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**Meta-analysis of short- and mid-term efficacy of ketamine
in unipolar and bipolar depression**

Bruno Romeo,^a Walid Choucha,^a Philippe Fossati,^{a,b} Jean-Yves Rotge.^{a,b}

^aAP-HP, Pitié-Salpêtrière Hospital, Department of Psychiatry, F-75013 Paris, France; ^bInserm U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06, UMR S 1127, Institut du Cerveau et de la Moelle, ICM, Social and Affective Neuroscience (SAN) Laboratory, F-75013 Paris, France.

Corresponding author: Jean-Yves Rotge, Service de Psychiatrie Adulte, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France. Tel: +33142160000. Email: jeanyves.rotge@mac.com

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**Meta-analysis of short- and mid-term efficacy of ketamine
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Abstract

Among treatments currently assessed in major depression, ketamine, has been proposed of great interest, especially because of its very rapid action. However, the time-course of the antidepressive action of ketamine remained unclear. In the present meta-analysis, we provided a clear and objective view regarding the putative antidepressive effect of ketamine and its time-course. We searched the MEDLINE and PsycINFO databases through December 2013, without limits on year of publication, using the key words ketamine and synonyms for mood disorder or episode. Six randomized, double-blind and placebo-controlled trials of ketamine in major depression (n=103 patients) were thus identified. Authors were contacted and they all provided original data necessary for this meta-analysis. Standardized mean differences (SMD) were calculated between the depression scores in ketamine and placebo groups at days 1, 2, 3-4, 7 and 14. Ketamine showed an overall antidepressive efficacy from day 1 to day 7. However, the maintenance of its efficacy over time failed to reach significance in bipolar depression after day 3-4. Significant SMDs were

not explained by demographic or clinical characteristics of included samples. The present meta-analysis provides a high level of evidence that ketamine has a rapid antidepressive action during one week, especially in unipolar disorder.

Keywords: Unipolar disorder; Depression; Glutamate; Ketamine; Meta-analysis; Mood disorder.

1. Introduction

Major depression is highly frequent and disabling with important functional and health consequences, possibly with vital prognosis (Kessler et al., 2003; Collins et al., 2011). Pharmacological treatments currently available contribute to largely improve the depressive symptomatology, mainly by modulating the monoamine systems (Murrough and Charney, 2012). However, the improvement of depressive symptomatology may occur several weeks after the pharmacological administration. This situation makes necessary research in the field, especially to assess drugs capable of modulating systems other than monoamine systems with the aim to shorten the time for obtaining the improvement of depressive symptoms.

These last years, ketamine, a N-methyl-D-aspartate (NMDA) glutamate receptor antagonist which may affect the glutamatergic system, has been proposed of major interest in depression since many reports showed a marked antidepressive effect in the very hours following the administration

of a single dose (Stahl, 2013; Ghasemi et al., 2014; Dutta et al., 2015). However, these reports included small clinical samples with a great clinical and medical heterogeneity. For example, some studies assessed the ketamine's effects in unipolar samples, others in bipolar samples; some studies reported the ketamine's effects in the hour, others in the 14 days following its administration (Berman et al., 2000; Zarate et al., 2006; Diazgranados et al., 2010; Zarate et al., 2012; Sos et al., 2013; Lapidus et al., 2014). Regarding this heterogeneous literature and its potential clinical impact, a quantitative analysis of the putative antidepressive effect of ketamine and its time-course is now required. Furthermore, assessing whether the clinical heterogeneity concerning the age, gender, duration of illness, episode duration or comorbidities, as observed across ketamine studies, may contribute, or not, to explain ketamine's efficacy in depression is a question of importance in the possible use of ketamine in clinical practice.

This year, three meta-analyses on the antidepressive effects of ketamine were published (Caddy et al., 2014; Fond et al., 2014; McGirr et al., 2015). However, two of them failed to assess the time-course of ketamine's effects, which were only assessed for the first day of treatment (Caddy et al., 2014; Fond et al., 2014). The third one assessed the ketamine's effects on the first week following its administration, but analyses were not conducted on depression scores, but on remission rates (McGirr et al., 2015). When considering analyses based on depression scores, results were only given for the first day of treatment (McGirr et al., 2015). To our knowledge, these remarkable meta-analyses did not benefit from the seminal data allowing to assess the time-course of the antidepressive effects of ketamine and to properly assess the impact of the clinical heterogeneity across studies on ketamine's effects. Despite these recent meta-analyses, a quantitative analysis has yet to be published that

addresses these issues in order to provide a clear and objective view regarding the putative antidepressive effect of ketamine and its time-course. The aim of the present meta-analysis was to determine ketamine's efficacy in depression at day 1, day 2, day 3-4, day 7 and day 14 in treatment-resistant depression. Furthermore, we explored the influence of demographic and clinical characteristics on the meta-analysis effect sizes.

2. Methods

2.1. Data sources and study selection process

We searched the MEDLINE and PsycINFO databases through December 2013, without limits on year of publication, using the key words ketamine and any of the following terms: depression, major depressive disorder, melancholia, bipolar disorder, antidepressants, resistant depression, refractory depression, depressive disorder, major depressive episode, mood disorder, bipolar depression, affective disorder, psychotic disorder and depressive episode. Studies were included if (i) they were published in English in a peer-reviewed journal, (ii) they were randomized, double-blind and placebo-controlled trials of ketamine, (iii) they included patients with the diagnosis of major depressive episode based on DSM, III, IV or V criteria. Studies that did not fulfill all these three criteria were systematically excluded from analyses. In particular, trials controlled by an active drug, such as midazolam (McGirr et al., 2015; Murrough et al., 2013), or ECT studies (Fond et al., 2014) were not included in the present meta-analysis. In order to obtain additional data, an email alert was created after December 2013 in MEDLINE with the

same keywords for detecting putative publications of interest. Finally, a search of unpublished data was conducted by emails to all pharmaceutical laboratories developing psychotropics. Thus, database searches identified 5 trials (Berman et al., 2000; Zarate et al., 2006; Diazgranados et al., 2010; Zarate et al., 2012; Sos et al., 2013), the email alert identified an additional one (Lapidus et al., 2014) and the search from pharmaceutical laboratories retrieved no unpublished data (Figure 1). Study selection was performed by one author (BR) and verified by another (JYR).

2.2. Data extraction

All corresponding authors of each included trial were systematically contacted by email in order to improve the collection of data. All of the teams involved in the authorship gave us access to their seminal data (see Acknowledgments). For each study, we thus obtained means and standard deviations (SD) of all depression scores, as measured with the Hamilton Depression Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI). Authors also gave us Scores of Brief Psychiatric Rating Scale (BPRS) and all demographic data missing or unclear in the seminal publication. Articles written by a given research group were carefully scrutinized to ensure the absence of redundancy among populations included in trials.

A set of clinical variables was defined for the meta-regression analysis. We extracted the means and SD of age (variable “age”), the percentages of females (variable “sex”), the means and SD of years of illness (variable “duration of illness”), the means and SD of the duration of the current episode (variable “episode duration”), the percentages of comorbid anxiety disorder (variable “anxiety disorder”), the percentages of substance use disorder (variable “substance disorder”) and alcohol use disorder (variable “alcohol disorder”). Data extraction was performed by one author (BR) and verified by another (JYR).

2.3. Data analyses

Data analyses were performed using RevMan, version 5.3 (Copenhagen, Denmark; the Nordic Cochrane Centre, Cochrane Collaboration). Effect sizes consisted in the standardized mean differences (SMD) between depression scores in the ketamine and placebo groups at baseline, day 1, day 2, day 3 & 4, day 7 and day 14. According to Cohen’s method (Cohen 1988) SMD was calculated as the difference between group means, divided by the pooled standards deviation. SMDs were calculated for each study at each time and were then combined to estimate the overall effect size at each time (baseline, day-1, -2, -3 & 4, -7, -14). All analyses were performed with a random-effects model, which considers both between-study and within-study variability (DerSimonian and Laird, 1986). An effect size was considered significant when the 95% confidence interval (95% CI) excluded 0 and when the p value was less than .05.

The study heterogeneity was estimated with the Q statistic which was calculated for all analyses and considered significant when $p < .1$. When a significant level of heterogeneity was reached, the I^2 index, an estimate of the total variation across included studies that was due to heterogeneity rather than chance, was determined by the equation $I^2 = [(Q - df)/Q] * 100\%$ (Higgins et al., 2003). I^2 values of 25, 50, and 75 were indicative of a mild, moderate, and high heterogeneity between trials, respectively. Moreover, to ensure that the overall results were not influenced by one single study, leave-one-out sensitivity analyses performed by repeating the analyses with the consecutive exclusion of each study were carried out for each analysis. Finally, we conducted some more specific secondary analyses regarding the primary diagnoses and the route of administration of ketamine. Indeed, specific analyses were conducted with studies including (i) subjects with a diagnosis of bipolar disorder or (ii) subjects with a diagnosis of recurrent unipolar depression, and studies based on (i) intravenous infusion or (ii) intranasal administration of ketamine.

Funnel plots, plotting the standard error of each SMD against the SMD calculated of each included study, were drawn when at least five individual studies contributed to an overall result and their asymmetry was analyzed to assess the possible influence of publication and location biases (Green and Higgins, 2006).

Finally, we conducted meta-regression analyses based on simple linear regression models for assessing the influence of clinical heterogeneity of study populations on meta-analysis effect sizes. Regression analyses were performed only when SMDs or heterogeneity were significant.

3. Results

The article selection process was depicted in Figure 1. Six double blind, randomized, placebo-controlled, cross-over trials fulfilled our inclusion criteria and were included in the present meta-analysis (Berman et al., 2000; Zarate et al., 2006; Diazgranados et al., 2010; Zarate et al., 2012; Sos et al., 2013; Lapidus et al., 2014). Main characteristics of each included study and their primary results were described in Table 1. A total of 110 patients with a major depressive episode were included in the six selected studies, as follows: 12 suffered from a first depressive episode, 64 from recurrent depressive disorder and 34 from bipolar depression. Among these 110 patients, 103 patients were included in the final analyses described in the selected studies and were thus included in the present meta-analysis. With the exception of the study by Berman et al. (2000) (n = 8 patients), all others studies included patients with resistant major depressive episode. Specifically, patients could be included when (i) an adequate antidepressant trial and a prospective trial of a mood stabilizer (either lithium or valproate) failed (Diazgranados et al., 2010; Zarate et al., 2012), (ii) an adequate antidepressant trial failed (Lapidus et al., 2014); (iii) two adequate antidepressant trials failed (Zarate et al., 2006), or (iv) patients were on a stable dose of antidepressant medication for a minimum of three weeks with a MADRS score > 20 (Sos et al., 2013).

Individual SMDs for each included study at each period of measurements were described in details in Supplementary Material. Overall SMDs were calculated at baseline (n = 6 studies; test for overall effect: SMD = 0.06, 95% CI: -0.22 to 0.33, p = 0.67; test for heterogeneity: $\chi^2 = 3.12$, df

= 5, $p = 0.05$, $I^2 = 0\%$), at day 1 ($n = 6$ studies; test for overall effect: $SMD = -1$, 95% CI: -1.3 to -0.71, $p < 0.00001$; test for heterogeneity: $\chi^2 = 4.3$, $df = 5$, $p < 0.51$, $I^2 = 0\%$), at day 2 ($n = 5$ studies; test for overall effect: $SMD = -1.03$, 95% CI: -1.45 to -0.6, $p < 0.00001$; test for heterogeneity: $\chi^2 = 5.98$, $df = 4$, $p = 0.2$, $I^2 = 33\%$), at day 3-4 ($n = 6$ studies; test for overall effect: $SMD = -0.77$, 95% CI: -1.1 to -0.44, $p < 0.00001$; test for heterogeneity: $\chi^2 = 6.43$, $df = 5$, $p = 0.27$, $I^2 = 22\%$), at day 7 ($n = 5$ studies; test for overall effect: $SMD = -0.36$, 95% CI: -0.65 to -0.08, $p = 0.01$; test for heterogeneity: $\chi^2 = 1.43$, $df = 4$, $p = .84$, $I^2 = 0\%$) and at day 14 ($n = 2$ studies; test for overall effect: $SMD = -0.38$, 95%CI: -0.87 to 0.11, $p = 0.13$; test for heterogeneity: $\chi^2 = 0.01$, $df = 1$, $p = 0.93$, $I^2 = 0\%$), showing a significant antidepressive action of ketamine from day 1 to day 7 in comparison with placebo. The time course of SMDs indicating the ketamine efficacy on depression was illustrated in Figure 2A. Finally, the mean percentages of improvement, weighted for sample size, from baseline depression scores were calculated for both ketamine and placebo groups and showed a major efficacy in ketamine group at day 1 (-41.17% vs -6.06%), at day 2 (-41.24% vs -5.94%), at day 3-4 (-34.24% vs -7.03%), at day 7 (-20.04% vs -7.18%) and at day 14 (-15.38% vs -5.87%) (Figure 3A).

In order to make sure that the route of administration did not affect our results, analyses were repeated by excluding the intranasal data and no marked difference was observed neither at day 1 ($n = 5$ studies; test for overall effect: $SMD = -1.04$, 95% CI: -1.37 to -0.71, $p < 0.00001$; test for heterogeneity: $\chi^2 = 4.11$, $df = 4$, $p = 0.39$, $I^2 = 3\%$), day 2 ($n = 4$ studies; test for overall effect: $SMD = -1.24$, 95% CI: -1.64 to -0.83, $p < 0.00001$; test for heterogeneity: $\chi^2 = 2.11$, $df = 3$, $p = 0.55$, $I^2 = 0\%$), day 3-4 ($n = 5$ studies; test for overall effect: $SMD = -0.87$, 95% CI: -1.19 to -0.55, p

< 0.00001; test for heterogeneity: $\chi^2 = 3.56$, $df = 4$, $p = 0.47$, $I^2 = 0\%$), or at day 7 ($n = 4$ studies; test for overall effect: $SMD = -0.42$, 95% CI: -0.74 to -0.11, $p = 0.009$; test for heterogeneity: $\chi^2 = 0.71$, $df = 3$, $p = 0.87$, $I^2 = 0\%$).

In order to assess whether ketamine's efficacy may differ in bipolar or unipolar disorders, analyses were repeated by including studies with patients suffering from bipolar depression and studies with patients suffering from unipolar depression. In the study by Berman et al. (2000), 1 patient with bipolar disorder and 8 patients with recurrent depressive disorder were included; therefore, the clinical sample was considered as patients with unipolar depression. The efficacy of ketamine from day 1 to day 7 was not markedly affected when including only patients with unipolar disorder. However, SMDs when including only bipolar disorder excluded 0 at day 1, day 2, day 3-4 but the statistical significance was lost for all other measures, i.e. days 7 and day 14 (Figure 2B). Details of these analyses were provided in Supplementary Material. Finally, the mean percentages of improvement, weighted for sample size, from baseline depression scores were calculated in the ketamine group for both unipolar and bipolar depression. Unipolar group demonstrated a greater ketamine's efficacy as compared with the bipolar group at day 1 (-41.25% vs -40.99%), at day 2 (-41.74% vs -40.58%), at day 3-4 (-35.57% vs -31.42%), and at day 7 (-22.06% vs -16.18%) (Figure 3B).

Leave-one-out sensitivity analyses showed no marked difference after the exclusion of each single study, showing that the overall results were not driven by one study for day 1, day 2, day 3-4, and day 14. However, when excluding the data from Sos et al. (2013) or from Zarate et al. (2006) the significance of SMD at day 7 was lost. Meta-regression models were used to explore whether some clinical variables (age, sex,

alcohol abuse, substance abuse, anxiety disorder, lifetime antidepressant medication, and duration of current episode and illness) may contribute to significant SMDs or heterogeneity. No significant relationship was found (all $p > 0.05$).

No serious events occurred during the studies. The most commonly reported adverse effects were transitory dissociation, psychotic symptoms, confusion, mild increase in blood pressure, headache or anxiety. These adverse effects usually declined in the 80 min following ketamine's administration. The positive psychotic symptoms were evaluated with the Brief Psychiatric Rating Scale (BPRS) in the six studies (Berman et al., 2000; Zarate et al., 2006; Diazgranados et al., 2010; Zarate et al., 2012; Sos et al., 2013; Lapidus et al., 2014). At baseline, no significant difference was found between ketamine and placebo ($n = 6$ studies; test for overall effect: SMD = 0.13, 95% CI: -0.14 to 0.40, $p = 0.35$; test for heterogeneity: $\chi^2 = 0.62$, $df = 5$, $p = 0.99$, $I^2 = 0\%$). At 30-40 min, BPRS scores were higher with ketamine in comparison with placebo ($n = 6$ studies; test for overall effect: SMD = 1.08, 95% CI: 0.62 to 1.55, $p < 0.00001$; test for heterogeneity: $\chi^2 = 11.27$, $df = 5$, $p = 0.05$, $I^2 = 56\%$), but no more difference was observed at 80 min ($n = 4$ studies; test for overall effect: SMD = 0.06, 95% CI: -0.37 to 0.49, $p = 0.78$; test for heterogeneity: $\chi^2 = 3.97$, $df = 3$, $p = 0.26$, $I^2 = 25\%$).

4. Discussion

This meta-analysis, based on the primary data obtained from authors of seminal studies, showed that ketamine was effective, as compared with placebo, in treatment-resistant major depressive episode and that this efficacy was significant since the first day and persisted during one week. Ketamine was also relatively safe and possible induced-positive symptoms tend to disappear in the minutes following its administration. Furthermore, the present results suggested that ketamine may be particularly useful in unipolar disorder, whereas the maintenance of its efficacy in bipolar depression failed to reach significance after 4 days. Finally, demographic and clinical characteristics on the included samples did not explain the time course of ketamine's efficacy.

Our results showing that the ant glutamatergic drug, ketamine, was rapidly effective in major depression were in accordance with the involvement of the glutamatergic system in the pathophysiology of the disorder, as demonstrated by several brain imaging, genetic or post-mortem studies (Manji et al., 2003; Sanacora et al., 2008; Skolnick et al., 2009). The blockade of N-methyl-D-aspartate receptors (NMDA) by ketamine may contribute to antidepressive effects by different mechanisms, recently described by Krystal et al. (2013). Briefly, ketamine might rapidly increase synaptic glutamate release, which may contribute to rapidly increase synaptic connections in the prefrontal cortex (Krystal et al., 2013; Duman, 2014). Furthermore, by blocking extrasynaptic NMDA receptors, ketamine could enable the regrowth of dendritic spines by relieving inhibition of BDNF synthesis (Krystal et al., 2013). Furthermore, Chandley et al. (2014) found a higher expression levels of the NMDA receptor genes in noradrenergic neurons within the locus coeruleus in patients with major depression, suggesting that glutamate-norepinephrine interactions might contribute to the rapid antidepressive effect of the NMDA antagonist (Ghasemi et al., 2014; Dutta et al., 2015). Resolving the

pathophysiological mechanisms of the early antidepressive effects, but also the mid-term antidepressive effects of ketamine, and their possible relationship should contribute to a better understanding of depression pathophysiology and to the development of antidepressants with a rapid, and sustained over time, effect.

One of the most striking results of the present meta-analysis was the given evidence that ketamine contributed to a rapid improvement in both unipolar and bipolar depression, but this effect was sustained over time only in unipolar depression. This observation was in accordance with a differential involvement of the glutamatergic system in both disorders. A recent meta-analysis of spectroscopy studies in bipolar and unipolar depression showed that measurements of total glutamate and glutamine in the anterior cingulate cortex could represent a biological marker differentiating both disorders (Taylor, 2014). Indeed, individuals suffering from unipolar depression had a lower level of glutamate - glutamine than healthy controls whereas people with bipolar disorder had a higher level than healthy controls, suggesting that glutamate differentially contributed to both unipolar or bipolar disorders. However, this apparent difference regarding the time-course of ketamine's effects in unipolar and bipolar depression should be interpreted cautiously. Further studies assessing which demographic or clinical characteristics, especially regarding possible differences between unipolar and bipolar depression, could predict the response to ketamine remained to be performed.

No serious side effect was found in the different included studies. The tolerability of ketamine's infusion was generally good and the majority of reported side effects were transitory. In the present meta-analysis, ketamine-induced psychotic symptoms were found significantly increased 40

min after ketamine administration, but the difference with placebo disappeared 80 min after ketamine administration. Accordingly, possible manic switch seemed to have a similar pattern. Indeed, some authors had reported an increase in manic scores at 40 min but no difference was reported at 80 min (Zarate et al., 2006; Diazgranados et al., 2010; Zarate et al., 2012). Unfortunately, these data were described in very few studies and, therefore, they were not entered in the present meta-analysis. These observations suggested that both psychotic or manic symptoms possibly induced by ketamine were transient and should spontaneously be controlled in the first two hours following drug administration. Furthermore, the present results argue that the route of administration may not affect the antidepressive effect of ketamine. Indeed, antidepressive effects from nasal administration (Lapidus et al., 2014) did not differ from those following intravenous administration (Berman et al., 2000; Zarate et al., 2006; Diazgranados et al., 2010; Zarate et al., 2012; Sos et al., 2013). This observation was in accordance with studies having reported antidepressive effects after oral (Lara et al., 2014; Irwin et al., 2013) or intramuscular (Chilukuri et al., 2014) administration of ketamine.

The main limitation of our meta-analysis was the limited number of trials and data included in the analyses. Poor available data may be responsible of poor statistical power, especially for meta-regression analyses. Indeed, these analyzes were conducted with six data points for the most. This point could explain a poor statistical power and the absence of significant relationship between demographic and clinical characteristics and ketamine's efficacy.

By using seminal data of randomized and controlled trials obtained directly from authors, the present meta-analysis provided a high level of evidence that ketamine is relatively safe and contributes to a rapid antidepressive action that persist to one week with only a single dose treatment. Our results highlight some perspectives, especially regarding the possible differential action in bipolar or unipolar depression.

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Contributors

Conception and design: BR, WC, PF, JYR; Data analysis and interpretation: BR, WC, PF, JYR; Drafting of the manuscript: BR, JYR; Revision for important intellectual content: WC, PF. All the authors approved the final version of the manuscript.

Conflict of interest: None.

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Figures and Tables

Figure 1. Article identification process of randomized, double-blind and placebo-controlled trials of ketamine in major depression.

Figure 2. Time-course of overall standardized mean differences (SMD) between ketamine and placebo in major depression (A), and in unipolar (white) and bipolar (grey) depression (B).

Figure 3. The evolution of the mean percentages of improvement, weighted for sample size, from baseline depression scores. Black diamond corresponded to the placebo group, grey diamond to the ketamine group. Clear grey corresponded to unipolar depression and deep grey to bipolar depression. Error bars represented SEM.

Table 1. Included Ketamine trials articles

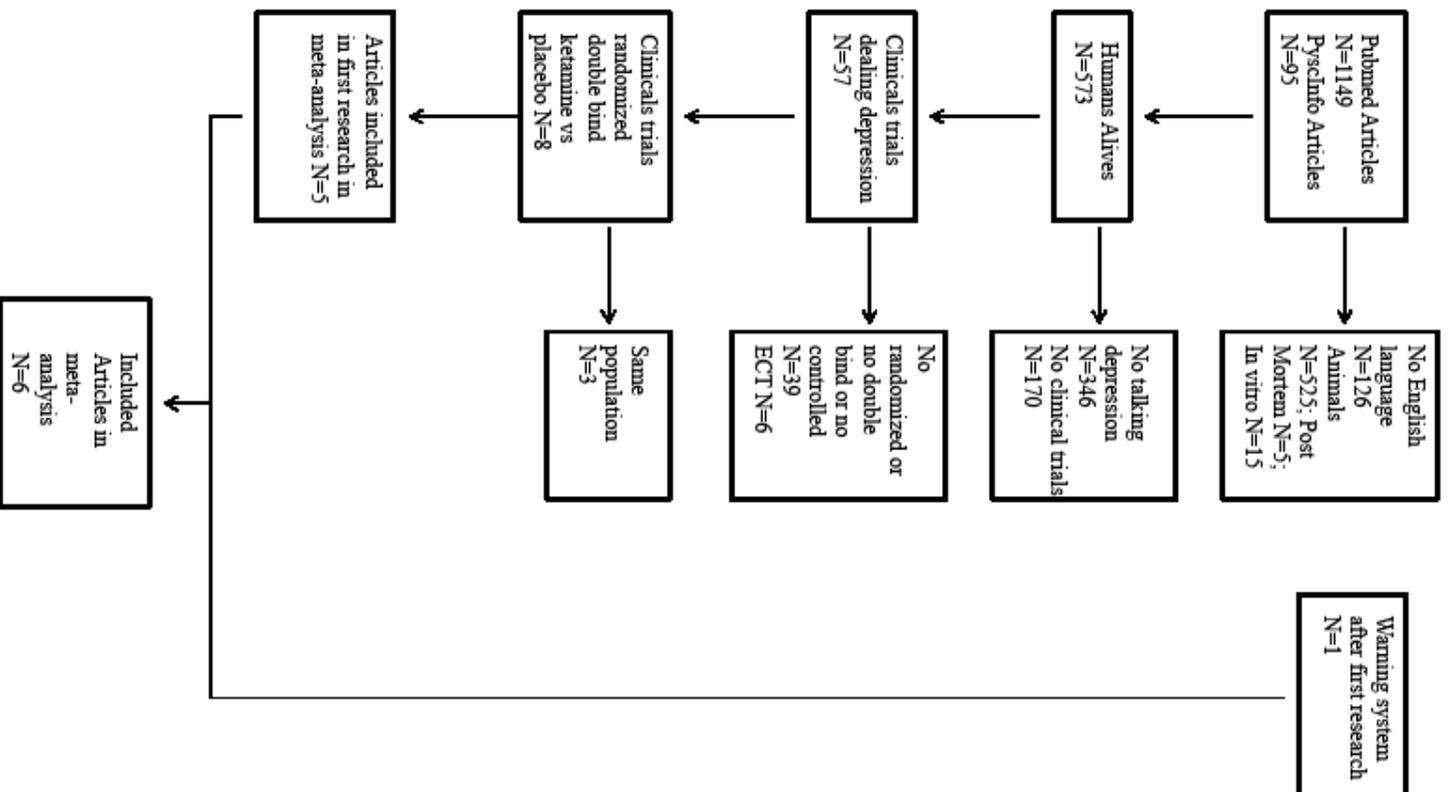
Distribution of the clinical
characteristics

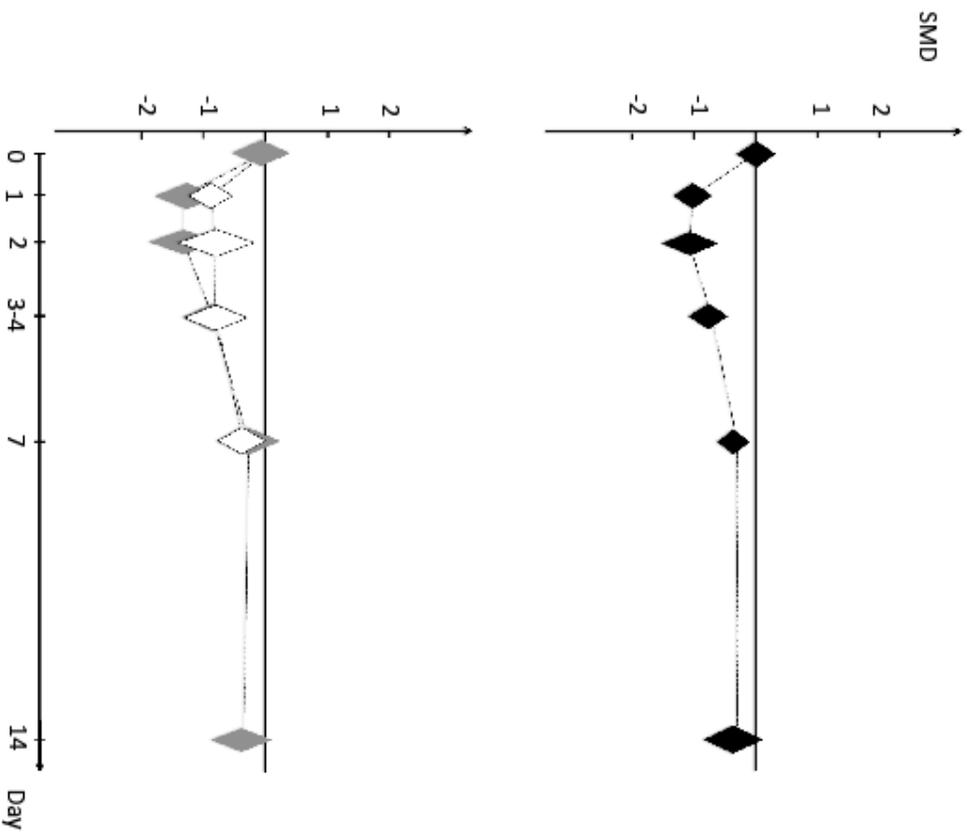
Baseline depression scores

Study*	Ketamine administration	n§	Mean age (SD)	% male	% first episode	% bipolar depression	% recurrent unipolar depression	Months of current episode (SD) [¶]	Years of illness (SD)	Failed antidepressant trials (SD)	Depression scale	Ketamine score	Placebo score	Main findings
Berman et al., 2000	IV: 0.5mg/kg over 40min	7	37 (10)	44	0	11	89	NA	NA	1.33 (1.21)	25-items HDRS	33 (6.2)	26.9 (5.8)	Depression improvement at days 1, 2 and 3 for ketamine group
†Zarate et al., 2006	IV: 0.5mg/kg over 40min	18	46.7 (11.2)	33	0	0	100	33.6 (37.4)	23.7 (12.5)	5.7 (3.4)	21-items HDRS	25.5 (8.5)	24.1 (8.5)	Depression improvement at days 1, 2, 3 and 7 for ketamine group
‡Diazgranados et al., 2010	IV: 0.5mg/kg over 40min	18	47.9 (13.1)	33	0	100	0	15.1 (13.3)	27.6 (11.2)	7.2 (4)	MADRS	31.3 (9.4)	32.9 (9.6)	Depression improvement at days 1, 2, 3, not at days 7, 10 and 14 for ketamine group
‡Zarate et al., 2012	IV: 0.5mg/kg over 40min	15	46.7 (10.6)	47	0	100	0	20.9 (27.5)	30.6 (11.2)	9.7 (4.3)	MADRS	34.0 (8.5)	33.5 (9)	Depression improvement at days 1, 2, 3, not at days 7, 10 and 14 for ketamine group
**Sos et al., 2013	IV: 2×0.27mg/kg over 30min	27	43.7 (NA)	50	30	0	70	11.5 (NA)	10.3 (NA)	NA	MADRS	20.8 (6)	20.7 (7.8)	Depression improvement at days 1, 4 and 7 for ketamine group
¥Lapidus et al., 2014	IN: 50mg	18	48 (12.8)	50	15	0	85	15.2 [¶] (17.4)	27.4 (13.7)	4.1 (3.9)	MADRS	30 (5.4)	30.2 (5.8)	Depression improvement at day 1 for ketamine group

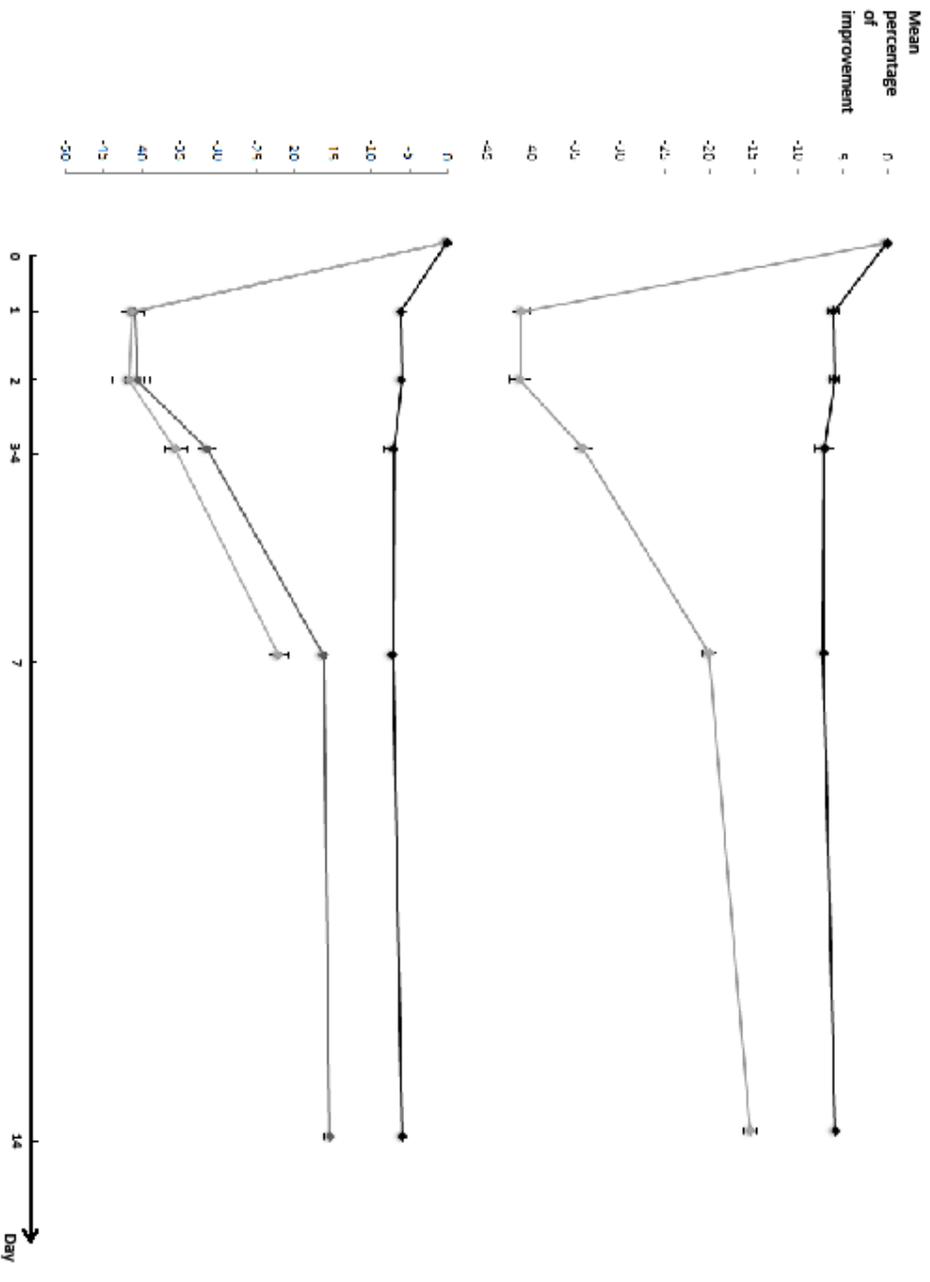
SD: Standard deviations; NA: Not available; IN: Intranasal; IV: Intravenous.

Footnotes: *All studies were randomized, double-blind and placebo-controlled cross-over, §Only subjects included in statistical analyses were considered, [¶]The duration of the current episode was given in years in Lapidus et al., 2014. This information was checked and confirmed by the authors, †Patients had a wash-out period between antidepressant and ketamine, ‡Patients had a concomitant treatment by valproate or lithium, **Patients had a stable dose of antidepressant for a minimum of three weeks before ketamine administration and during the study, ¥Patients had a stable dose of antidepressant.





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Highlights

Ketamine had an antidepressive efficacy from day 1 to day 7

The maintenance of ketamine's efficacy over time failed in bipolar disorder

Ketamine-induced psychotic symptoms were no more significant 80 min after its administration