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Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis☆

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ABSTRACT

Objective: Given the significant disability, morbidity and mortality associated with depression, the promising recent trials of ketamine highlight a novel intervention. A meta-analysis was conducted to assess the efficacy of ketamine in comparison with placebo for the reduction of depressive symptoms in patients who meet criteria for a major depressive episode.

Method: Two electronic databases were searched in September 2013 for English-language studies that were randomized placebo-controlled trials of ketamine treatment for patients with major depressive disorder or bipolar depression and utilized a standardized rating scale. Studies including participants receiving electroconvulsive therapy and adolescent/child participants were excluded. Five studies were included in the quantitative meta-analysis.

Results: The quantitative meta-analysis showed that ketamine significantly reduced depressive symptoms. The overall effect size at day 1 was large and statistically significant with an overall standardized mean difference of 1.01 (95% confidence interval 0.69–1.34) ($P<.001$), with the effects sustained at 7 days postinfusion. The heterogeneity of the studies was low and not statistically significant, and the funnel plot showed no publication bias.

Conclusions: The large and statistically significant effect of ketamine on depressive symptoms supports a promising, new and effective pharmacotherapy with rapid onset, high efficacy and good tolerability.

Introduction

With its high prevalence, disability, morbidity and mortality, depression poses a significant public health issue [1–4]. Patients with depression have elevated risk of suicide and increased medical and psychiatric comorbidities [5]. Yet only half of individuals with major depressive episodes respond to the first-line treatment, and symptom response time can be as high as 3 to 4 weeks [6–8]. With the challenges of existing pharmacotherapies, novel more rapidly acting treatments for major depression are clearly needed.

Ketamine, an *N*-methyl-D-aspartate (NMDA)-receptor antagonist and FDA-approved anesthetic, has been used in rodent models of depression with consistently positive results [9–14]. Existing literature suggests that glutamate levels and NMDA receptor mRNA expression are abnormal in patients with major depressive disorder (MDD) and bipolar affective disorder (BPAD), and long-term antidepressant treatment reduces NMDA receptor mRNA transcription [15–19]. Additionally, prior studies evaluating postmortem hippocampal samples of people who have committed suicide report decreased NMDA receptor expression, suggesting an alteration in the glutamatergic system [20,21]. These findings led to the experimental use of ketamine for treatment of depression. Results of early studies of ketamine's use as an antidepressant in humans were promising. Specifically, several open-label trials suggested that ketamine had a rapid antidepressant effect [22,23]. Follow-up randomized controlled trials confirmed that ketamine performed significantly better than placebo with relatively few safety concerns [24–29].

Given the public health burden of major depression, challenges of existing depression treatments, and promising basic and clinical evidence, ketamine may be an important rapid-acting treatment for major depression. However, controversy exists regarding the use of ketamine. Ketamine has notoriety as a club drug with a brief hallucinogenic and euphoric effect that can last 1 to 2 h and thus must be administered in controlled settings [30]. Reports of off-label ketamine use in emergency rooms, pain clinics and private psychiatric clinics are alarming given the lack of close monitoring outside a research environment, unclear clinical context and short duration of effects [31]. Additionally, ketamine's rapid but short-lived effects provide practical challenges for appropriate clinical use. One recent systematic review concluded that single dosages of intravenous, oral and intramuscular ketamine were useful for treating unipolar and bipolar depression [32]. Another recent meta-analysis reported that ketamine intervention had higher rates of response and remission of depression compared to placebo in seven randomized controlled trials [33]. Two other meta-analyses have similarly shown ketamine's efficacy as an antidepressant [34,35]. Limitations of these approaches include reliance on published data rather than using original data collected from the investigators, presentation of outcomes using odds ratios that may overestimate the intended effect, inclusion of studies with high risk of bias, and inclusion of both intravenous and intranasal ketamine interventions when the intravenous route may deliver a more consistent dose of medication.

☆ Conflict of interest: Authors E.E.L., M.P.D., A.L. and S.H. declare no conflicts of interest.

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This meta-analysis was conducted to assess the efficacy of intravenous ketamine in comparison with placebo for the reduction of depressive symptoms in adult individuals who meet criteria for a major depressive episode. Additionally, this analysis sought to better understand the rapid (i.e., 1 day) versus intermediate-term (i.e., 7 days) effect of ketamine.

Methods

Eligibility criteria

English-language articles from January 1990 to September 2013 were searched in two electronic databases (Pubmed, PsycInfo). The criteria for inclusion required studies to be randomized placebo-controlled trials of ketamine in the treatment of patients with treatment-refractory MDD or BPAD depression by the current *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria. The studies were restricted to adult outpatient samples; those that included children or adolescents below the age of 18 years were excluded. Studies that had participants on therapeutic doses of antidepressants were included, while those receiving electroconvulsive therapy (ECT) were not. In addition, the included studies administered ketamine or placebo therapy for a minimum of one treatment and measured depressive symptoms with a standardized rating scale. These eligibility criteria were chosen to ensure that the participants had a standardized way of being diagnosed and evaluated through the course of the study, without concurrent treatments that could confound the results over the short time frame of evaluation.

Information sources

Pubmed and PsycInfo were searched for appropriate articles. In addition, the online clinical database (clinicaltrials.gov) was searched to investigate if there were any current trials relevant to this topic. Authors of several papers were contacted to obtain the data sets from their published trials; however, no new data from ongoing studies were discovered. The database searches were last performed on August 22nd, 2014.

Search

A computer search of PubMed was performed initially on September 10th, 2013. The search terms used were: (((((((((("Depressive Disorder, Treatment-Resistant"[Majr]) OR treatment resistant depression) OR major depressive disorder) OR major depression) OR depression) OR "Depression"[Majr])) AND (("Ketamine"[Mesh]) OR ketamine))). Search filters restricted the studies to randomized controlled trials published in English with human subjects.

A computer search of PsycInfo was performed initially on September 10th, 2013. The search terms used were: (“Depression” OR “Treatment resistant depression” OR “major depression” OR “Major depressive disorder” OR MM "Major Depression" OR MM "Treatment Resistant Depression" DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression") AND (“Ketamine” OR MM "Ketamine"). Search filters restricted the studies to randomized controlled trials.

Study selection

Searches performed on two databases, Pubmed and PsycInfo, resulted in a total of 128 articles. After removing duplicates, the authors were left with 111 articles to screen. Two authors (E.E.L. and M.P.D.) independently reviewed all study titles and abstracts for defined eligibility criteria. These lists were then sent to a third author (A.L.), who was designated to mediate any disparities.

Upon reviewing the search results, duplicate studies were removed. Full article texts were obtained for potential studies appearing to meet eligibility criteria. Initially, searches were built to find studies using ketamine in patients with MDD. As the searches can only be built to be inclusive and not exclusive, the search results included participants with bipolar depression. Initially, these studies were excluded, and the meta-analysis was focused on unipolar depression alone. The initial search produced three studies. In order to gain better understanding of ketamine’s effects in affective disorders, the decision was made to incorporate studies that included participants with bipolar depression as well as unipolar depression. The final search resulted in a total of six studies (Fig. 1). The kappa statistic for study selection was 1.0, consistent with excellent agreement.

Data collection process

Data were extracted from each of the six studies in duplicate. Additionally, the authors of the Zarate et al. 2012 study, the Zarate et al. 2006 study, the Diazgranados et al. study and the Sos et al. study were contacted by e-mail and provided complete data sets for inclusion in the quantitative meta-analysis. The mean Montgomery–Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HDRS) scores at baseline, day 1 and day 7 were extracted from the original data sets provided, with the exception of the Murrough et al. study which listed these data in Table 2 of the paper. Despite the authors’ many outreach attempts by e-mail and phone correspondence, the exact time point of the post-ketamine Beck Depression Inventory (BDI) scores in the Berman et al. study is not known. Thus, the Berman et al. study results were not included in the quantitative meta-analysis.

Data items

Data extracted from the studies included the mean scores on standardized rating scales at baseline, after ketamine infusion and after placebo infusion. The scales used by the six studies included the MADRS, BDI and HDRS. For five of the studies, the day 1 and day 7 postinfusion time points were utilized. For the Berman et al. study, the exact time point of the postinfusion score is not known. While all of the studies reported depression rating scores beyond 1 day, this data point was chosen as it often exhibited the most significant change and was shared by all selected studies. The standard deviations of each of these means were also obtained.

Risk of bias in individual studies

This was assessed with multiple criteria taken from the Cochrane handbook. These included (a) sequence generation; (b) allocation concealment; (c) blinding of the participants, personnel and outcome assessors; (d) reporting of incomplete data outcomes; (e) selective outcome reporting and (f) other sources of bias.

Summary measures

The principal study measure was the raw change in score on the standardized rating scale for depression from baseline to a postinfusion time point with either ketamine or placebo.

Synthesis of results

We calculated the relative risk ratios and the weighted pooled relative risk ratios across studies (Stata 12.0: metan command). We used the DerSimonian and Laird (random effects) model to provide weight estimates for each study. We chose the random-effects model as it provides a more conservative estimate of weighting than the fixed effect (Mantel–Haenszel method) when one is concerned that the fixed-effects assumption, namely, that the true effect is the same in each study, may not be

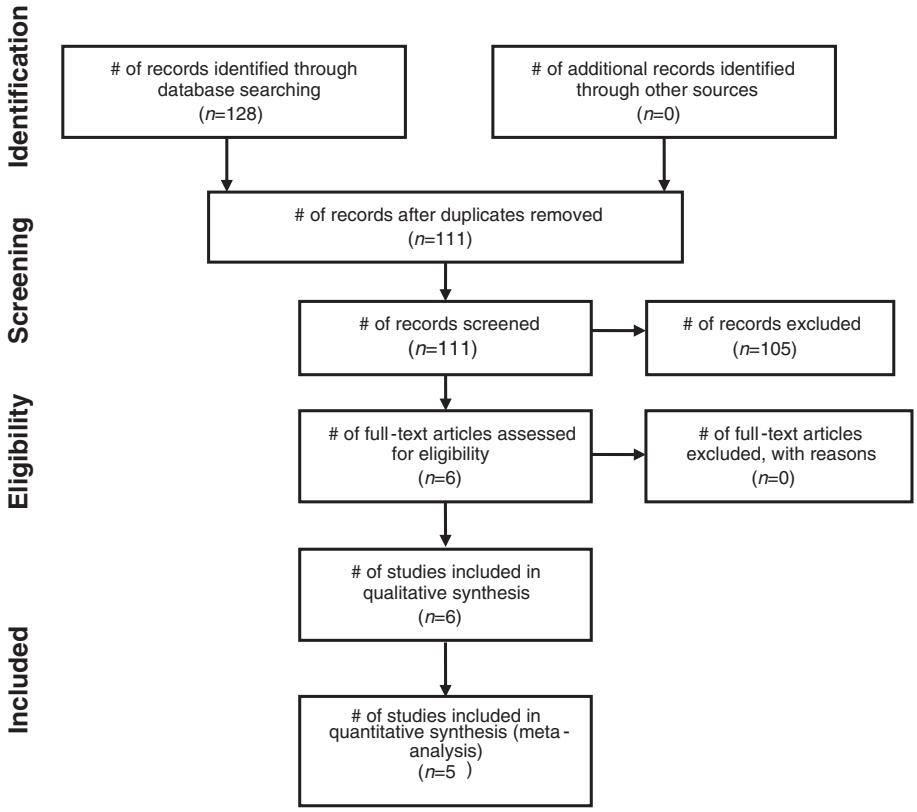

Fig. 1. PRISMA flow diagram delineating the identification of independent studies for inclusion in the qualitative and quantitative meta-analysis.

met. The *Q* statistic and I^2 statistic were used to evaluate heterogeneity. The *Q* statistic quantifies the magnitude of heterogeneity, while the I^2 statistic quantifies the total variation due to between-study variance. Publication bias was evaluated using a funnel plot.

Results

Study characteristics

A total of six randomized, double-blind, placebo-controlled studies were included in this meta-analysis (Table 1). All six of these studies included both male and female patients older than 17 years. There are some notable differences between the studies. Three of the studies (Zarate 2006, Murrough, Sos) included participants with a diagnosis of MDD while excluding those with BPAD. The other three studies (Zarate 2012, Berman, Diazgranados) included patients with BPAD I and II depression. All were randomized, double-blind, placebo-controlled studies, and five were crossover studies (Zarate 2012, Zarate 2006, Diazgranados, Berman, Sos), in which participants received both ketamine and placebo in randomized order. All used the same dose of ketamine hydrochloride (0.5 mg/kg) infused over the same time period (40 min) except for the Sos et al. study, which used an intravenous loading ketamine dose of 0.27 mg/kg infused over 10 min and then a maintenance dose of 0.27 mg/kg over 20 min. One study (Murrough) used an active placebo, midazolam, as opposed to the other studies that used saline as the placebo. All used a standardized rating scale to track the depressive symptoms of participants at multiple time points following infusion.

Risk of bias within studies

All six of the studies had adequate sequence generation and descriptions of blinding. The allocation concealment was not adequately explained in any of the studies and was deemed unclear. Given the short half-life of the ketamine treatments, none of the studies looked at outcomes at 2 weeks postinfusion. Thus, this particular risk of bias criteria may not apply to these studies. All six studies were free of selective outcome reporting and were free of other sources of bias.

Results of individual studies

At day 1 postinfusion, the studies by Zarate et al. (2012 and 2006) were found to have large effect sizes, with standardized mean differences (SMDs) of 1.35 [confidence interval (CI) 0.55–2.15] and 1.49 (CI 0.75–2.24), respectively. Data from Berman et al. and Diazgranados et al. also revealed large effect sizes, with SMDs of 0.94 (CI −0.67 to 2.54) and 1.23 (CI 0.52–1.95), respectively. Data from Murrough et al. and Sos et al. demonstrated medium effect sizes, with SMDs of 0.77 (CI 0.27–1.27) and 0.65 (CI 0.11–1.20), respectively

Similarly, all the studies showed a robust response rate to ketamine. The Sos et al., Diazgranados et al., Murrough et al. and Zarate et al. (2012) studies defined responding participants as having a 50% or greater reduction in MADRS score as compared to baseline MADRS score. Berman et al. and Zarate et al. (2006) defined responding participants as having 50% or great reduction in HDRS score. Sos et al. and Berman et al. reported the lowest response rates of 37% and 50%, respectively. The other studies reported response rates of 64% to 71%. Of note, Murrough et al. noted the highest placebo response rate (28%) to the midazolam infusion. The Berman study did not specify the time point of the reported data; thus, this study was not included in the quantitative meta-analysis.

At day 7 postinfusion, ketamine was shown to have medium effect sizes in the Zarate (2006) and Sos studies with SMDs of 0.70 (CI 0.02–1.37) and 0.51 (CI −0.04 to 1.05), respectively, and small effect sizes in the Zarate (2012), Diazgranados and Murrough studies with SMDs of 0.25 (CI −0.46 to 0.97), 0.30 (CI −0.36 to 0.96) and 0.31 (CI −0.18 to 0.80), respectively.

Table 1
Characteristics of individual studies.

Primary author	Year	Study design	Diagnoses	Control group	Intervention group	Intervention	Retention rate	Study Effect
Zarate et al.	2012	Single-center, double-blind, randomized, crossover, placebo-controlled	BPAD I or BPAD II depression	Crossover	*N*=15 Mean age of 46.7 years, 53% female and 47% male, 60% with BPAD I and 40% with BPAD II	Single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) administered over 40 min	11 (73%) subjects completed both phases of the study. All 3 who dropped out did so in the first phase of the study (3 in ketamine group, 1 in placebo)	MADRS score at day 1
Berman et al.	2000	Single-center, double-blind, randomized, crossover, placebo-controlled	MDE (MDD or BPAD)	Crossover	*N*=9 Mean age 37 years, 4 men and 5 women	Single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) administered over 40 min	7 completed both phases of the study. 1 terminated after tx with ketamine and 1 after placebo	BDI score
Zarate et al.	2006	Single-center, double-blind, randomized, crossover, placebo-controlled	MDD, recurrent without psychotic features, treatment-resistant	Crossover	*N*=18 Mean age of 46.7 years, 6 men and 12 women.	Single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) administered over 40 min	13 completed both phases of the study. 4 terminated after ketamine, 1 after placebo	HDRS score at day 1
Diazgranados et al.	2010	Single-center, double-blind, randomized, crossover, placebo-controlled, add-on	BPAD I or II depression without psychotic features	Crossover	*N*=18 Mean age of 46.9 years, 6 men and 12 women, 8 with BPAD I and 10 with BPAD II	Single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) administered over 40 min	13 subjects completed both phases of the study. 3 dropped out in the first phase and 1 after the second phase.	MADRS score at day 1
Murrough et al.	2013	Two-site, double-blind, randomized, active placebo-controlled, parallel-arm	MDD (treatment-resistant)	*N*=25 Mean age of 42.7 years, 66% male, 44% female	*N*=47 Mean age of 46.9 years, 45% male, 55% female	Single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) administered over 40 min	67 subjects completed the full 7-day study. One subject dropped out before receiving any medication; the others after.	MADRS score at day 1
Sos et al.	2013	Single-center, double-blind, randomized, crossover, placebo-controlled	MDD (single or recurrent)	Crossover	*N*=27 total Ketamine first: *N*=11 Mean age of 42.2 years, 5 men and 6 women Placebo first: *N*=19 Mean age of 44.6 years, 10 men and 9 women	Ketamine was administered in a loading dose of 0.27 mg/kg over 10 min followed by maintenance infusion of 0.27 mg/kg over 20 min	22 subjects completed the study, with 5 dropping out prior to all of the follow-up visits. Data were carried forward for 27 patients in each group.	MADRS score at day 1

MDE, major depressive episode.

Risk of bias across studies

The five studies included in the quantitative meta-analysis had low–moderate risk of bias. The Zarate et al. (2012), Diazgranados et al., Murrough et al. and Sos et al. studies used the raw MADRS score at 1 day and 7 days postintervention for their outcome, while the Zarate et al. (2006) study used the HDRS score at 1 day and 7 days postintervention.

Synthesis of results

The meta-analysis of the five studies that examined the effects of ketamine on MDD and BPAD showed that ketamine significantly reduced depressive symptoms at both 1 and 7 days postinfusion (Figs. 2 and 3). At day 1 postinfusion, the calculated effect size was large and statistically significant with an overall SMD of 1.01 (95% CI 0.69–1.34) ($P<.001$). Each individual study had a large effect size that showed ketamine's positive effect on depression, with the Murrough et al. study the most heavily weighted due to its large number of subjects. All studies showed statistically significant effects. The antidepressant effects of ketamine were sustained 7 days postinfusion and were medium and statistically significant with an overall SMD of 0.41 (95% CI 0.14–0.68) ($P=.003$). We conducted a sensitivity analysis of our study results stratified by the studies that focused on MDD and those that focused on BPAD. For day 1 outcomes, the two studies that included BPAD participants had an effect size of 1.29 (0.75–1.89) ($P<.001$; large effect), while the three studies that included MDD participants had an effect size of 0.90 (0.46-1.35) ($P<.001$; large effect). No heterogeneity was found. For day 7 outcomes, the results were slightly more nuanced. The two studies that included BPAD participants had an effect size of 0.28 (CI −0.21 to 0.76) ($P<.26$; no effect), while the three studies that included MDD participants had an effect size of 0.46 (CI 0.14–0.78) ($P=.004$; medium effect). No heterogeneity was found. This may suggest that there may be less of an effect at 7 days for those with BPAD depression. However, given that there are only two studies within the BPAD category and given that the effect size point estimates for both these studies suggest a small effect [Zarate 2012: 0.25 (CI −0.46 to 0.97) and Diazgranados: 0.30 (CI −0.36 to 0.96)], it may be premature to conclude that any real difference exists.

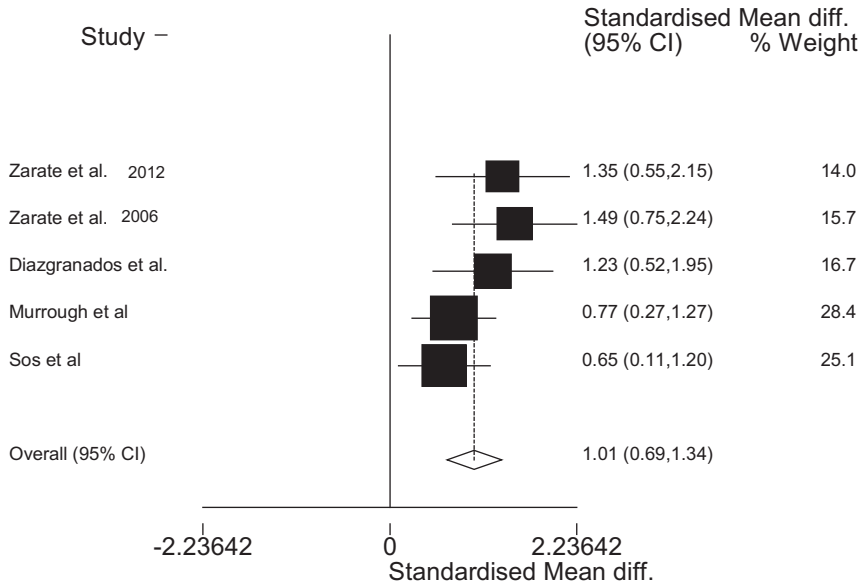

Fig. 2. Forest plot at day 1 postinfusion.

Heterogeneity of the studies at day 1 was assessed statistically and found to be low and not statistically significant ($I^2 = 30.0\%$, $\chi^2 = 5.2$, d.f. = 4, $P = .27$). The between-study variance in the random-effects meta-analysis similarly shows low heterogeneity ($\tau^2 = 0.034$). A funnel plot was created for this meta-analysis and showed no publication bias. Heterogeneity of the studies at day 7 was not statistically significant ($I^2 = 0\%$, $\chi^2 = 1.26$, d.f. = 4, $P = .87$). The between-study variance in the random-effects meta-analysis similarly shows low heterogeneity ($\tau^2 < 0.0001$).

Discussion

The results of this meta-analysis signify that ketamine has a significant impact on depressive symptoms in subjects with MDD and BPAD at 1 day and 7 days postinfusion. Although these findings are consistent with previous results in suggesting that ketamine treatment is associated with a large and significant antidepressant effect at 24 h postinfusion, the results of this meta-analysis may be: (a) more reliable, as our results used data provided directly from study authors of manuscripts reviewed for this meta-analysis; (b) more interpretable and accurate, as the results are presented using effect sizes rather than ORs which are known to overestimate treatment effect; and (c) more specific, as the results pertain to intravenous administration rather than combining both intravenous and intranasal administration. Our study also found that the positive effects of ketamine were sustained for a period of 7 days. In contrast to a previously reported meta-analysis, our study found that the antidepressant effect of ketamine was reduced to a medium effect size at 7 days postinfusion rather than maintaining a large effect. This is consistent with ketamine's pharmacokinetic properties, as ketamine has a short half-life of 3 h and is extensively hepatically metabolized; thus, its treatment effect would logically be reduced over time. Additionally, ketamine's persistent antidepressant effects beyond its half-life may reflect how it activates different signaling cascades, including the AMPA/kinase receptor system [36].

Several recent meta-analyses have also shown ketamine to be effective in managing depressive symptoms [33–35]. However, these meta-

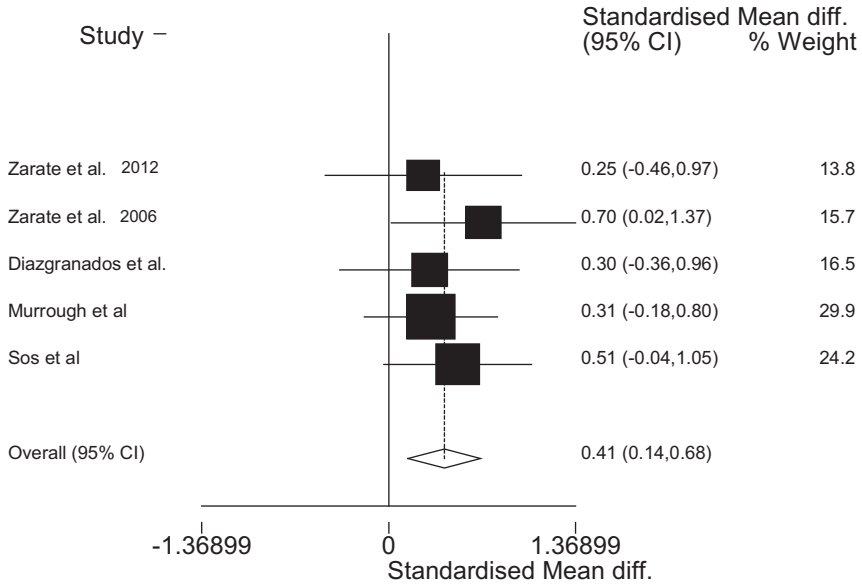

Fig. 3. Forest plot at day 7 postinfusion.

analyses included studies involving patients who underwent ECT [37], surgery [38] or administration of intranasal ketamine [39,40], as well as having issues with single-blind conditions [39] and lacking a placebo control [37]. Due to concerns of potential confounding from surgical factors, ECT's antidepressive effects, variable ketamine bioavailability [22] as well as high risk of bias from a single-blind design, these trials were not included in this meta-analysis. Many studies have illustrated ketamine's nonsustained antidepressant effect, with primary outcomes often measured at 1 day postinfusion and relapses noted at 19 days after repeated infusions [41]. Our data may suggest that weekly dosing of intravenous ketamine may make sense, yet it may be burdensome. Logistically, given the chronic nature of depressive symptoms, an oral formulation would be preferable and has been shown to be an effective add-on to standard antidepressants in a few case studies [42]. Unfortunately, oral ketamine shares the difficulties of abuse potential, no randomized controlled trials as well as dosing concerns given the lower bioavailability (estimated at 20%) [42]. Other strategies using oral adjunctive agents and repeated intravenous dosing have not been successful thus far [43–45]. Finally, it is important to note that only a small proportion of patients treated with a single dose of intravenous ketamine can maintain their response for several weeks, but reasons for this sustained treatment response are not well understood.

Minimal adverse events were noted throughout all studies. Most seriously, psychotomimetic symptoms or transient mild elevations in blood pressure and heart rate were reported. The psychotomimetic effects were short-lived, resolving completely by 60 min postinfusion. Yet controversy persists regarding the use of ketamine given its history of abuse. In particular, its illicit use in the dance club scene as an adjunct to ecstasy's euphoric effects and growing popularity internationally are concerning for its potential for misuse [46,47]. Observations of ketamine use demonstrate its large safety margin with a low risk of death by acute toxicity, though there are risks of ulcerative cystitis, abdominal cramping and short-term memory impairment with chronic use [48]. Additionally, the appropriate clinical context for ketamine use remains unclear. Ketamine may have a specific and unique role in acute suicidality in an emergency room setting and as an anesthetic prior to ECT therapy, where trials are currently under way to investigate ketamine's efficacy [23,49,50]. In general, most reviews encourage caution and further study before administering ketamine outside of controlled hospital settings.

The meta-analysis included studies of individuals with MDD and BPAD in order to better elucidate ketamine's role in affective disorders. Several studies differ on whether ketamine has superior efficacy for bipolar versus unipolar depression. Our data suggest that, on day 1, ketamine treatment for either BPAD or MDD has a significant and large effect. However, our data suggest that, on day 7, ketamine still has a small to medium effect but that this effect may be greater among those with MDD. Clearly, future studies will help further our understanding regarding day 7 treatment effects. Our study does support a recent letter by Fond et al. that indicates that ketamine is an effective treatment for both types of depression and that further studies designed to compare the two conditions are required [51]. One limitation is that this meta-analysis includes a small number of studies, running the risk of publication bias.

The association between ketamine's psychotomimetic and antidepressant effects was inconsistent, although blinding of the intervention may have been affected by the psychotomimetic effects. Only the Murrough et al. study employed an active control (midazolam) and showed that ketamine had a significantly higher antidepressant effect compared to control, which was consistent with the other studies that employed a saline control.

The promising results of ketamine have stimulated future research into characterizing predictors of ketamine response, finding specific usages for ketamine and investigating other glutamatergic compounds. Patient characteristics that predict ketamine response are poorly understood, though there may be a response correlation with specific patterns of neural activity, family histories of alcoholism and not previously failing ECT [52–55]. The success of ketamine as a treatment for depression has instigated numerous investigations into similar compounds. Studies of approved medications have shown some promising results from amantadine [56–58]. Recent drug development has focused on subunit-selective NMDA receptor antagonists because the psychotomimetic side effects are reduced compared to ketamine. CP-101,606 (an NR2B subunit-selective NMDA receptor antagonist) has been found be well tolerated and more effective than placebo when given as an adjunct to paroxetine treatment [59]. Similarly, MK-0657, another NR2B subunit-selective NMDA receptor antagonist that is dosed orally, was found to have significant antidepressant effects without any dissociative side effects during a placebo-controlled crossover pilot study [60]. The reduction of depression symptoms was seen with the BDI and HDRS, but not on the MADRS, which may be related to the varying sensitivities of these scales. Both compounds warrant further larger-scale trials. Four other glutamatergic agents are currently in Phase I and II trials for treatment of MDD [61]. Other work has focused on better understanding ketamine's mechanism of action and identifying mediators of its antidepressant cascade as potential drug targets.

In general, the findings of this meta-analysis add to the existing evidence supporting ketamine as a novel treatment for depression. This has been consistently demonstrated across basic research studies, case studies and open-label trials. Compared to existing treatments for depression, ketamine has been shown to have a high response rate and rapid effect. This meta-analysis confirms and strengthens these results with multiple double-blinded, randomized, placebo-controlled trials and an overall large effect size.

References

[1] Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry 2005;62(6):617–27. http://dx.doi.org/10.1001/archpsyc.62.6.617.

[2] World Health Organization. The global burden of disease: 2004 update; 2008.

[3] Collins PY, Patel V, Joestl SS, et al. Grand challenges in global mental health. Nature 2011;475(7354):27–30. http://dx.doi.org/10.1038/475027a.

[4] Bloom DE, Cafiero ET, Jané-Llopis E. The global economic burden of noncommunicable diseases. Geneva: World Economic Forum; 2011.

[5] Chisholm D, Diehr P, Knapp M, et al. Depression status, medical comorbidity and resource costs. evidence from an international study of major depression in primary care (LIDO). Br J Psychiatry 2003;183:121–31.

[6] Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006;354(12):1243–52 [doi: 354/12/1243 [pii]].

[7] Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry 2008;165(3):342–51. http://dx.doi.org/10.1176/appi.ajp.2007.06111868 [doi].

[8] Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163(11):1905–17 [doi: 163/11/1905 [pii]].

[9] Layer RT, Popik P, Olds T, Skolnick P. Antidepressant-like actions of the polyamine site NMDA antagonist, eliprodil (SL-82.0715). Pharmacol Biochem Behav 1995;52(3):621–7 [doi: 0091-3057(95)00155-P [pii]].

[10] Meloni D, Gambarana C, De Montis MG, Dal Pra P, Taddei I, Tagliamonte A. Dizocilpine antagonizes the effect of chronic imipramine on learned helplessness in rats. Pharmacol Biochem Behav 1993;46(2):423–6.

[11] Moryl E, Danysz W, Quack G. Potential antidepressive properties of amantadine, memantine and bifemelane. Pharmacol Toxicol 1993;72(6):394–7.

[12] Papp M, Moryl E. Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. Eur J Pharmacol 1994;263(1-2):1–7 [doi: 0014-2999(94)90516-9 [pii]].

[13] Przegalinski E, Tatarczynska E, Deren-Wesolek A, Chojnacka-Wojcik E. Antidepressant-like effects of a partial agonist at strychnine-insensitive glycine receptors and a competitive NMDA receptor antagonist. Neuropharmacology 1997;36(1):31–7 [doi: S0028390896001578 [pii]].

[14] Trullas R, Skolnick P. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur J Pharmacol 1990;185(1):1–10 doi: 0014-2999(90)90204-J [pii].

[15] Sanacora G, Gueorguieva R, Epperson CN, et al. Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. Arch Gen Psychiatry 2004;61(7):705–13. http://dx.doi.org/10.1001/archpsyc.61.7.705 [doi].

[16] Sanacora G, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nat Rev Drug Discov 2008;7(5):426–37. http://dx.doi.org/10.1038/nrd2462 [doi].

[17] McCullumsmith RE, Kristiansen LV, Beneyto M, Scarr E, Dean B, Meador-Woodruff JH. Decreased NR1, NR2A, and SAP102 transcript expression in the hippocampus in bipolar disorder. Brain Res 2007;1127(1):108–18 [doi: S0006-8993(06)02719-3 [pii]].
[18] Paul IA, Nowak G, Layer RT, Popik P, Skolnick P. Adaptation of the *N*-methyl-D-aspartate receptor complex following chronic antidepressant treatments. J Pharmacol Exp Ther 1994;269(1):95–102.
[19] Boyer PA, Skolnick P, Fossom LH. Chronic administration of imipramine and citalopram alters the expression of NMDA receptor subunit mRNAs in mouse brain. A quantitative in situ hybridization study. J Mol Neurosci 1998;10(3):219–33. http://dx.doi.org/10.1007/BF02761776 [doi].
[20] Nowak G, Ordway GA, Paul IA. Alterations in the *N*-methyl-D-aspartate (NMDA) receptor complex in the frontal cortex of suicide victims. Brain Res 1995;675(1–2):157–64.
[21] Holemans S, De Paermentier F, Horton RW, Crompton MR, Katona CL, Maloteaux JM. NMDA glutamatergic receptors, labelled with [3H]MK-801, in brain samples from drug-free depressed suicides. Brain Res 1993;616(1-):138–43 [doi: 0006-8993(93)90202-X [pii]].
[22] Aan Het Rot M, Zarate Jr CA, Charney DS, Mathew SJ. Ketamine for depression: where do we go from here? Biol Psychiatry 2012;72(7):537–47. http://dx.doi.org/10.1016/j.biopsych.2012.05.003.
[23] DiazGranados N, Ibrahim LA, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an *N*-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry 2010;71(12):1605–11. http://dx.doi.org/10.4088/JCP.09m05327blu.
[24] Zarate Jr CA, Singh JB, Quiroz JA, et al. A double-blind, placebo-controlled study of memantine in the treatment of major depression. Am J Psychiatry 2006;163(1):153–5 [doi: 163/1/153 [pii]].
[25] Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry 2010;67(8):793–802. http://dx.doi.org/10.1001/archgenpsychiatry.2010.90.
[26] Zarate Jr CA, Singh JB, Carlson PJ, et al. A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006;63(8):856–64. http://dx.doi.org/10.1001/archpsyc.63.8.856.
[27] Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47(4):351–4.
[28] Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 2013;170(10):1134–42. http://dx.doi.org/10.1176/appi.ajp.2013.13030392 [doi].
[29] Sos P, Klirova M, Novak T, Kohutova B, Horacek J, Palenicek T. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. Neuro Endocrinol Lett 2013;34(4):287–93.
[30] Corazza O, Assi S, Schifano F. From "special K" to "special M": the evolution of the recreational use of ketamine and methoxetamine. CNS Neurosci Ther 2013;19(6):454–60. http://dx.doi.org/10.1111/cns.12063 [doi].
[31] Schatzberg AF. A word to the wise about ketamine. Am J Psychiatry 2014;171(3):262–4. http://dx.doi.org/10.1176/appi.ajp.2014.13101434 [doi].
[32] Kalinic N, Lai R, Somogyi A, Mitchell PB, Glue P, Loo CK. Ketamine as a new treatment for depression: a review of its efficacy and adverse effects. Aust N Z J Psychiatry 2013;47(8):710–27. http://dx.doi.org/10.1177/0004867413486842 [doi].
[33] McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med 2014:1–12 [doi: S0033291714001603 [pii]].
[34] Caddy C, Giaroli G, White TP, Shergill SS, Tracy DK. Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and meta-analysis of efficacy. Ther Adv Psychopharmacol 2014;4(2):75–99. http://dx.doi.org/10.1177/2045125313507739 [doi].
[35] Fond G, Loundou A, Rabu C, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. Psychopharmacology (Berl) 2014;231(18):3663–76. http://dx.doi.org/10.1007/s00213-014-3664-5 [doi].
[36] Walter M, Li S, Demenescu LR. Multistage drug effects of ketamine in the treatment of major depression. Eur Arch Psychiatry Clin Neurosci 2014;264(Suppl. 1):S55–65. http://dx.doi.org/10.1007/s00406-014-0535-3 [doi].
[37] Ghasemi M, Kazemi MH, Yoosefi A, et al. Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. Psychiatry Res 2014;215(2):355–61. http://dx.doi.org/10.1016/j.psychres.2013.12.008 [doi].
[38] Kudoh A, Takahira Y, Katagai H, Takazawa T. Small-dose ketamine improves the postoperative state of depressed patients. Anesth Analg 2002;95(1):114–8 [table of contents].
[39] Valentine GW, Mason GF, Gomez R, et al. The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [(1)H]-MRS. Psychiatry Res 2011;191(2):122–7. http://dx.doi.org/10.1016/j.pscychresns.2010.10.009 [doi].
[40] Lapidus KA, Levitch CF, Perez AM, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry 2014;76(12):970–6. http://dx.doi.org/10.1016/j.biopsych.2014.03.026 [doi].
[41] aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry 2010;67(2):139–45. http://dx.doi.org/10.1016/j.biopsych.2009.08.038 [doi].
[42] Paslakis G, Gilles M, Meyer-Lindenberg A, Deuschle M. Oral administration of the NMDA receptor antagonist S-ketamine as add-on therapy of depression: a case series. Pharmacopsychiatry 2010;43(1):33–5. http://dx.doi.org/10.1055/s-0029-1237375 [doi].
[43] Ibrahim L, Diazgranados N, Franco-Chaves J, et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology 2012;37(6):1526–33. http://dx.doi.org/10.1038/npp.2011.338; 10.1038/npp.2011.338.
[44] Mathew SJ, Murrough JW, aan het Rot M, Collins KA, Reich DL, Charney DS. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. Int J Neuropsychopharmacol 2010;13(1):71–82. http://dx.doi.org/10.1017/S1461145709000169.
[45] Moukaddam NJ, Hirschfeld RM. Intravenous antidepressants: a review. Depress Anxiety 2004;19(1):1–9. http://dx.doi.org/10.1002/da.10135 [doi].
[46] Dalgarno PJ, Shewan D. Illicit use of ketamine in scotland. J Psychoactive Drugs 1996;28(2):191–9. http://dx.doi.org/10.1080/02791072.1996.10524391 [doi].
[47] McCambridge J, Winstock A, Hunt N, Mitcheson L. 5-year trends in use of hallucinogens and other adjunct drugs among UK dance drug users. Eur Addict Res 2007;13(1):57–64 [doi: 000095816 [pii]].
[48] Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: a new clinical entity. Urology 2007;69(5):810–2 [doi: S0090-4295(07)00101-X [pii]].
[49] Price RB, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry 2009;66(5):522–6. http://dx.doi.org/10.1016/j.biopsych.2009.04.029 [doi].
[50] Zarate Jr CA, Brutsche N, Laje G, et al. Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. Biol Psychiatry 2012;72(4):331–8. http://dx.doi.org/10.1016/j.biopsych.2012.03.004 [doi].
[51] Fond G, Boyer L. Ketamine's effectiveness in unipolar versus bipolar depression. Psychopharmacology (Berl) 2014;231(22):4417–8. http://dx.doi.org/10.1007/s00213-014-3773-1 [doi].
[52] Salvadore G, van der Veen JW, Zhang Y, et al. An investigation of amino-acid neurotransmitters as potential predictors of clinical improvement to ketamine in depression. Int J Neuropsychopharmacol 2012;15(8):1063–72. http://dx.doi.org/10.1017/S1461145711001593 [doi].
[53] Salvadore G, Cornwell BR, Sambataro F, et al. Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. Neuropsychopharmacology 2010;35(7):1415–22. http://dx.doi.org/10.1038/npp.2010.24 [doi].
[54] Salvadore G, Cornwell BR, Colon-Rosario V, et al. Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. Biol Psychiatry 2009;65(4):289–95. http://dx.doi.org/10.1016/j.biopsych.2008.08.014 [doi].
[55] Phelps LE, Brutsche N, Moral JR, Luckenbaugh DA, Manji HK, Zarate Jr CA. Family history of alcohol dependence and initial antidepressant response to an *N*-methyl-D-aspartate antagonist. Biol Psychiatry 2009;65(2):181–4. http://dx.doi.org/10.1016/j.biopsych.2008.09.029.
[56] Dietrich DE, Bode L, Spannhuth CW, et al. Amantadine in depressive patients with borna disease virus (BDV) infection: an open trial. Bipolar Disord 2000;2(1):65–70.
[57] Ferszt R, Severus E, Bode L, et al. Activated borna disease virus in affective disorders. Pharmacopsychiatry 1999;32(3):93–8. http://dx.doi.org/10.1055/s-2007-979201 [doi].
[58] Ferszt R, Kuhl KP, Bode L, et al. Amantadine revisited: an open trial of amantadinesulfate treatment in chronically depressed patients with borna disease virus infection. Pharmacopsychiatry 1999;32(4):142–7. http://dx.doi.org/10.1055/s-2007-979220 [doi].
[59] Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective *N*-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. J Clin Psychopharmacol 2008;28(6):631–7. http://dx.doi.org/10.1097/JCP.0b013e31818a6cea [doi].
[60] Ibrahim L, Diaz Granados N, Jolkovsky L, et al. A randomized, placebo-controlled, crossover pilot trial of the oral selective NR2B antagonist MK-0657 in patients with treatment-resistant major depressive disorder. J Clin Psychopharmacol 2012;32(4):551–7. http://dx.doi.org/10.1097/JCP.0b013e31825d70d6 [doi].
[61] Murrough JW, Charney DS. Is there anything really novel on the antidepressant horizon? Curr Psychiatry Reps 2012;14(6):643–9. http://dx.doi.org/10.1007/s11920-012-0321-8 [doi].

References to studies included in this meta-analysis

[62] Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47(4):351–4.
[63] Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry 2010;67(8):793–802. http://dx.doi.org/10.1001/archgenpsychiatry.2010.90; 10.1001/archgenpsychiatry.2010.90.
[64] Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. Am J Psychiatry 2013;170(10):1134–42. http://dx.doi.org/10.1176/appi.ajp.2013.13030392 [doi].
[65] Sos P, Klirova M, Novak T, Kohutova B, Horacek J, Palenicek T. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. Neuro Endocrinol Lett 2013;34(4):287–93.
[66] Zarate Jr CA, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006;63(8):856–64. http://dx.doi.org/10.1001/archpsyc.63.8.856.
[67] Zarate Jr CA, Brutsche NE, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: A randomized controlled add-on trial. Biol Psychiatry 2012;71(11):939–46. http://dx.doi.org/10.1016/j.biopsych.2011.12.010; 10.1016/j.biopsych.2011.12.010.