vomiting ($p = 0.60$) (online Supplementary Fig. S9).

Risk assessment including publication bias—Out of seven risk-of-bias categories, most studies had incomplete outcome data; i.e. they did not report results for all outcomes listed in the clinical trial registrations. Moreover, Lai *et al.* (2014) used ascending doses to which participants were blinded, and a placebo infusion was inserted at some point to which both raters and participants were blinded. We considered that these procedures might have compromised blinding, rating this study as being at high risk for multiple risk of bias categories. Although there has been concern of functional unblinding due to the euphorogenic and dissociative effects of sub-anesthetic doses of ketamine, we considered this effect as inevitable and regarded this fact as low risk, similar to many other agents that have substantial side effects that could be noticed by participants and raters (e.g. sedation, weight gain, muscle stiffness, restlessness, etc.) and that are generally regarded as having low risk of bias in clinical trials (online Supplementary Table S2).

Inspecting funnel plots did not indicate publication bias regarding depressive symptom reduction, response or remission.

Discussion

In this meta-analysis of randomized, placebo/pseudo-placebo-controlled trials of single-dose, intravenous ketamine or non-ketamine NMDAR antagonists for patients with MDD and BD refractory/unresponsive to trials with standard antidepressants, we examined the time trajectory of efficacy in greater detail than previous meta-analyses. Pooling six crossover trials and three parallel-group studies, single ketamine infusion was significantly superior to placebo/pseudo-placebo regarding antidepressant efficacy. The significantly greater reduction in depressive symptoms started as early as within 40–60 min, peaking on day 1, and lasting until days 5–8, with maintenance of superior remission and response status until days 3–5 and 7, respectively. Effect sizes ranged from medium to large (–0.38 to –1.00) for the reduction in depressive symptoms, being large for response (NNT = 2–5, peaking at 230–240 min) and remission (NNT = 3–7, peaking at 1 day). At 24 h, 54.1% responded and 34.0% remitted on ketamine compared with only 7.8% and 0% on placebo. Furthermore, the findings were homogeneous throughout. In contrast to ketamine, single infusion of non-ketamine NMDAR antagonists was only significantly superior to placebo at one assessment time point (days 5–8) with a small to medium effect size (–0.37). Although non-ketamine NMDAR antagonists had significantly higher response rates on days 2 and 3–5 (NNT = non-significant), remission was not significantly superior to placebo. Like with ketamine, results were homogeneous throughout. The reason for non-ketamine NMDAR antagonists having smaller effect sizes than ketamine remains unknown. However, lower NMDAR affinity may be one of the mechanisms that also explains their reduced side effect potential. Nevertheless, both single infusion of ketamine and non-ketamine NMDAR antagonists was well tolerated, not leading to greater drop-out than placebo/pseudo-placebo.

The magnitude as well as speed of effect of NMDAR antagonists are remarkable. Despite long suffering during a current depressive episode lasting 45.1 ± 49.0 months that was not relieved by 6.0 ± 1.1 treatment trials, NMDAR antagonism promptly and dramatically improved depressive symptoms. Effect sizes for symptom reduction were much higher for ketamine (–0.38 to –1.00) and similar for non-ketamine NMDAR antagonists (–0.37) in

patients with treatment-resistant depression compared with first-line antidepressants in acute, non-refractory depression (-0.31) (Turner *et al.* 2008), although effect sizes are lower when patients with milder depression are included due to greater placebo response (Kirsch *et al.* 2008). Effect sizes for response with ketamine (NNT = 2–5) and non-ketamine NMDAR antagonists (NNT = 4) (Melander *et al.* 2008) also compare very favorably to antidepressants in non-refractory depression (NNT = 7) and to second-generation antipsychotic augmentation of patients with suboptimal response to antidepressants (NNT = 7–10) (Spielmanns *et al.* 2013).

The transient efficacy lasting 1 week post-infusion have stimulated multi-infusion studies, which have yielded encouraging results. Repeated ketamine infusions resulted in significant antidepressant effect with an extended median time to recurrence of depressive symptoms in a 4-week open-label study (Aan het Rot *et al.* 2010), 18-day open-label study (Murrough *et al.* 2013*b*) and 12-month, naturalistic three-patient case series (Szymkowicz *et al.* 2013). Furthermore, a placebo-controlled RCT ($n = 152$) comparing three infusions of 100 or 150 mg AZD6765 within the first week with placebo showed superior antidepressant effects starting at week 2 and lasting until week 5 (Sanacora *et al.* 2014).

Treatment resistance occurs in approximately 15–20% of depressed patients (Rush *et al.* 2006). If safe, using a fast-acting antidepressant for non-refractory depression that could speed up response and remission while the first-line antidepressant unfolds its efficacy, as shown recently (Hu *et al.* 2016), would be an important treatment option. Such strategy could be used during emergency room visits to shorten or, even, prevent admissions. A related question includes whether patients will be able to maintain the response if standard antidepressants are started concurrently in non-refractory depression, or if repeated NMDAR antagonist doses would be necessary.

Despite these highly favorable results, several important questions remain (Aan Het Rot *et al.* 2012; Martinowich *et al.* 2013): (i) can NMDAR antagonists be developed that have similarly large effect sizes as ketamine?; (ii) can NMDAR antagonists without the potential for neurotoxicity be developed, enabling safe repeated/chronic administration?; (iii) how long would the repeated administration interval have to be?; (iv) what is the optimal dose/dose range?; (v) what non-intravenous administration routes can be developed?; (vi) to what degree can we generalize results to elderly and pediatric populations?; (vii) what clinical or biological markers predict NMDAR antagonist response?; (viii) are NMDAR antagonists useful anti-suicidal treatments?; (ix) are there any acute/chronic cognitive side effects of NMDAR antagonists?; (x) are NMDAR antagonists helpful for other psychiatric disorders?; and (xi) are NMDAR antagonists effective in monotherapy or as add-on treatment in non-refractory depressed patients?

Several limitations of this meta-analysis deserve mentioning. First, six studies applied a cross-over design. Clearly, parallel-group trials are needed; yet, at least, the one parallel-group ketamine study (Murrough *et al.* 2013*a*) showed very similar effects as the cross-over studies. Second, we grouped three different non-ketamine NMDAR antagonists together that have different mechanisms and that were studied to find optimal doses. Thus, findings may be a conservative estimate for some or all of the non-ketamine NMDAR antagonists. Further,

although fewer non-ketamine NMDAR antagonists studies reported outcomes at the same time point as ketamine studies, RCTs were larger with one and a half times as many participants ($n = 354$). Moreover, effect sizes in non-ketamine NMDAR antagonist studies were homogeneous and approximately two- to four-fold lower than those observed after ketamine infusion. Third, the number of studies and patients was still limited, and assessment time points differed across studies. Therefore, some effect sizes were based on one study, especially for non-ketamine NMDAR antagonists. Nevertheless, study results were homogeneous, suggesting similar results even with a larger database. Finally, significant sedative, euphoric or dissociative effects of ketamine could have unblinded patients and/or raters. In fact, a recent *post-hoc* analysis suggested that higher dissociation ratings were associated with greater antidepressant efficacy of ketamine (Luckenbaugh *et al.* 2014). While this result could have bolstered concerns about functional unblinding, it was interpreted as a lead toward a mechanisms of ketamine's efficacy. This interpretation is supported by our meta-analysis. Dissociative symptoms and BPRS scores were significantly higher with ketamine at 40–60 min, but BPRS scores became significantly lower at day 3, and antidepressant effects lasted until days 5–7. Moreover, non-ketamine NMDAR antagonists, not causing any psychogenic effects, also had antidepressant effects, supporting the NMDA hypothesis of depression. Finally, in the midazolam-controlled study, midazolam sub-anesthetic doses that could also have unblinded treatment did not diminish ketamine's effect sizes. However, considering that such unblinding effects of ketamine could have influenced the results, we have used the score of 'unclear' in the risk-of-bias assessment table for studies not using midazolam as the control.

In conclusion, results from this meta-analysis indicate that single-dose intravenous ketamine and, less so, non-ketamine NMDAR antagonists are effective in rapidly reducing depressive symptoms in patients with unresponsive/refractory MDD and BD. While these findings are highly encouraging and important for patients, clinicians, researchers and drug developers, several questions outlined above call for the conduct of sufficiently large, effectively blinded, parallel-group RCTs with single-dose and repeated-dose ketamine and, ideally, additional NMDAR antagonists.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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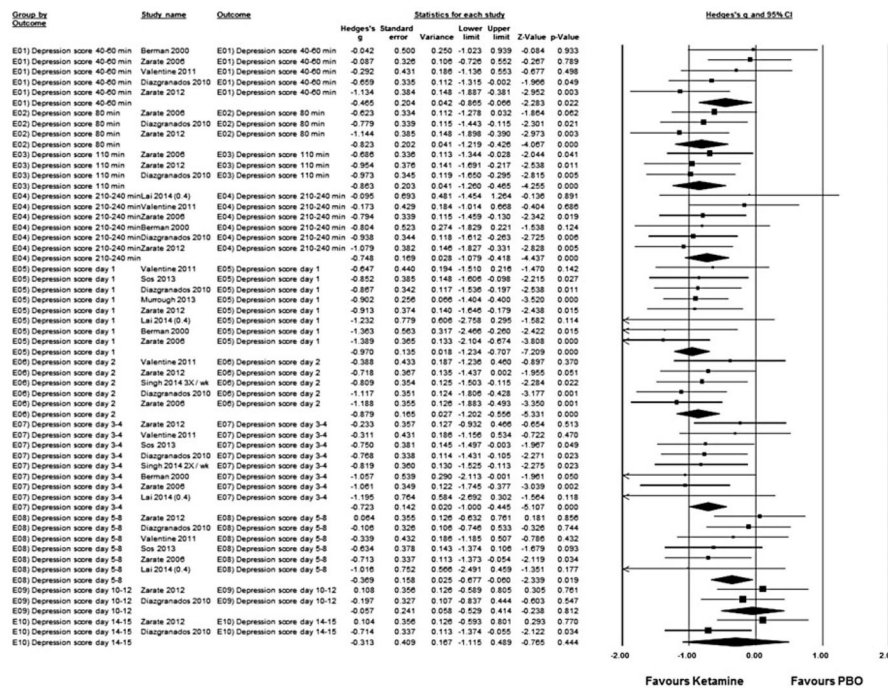


Fig. 1. Hedge's *g* in change in depression rating scale score between ketamine-treated and placebo (PBO) control subjects in the articles analysed. Squares are effect sizes of single studies, diamonds of pooled results. CI, Confidence interval.

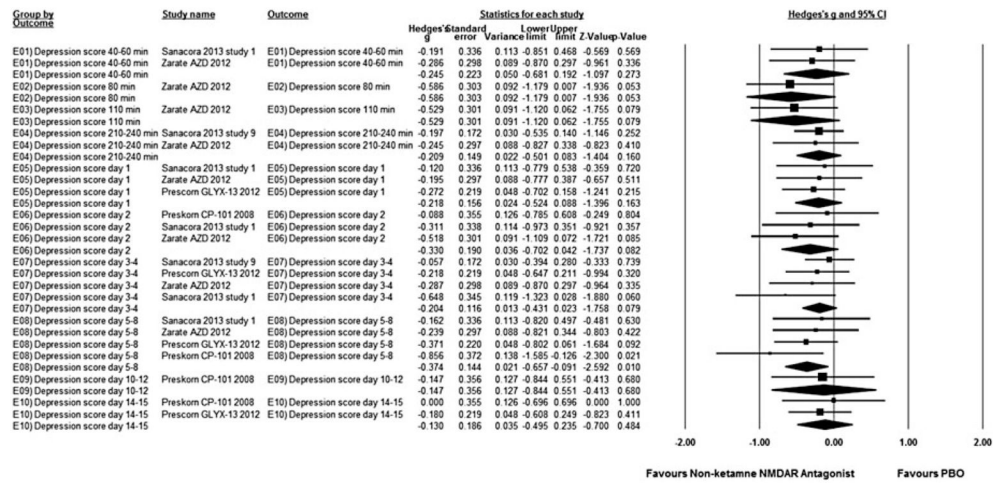


Fig. 2. Hedges's *g* in change in depression rating scale score between non-ketamine *N*-methyl-D-aspartate receptor (NMDAR) antagonist-treated and placebo (PBO) control subjects in the articles analysed. Squares are effect sizes of single studies, diamonds of pooled results. CI, Confidence interval.

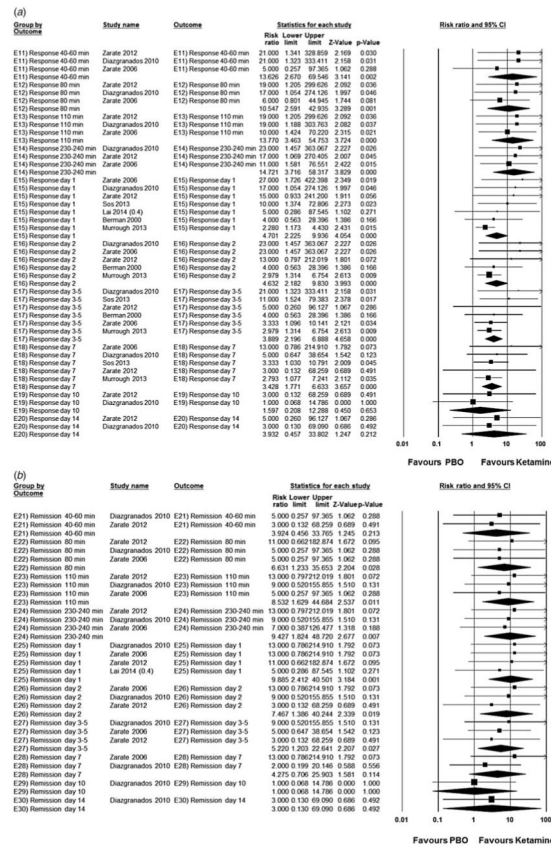


Fig. 3. Risk ratio in treatment response (a) (50% reduction in Hamilton Depression Rating Scale/ Montgomery–Åsberg Depression Rating Scale score) and remission (b) between ketamine-treated and placebo (PBO) control subjects in the articles analysed. Squares are effect sizes of single studies, diamonds of pooled results. CI, Confidence interval.

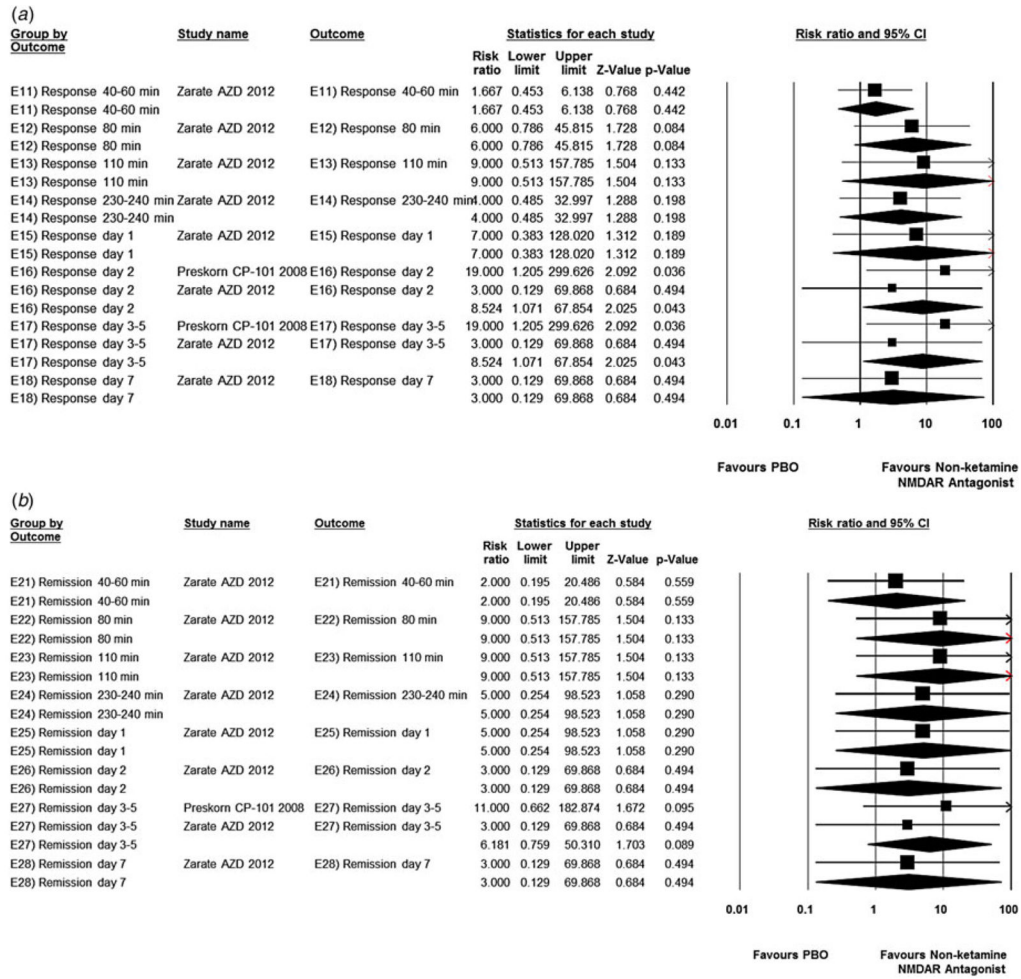


Fig. 4. Risk ratio in treatment response (a) (50% reduction in Hamilton Depression Rating Scale/ Montgomery–Åsberg Depression Rating Scale score) and remission (b) between non-ketamine *N*-methyl-D-aspartate receptor (NMDAR) antagonist-treated and placebo (PBO) control subjects in the articles analysed. Squares are effect sizes of single studies, diamonds of pooled results. CI, Confidence interval.