

Ketamine administration in depressive disorders: a systematic review and meta-analysis

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Abstract

Introduction Ketamine's efficacy in depressive disorders has been established in several controlled trials. The aim of the present study was to determine whether or not ketamine administration significantly improves depressive symptomatology in depression and more specifically in major depressive disorder (MDD), bipolar depression, resistant depression (non-ECT studies), and as an anesthetic agent in electroconvulsive therapy (ECT) for resistant depression (ECT studies). Secondary outcomes were the duration of ketamine's effect, the efficacy on suicidal ideations, the existence of a dose effect, and the safety/tolerance of the treatment.

Methods Studies were included if they met the following criteria (without any language or date restriction): design:

randomized controlled trials, intervention: ketamine administration, participants: diagnosis of depression, and evaluation of severity based on a validated scale. We calculated standardized mean differences (SMDs) with 95 % confidence intervals (CIs) for each study. We used fixed and random effects models. Heterogeneity was assessed using the I² statistic.

Results We included nine non-ECT studies in our quantitative analysis (192 patients with major depressive disorder and 34 patients with bipolar depression). Overall, depression scores were significantly decreased in the ketamine groups compared to those in the control groups (SMD=−0.99; 95 % CI −1.23, −0.75; $p<0.01$). Ketamine's efficacy was confirmed in MDD (resistant to previous pharmacological treatments or not) (SMD=−0.91; 95 % CI −1.19, −0.64; $p<0.01$), in bipolar depression (SMD=−1.34; 95 % CI −1.94, −0.75), and in drug-free patients as well as patients under medication. Four ECT trials (118 patients) were included in our quantitative analysis. One hundred and three patients were diagnosed with major depressive disorder and 15 with bipolar depression. Overall, depression scores were significantly improved in the 58 patients receiving ketamine in ECT anesthesia induction compared to the 60 patients (SMD=−0.56; 95 % CI −1.10, −0.02; $p=0.04$; $I^2=52.4$ %). The duration of ketamine's effects was assessed in only two non-ECT studies and seemed to persist for 2–3 days; this result needs to be confirmed. Three of four studies found significant decrease of suicidal thoughts and one found no difference between groups, but suicidal ideations were only studied by the suicide item of the depressive scales. It was not possible to determine a dose effect; 0.5 mg/kg was used in the majority of the studies. Some cardiovascular events were described (mostly transient blood pressure elevation that may require treatment), and ketamine's use should remain cautious in patients with a cardiovascular history.

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Conclusion The present meta-analysis confirms ketamine's efficacy in depressive disorders in non-ECT studies, as well as in ECT studies. The results of this first meta-analysis are encouraging, and further studies are warranted to detail efficacy in bipolar disorders and other specific depressed populations. Middle- and long-term efficacy and safety have yet to be explored. Extrapolation should be cautious: Patients included had no history of psychotic episodes and no history of alcohol or substance use disorders, which is not representative of all the depressed patients that may benefit from this therapy.

Keywords Ketamine · Major depression · Bipolar disorder · Resistant · Electroconvulsive therapy (ECT)

Introduction

Major psychiatric disorders such as major depressive disorder (MDD) and bipolar disorders are among the four most disabling mental, neurological, and substance-use related illnesses worldwide with a global social cost of respectively 66.5 and 16.8 million disability-adjusted life years (DALYs) (Collins et al. 2011). While forecasts predict an increase in the prevalence of mental disorders in the general population worldwide, a non-negligible proportion of patients do not respond to medication (Calabrese et al. 2008; Rush et al. 2006; Souery et al. 2006). They therefore represent a major and rising public health concern and there is an urgent need to develop more effective therapies to treat and delay the onset of these disorders or their deleterious phases by exploring new therapeutic approaches such as ketamine administration. The antidepressant properties of ketamine, an anesthetic agent with N-methyl-D-aspartic acid receptor (NMDAR) antagonist properties, were first described just over a decade ago (Berman et al. 2000). Since then, ketamine administration has been assessed in MDD, resistant depression, and bipolar depression and in electroconvulsive therapy (ECT) induction (Abdallah et al. 2012; Diazgranados et al. 2010; Kranaster et al. 2011; Kudoh et al. 2002; Murrough et al. 2013; Okamoto et al. 2010; Wang et al. 2012; Zarate et al. 2012). However, results are inconsistent and the qualities of some studies are questionable. Moreover, there is some reluctance to use ketamine in clinical practice (at least in France) due to the potential misuse of this drug (Morgan and Curran 2011), and clinical questions remain unclearly answered to date, such as indications, possible adverse events, recommended doses, duration of efficacy, and effect on suicidal ideations. A meta-analysis seemed warranted to draw the state of knowledge of ketamine use in depressive disorders.

The aim of this study was to perform a systematic review and meta-analysis of controlled trials to investigate the efficacy of the ketamine's administration on depressive

symptomatology and more specifically in MDD, resistant depression, and bipolar depression and as an anesthetic agent in ECT for resistant depression. Secondary outcomes were the duration of ketamine's effect on depressive symptomatology, the efficacy on suicidal ideations, the existence of a dose effect, and the safety/tolerability of the treatment.

Methods

Search strategy

This meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria (Moher et al. 2009). A specific search strategy was developed for the interface PubMed (MEDLINE database), based on a combination of MeSH terms "ketamine," as well as indexed terms related to depression ("Depression" OR "Depressive Disorders" OR "Mood Disorders" OR "Affective Disorders," OR "Anxiety") and study design ("controlled clinical trial"), and was used in different computerized databases: PubMed (from 1966 to September 2013), Embase (from 1980 to September 2013), PsycINFO (from 1806 to September 2013), BIOSIS (from 1926 to September 2013), Science Direct (from 2006 to September 2013), and Cochrane Central (from 1993 to September 2013). Furthermore, we searched ProQuest Dissertations and Theses full-text database to identify unpublished dissertations. The references of included studies were examined to search for further trials.

Criteria for selecting articles

Studies were included if they met the following criteria:

- Design: randomized controlled trials
- Intervention: ketamine administration (one administration or more, alone or with other anesthetic agent)
- Participants: participants with a diagnosis of depression (major depression or bipolar depression, resistant or not)
- Evaluation of depression severity based on a validated scale

There was no language or date restriction. The manuscripts with the following criteria were excluded: (1) absence of comparison between patients with ketamine administration and controls and (2) a standardized mean difference that could not be calculated.

Selection of studies and data extraction

One author (M.B.) screened titles and abstracts of database records and retrieved full texts for eligibility assessment. Two

authors independently checked the full-text records for eligibility (G.F. and L.B.). Disagreements were resolved by consensus discussion.

The manuscripts of the studies were then independently reviewed by two of the authors (G.F. and L.B.). Data was independently extracted into a standard electronic form: first author name, date of publication, design, country, sample size, number of MDD included subjects, depression assessment scales, delay to depression assessment, diagnoses of resistant depression in inclusion criteria, co-administration of ECT sessions, previous withdrawal of antidepressant medications (“drug-free studies”), administered treatment of the cases and the control groups, and ketamine administered dose. Any discrepancies were resolved by consensus with a third reviewer (A.L.).

Assessing the methodological quality of included studies

The methodological quality of included studies was assessed independently by two of the authors (G.F. and L.B.). Any discrepancies were resolved by consensus with a third reviewer (A.L.).

First, we used markers of internal validity from the Cochrane risk of bias tool (Higgins et al. 2011). The risk of selection bias was assessed at study level (sequence generation, allocation sequence concealment), the risk of performance bias at comparison level (blinding of medical personnel), and the risk of detection bias as well as attrition bias was assessed at outcome level (blinding of outcome assessors, handling incomplete outcome data). Studies’ risk of bias could then be qualified as low, unclear, or high.

Second, we further classified studies according to their level of evidence using the classification scheme requirements for therapeutic questions (Gross and Johnston 2009). The level of evidence was classified using a four-tiered system (class I through class IV), with class I indicating the strongest evidence and class IV the weakest.

Statistical analyses

We calculated standardized mean difference (SMD) with 95 % confidence intervals (CIs) for each study, defined as the difference in pre-post treatment mean changes between the two groups (depressed patients with ketamine administration vs those without) divided by the pooled standard deviation of the measurements. We used fixed effects (Mantel and Haenszel 1959) and random effects models (DerSimonian and Laird 1986) which account for between-study heterogeneity by weighting studies similarly. Heterogeneity was assessed using the I^2 statistic, which represents the percentage of variance due to between-study factors rather than sampling error (Higgins et al. 2003). We considered values of $I^2 > 50$ % as indicative of large heterogeneity (Vassos et al. 2013). We used

funnel plots, Rosenthal fail-safe N (i.e., which estimates the number of missing studies needed to change the results of the meta-analysis) and the Egger’s regression intercept (i.e., which assesses the degree of funnel plot asymmetry by the intercept from regression of standard normal deviates against precision) to estimate risk of bias (Borenstein et al. 2009). Forest plots were generated to show SMD with corresponding CIs for each study and the overall estimate of pooled random effects. We conducted several subgroups and sensitivity analyses to determine the impact of various factors (i.e., unipolar or bipolar depression, resistant depression, co-administration with thiopental, in drug-free/non-drug-free trials and placebo-controlled/non-placebo-controlled trials) on effect size estimates for ketamine effectiveness and also in order to explore potential reasons for heterogeneity or inconsistency. Analyses were performed with comprehensive meta-analysis software (version 2.0, National Institute of Health) (Borenstein et al. 2009).

Results

Study selection

Fifty-four abstracts were initially identified through database searches. We excluded 42 articles because they did not meet the inclusion criteria. The selection process is summarized in Fig. 1. Nine non-ECT studies (conducted between 2000 and 2013) and four ECT studies (conducted in 2012 and 2013) were included in our quantitative analysis (Abdallah et al. 2012; Berman et al. 2000; Diazgranados et al. 2010; Ghasemi et al. 2014; Jarventausta et al. 2013; Kudoh et al. 2002; Loo et al. 2012; Murrough et al. 2013; Sos et al. 2013; Valentine et al. 2011; Wang et al. 2012; Zarate et al. 2012; Zarate et al. 2006).

Quantitative analyses

Non-ECT studies

Study characteristics

Overall, 192 patients (cases +controls) with MDD and 34 (cases+controls) patients with bipolar depression were included (Tables 1 and 2). Some patients were their own controls in four crossover studies (Diazgranados et al. 2010; Sos et al. 2013; Zarate et al. 2012; Zarate et al. 2006). One hundred and sixty-three cases received ketamine hydrochloride. One hundred and forty eight controls received respectively placebo ($N=79$) or midazolam (Murrough et al. 2013), ECT (with thiopental as anesthetic agent for ECT induction) (Ghasemi et al. 2014), or propofol-fentanyl combination as anesthetic agents before surgery (that was also administered to cases)

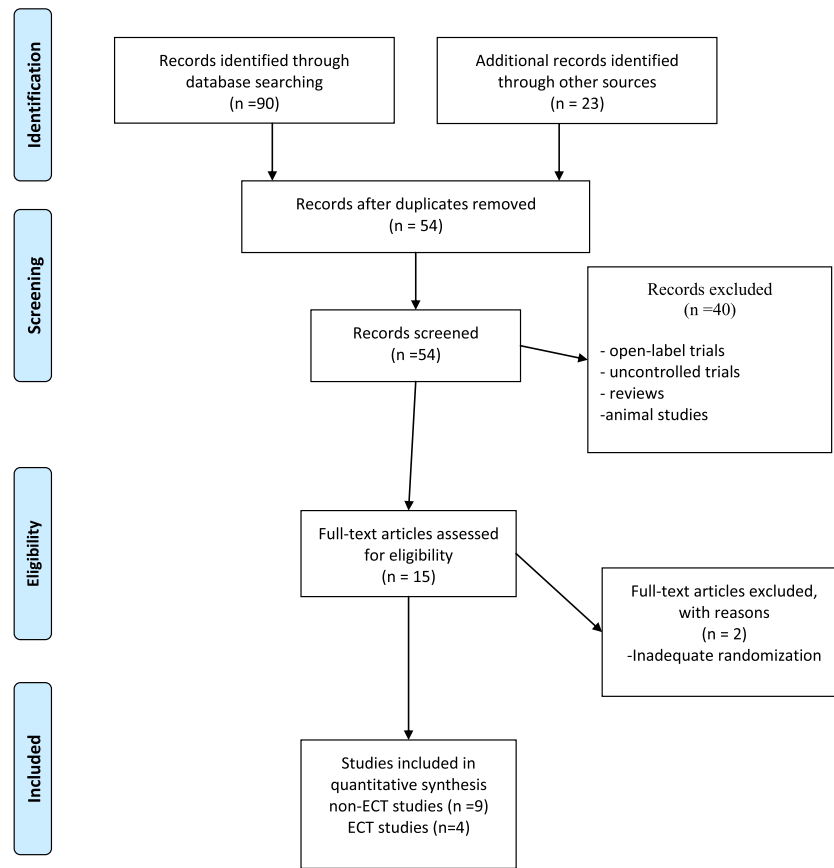


Fig. 1 Study selection process

(Kudoh et al. 2002). The Ghasemi et al. study was classified as “non-ECT study” because only controls received ECT (Ghasemi et al. 2014).

Diagnoses were made by Diagnostic and Statistical Manual (DSM)-IV-based structured interviews in all studies. The DSM diagnosis was completed by validated

scales for inclusion criteria to evaluate baseline severity (four used a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 20 (Diazgranados et al. 2010; Krystal et al. 2003; Sos et al. 2013; Zarate et al. 2012; Zarate et al. 2006), and one a mini-mental status examination (MMSE) score ≥ 27) (Murrough et al. 2013). Depression scores before

Table 1 Characteristics of the non-ECT (electro-convulsive therapy) included randomized controlled trials (RCTs)

Year	Author	Country	Population	Inclusion criterion	Treatment cases	Drug free	Treatment controls	<i>N</i> cases	<i>N</i> controls
2000	Berman et al.	USA	8 MDD+1 BP	DSM-IV MDD	Ketamine hydrochloride	Yes	Placebo	9	9
2002	Kudoh et al.	Japan	35 MDD	DSM-IV MDD	Ketamine hydrochloride + propofol+fentanyl	No	Propofol+fentanyl	35	35
2006	Zarate et al.	USA	18 MDD	MADRS ≥ 20	Ketamine hydrochloride	No	Placebo	17	14
2010	Diazgranados et al.	USA	18 BP	MADRS ≥ 20	Ketamine hydrochloride	No	Placebo	13	15
2011	Valentine et al.	USA	10 MDD	DSM-IV MDD	Ketamine hydrochloride	Yes	Placebo	10	10
2012	Zarate et al.	USA	15 BP	MADRS ≥ 20	Ketamine hydrochloride	No	Placebo	14	12
2013	Sos et al.	Czech Republic	30 MDD	MADRS ≥ 20	Ketamine hydrochloride	No	Placebo	9	19
2013	Ghasemi et al.	Iran	18 MDD	DSM-IV MDD	Ketamine hydrochloride+ thiopental	No	ECT+thiopental	9	9
2013	Murrough et al.	USA	73 MDD	MMSE ≥ 27	Ketamine hydrochloride	Yes	Midazolam	47	25

MDD major depressive disorder, BP bipolar disorder (all bipolar patients were in bipolar depression), DSM-IV Diagnostic and Statistical Manual, MADRS Montgomery-Asberg Depression Scale, HDRS Hamilton Depression Rating Scale, MMSE mini-mental status examination

Table 2 Characteristics of the included electroconvulsive therapy (ECT) randomized controlled trials (RCTs)

Year	Author	Country	Population	Inclusion score	Ketamine form	Additional anesthetic in ketamine group	Treatment controls	N cases	N controls	Depression scale
2012	Abdallah et al.	USA	MDD+BP	DSM-IV MDD	Ketamine hydrochloride	Thiopental	Thiopental	8	8	HDRS
2012	Loo et al.	Australia	MDD + BP	DSM-IV MDD	Ketamine hydrochloride	Thiopental	Thiopental	22	24	MADRS
2012	Wang et al.	China	MDD	HDRS≥20	Ketamine hydrochloride	No	Propofol	12	12	HDRS
2013	Jarventausta et al.	Finland	MDD (±psychotic symptoms)	DSM-IV MDD	S-ketamine	Propofol	Propofol	16	16	MADRS

Patients kept antidepressant medication if previously treated in all studies. As ECT is a treatment for resistant depression, most of the included patients can be considered as resistant, even in studies that did not mention resistance in inclusion criteria. Resistance designs the resistance to two or more previous pharmacological treatments.

MDD major depressive disorder, *BP* bipolar disorder (all patients were in bipolar depression), *DSM-IV* Diagnostic and Statistical Manual, *MADRS* Montgomery-Asberg Depression Scale, *HDRS* Hamilton Depression Rating Scale

and after treatment administration were assessed by the Hamilton Depression Rating Scale (HDRS) in five studies (Berman et al. 2000; Ghasemi et al. 2014; Kudoh et al. 2002; Valentine et al. 2011; Zarate et al. 2006) and MADRS in four studies (Diazgranados et al. 2010; Murrough et al. 2013; Sos et al. 2013; Zarate et al. 2012). Six studies were conducted in the USA, one in Iran (Ghasemi et al. 2014), one in Czech Republic (Sos et al. 2013), and one in Japan (Kudoh et al. 2002).

All patients received ketamine hydrochloride; S-ketamine was not used in the included studies. Table 3 contains further information on methodological quality indicators.

Global effect of ketamine in non-ECT studies

Overall, the depression score was significantly improved in patients receiving ketamine compared to controls (SMD=

Table 3 Summary of study methodology using the Cochrane risk of bias tool and the classification scheme requirements for therapeutic questions

ECT studies													
Author	The classification scheme requirements for therapeutic questions								The Cochrane risk of bias tool				
	R	MOA	BE	CA	PO	EID	D	Level	SG	AC	B	COD	Risk
Abdallah et al. (2012)	Y	Y	Y	Y	Y	Y	Y	Class I	Y	Y	Y	Y	Low risk of bias
Loo et al. (2012)	Y	Y	Y	Y	Y	Y	Y	Class I	Y	Y	Y	Y	Low risk of bias
Jarventausta et al. (2013)	Y	Y	Y	Y	Y	Y	Y	Class I	U	Y	Y	Y	Unclear risk of bias
Wang et al. (2012)	Y	Y	Y	Y	Y	Y	Y	Class I	Y	Y	Y	Y	Low risk of bias
Non-ECT studies													
Author	The classification scheme requirements for therapeutic questions								The Cochrane risk of bias tool				
	R	MOA	BE	CA	PO	EID	D	Level	SG	AC	B	COD	Risk
Berman et al. (2000)	Y	Y	Y	Y	Y	Y	Y	Class I	Y	Y	Y	Y	Low risk of bias
Diazgranados et al. (2010)	Y	Y	Y	Y	Y	Y	Y	Class I	Y	Y	Y	Y	Low risk of bias
Ghasemi et al. (2014)	Y	Y	Y	Y	Y	Y	Y	Class I	Y	Y	Y	Y	Low risk of bias
Kudoh et al. (2000)	Y	Y	Y	N	N	Y	N	Class III	Y	N	N	N	High risk of bias
Murrough et al. (2013)	Y	Y	Y	Y	Y	Y	Y	Class I	Y	Y	Y	Y	Low risk of bias
Sos et al. (2013)	Y	Y	Y	Y	Y	Y	Y	Class I	Y	Y	Y	Y	Low risk of bias
Valentine et al. (2011)	Y	N	Y	N	Y	Y	Y	Class III	Y	N	N	Y	High risk of bias
Zarate et al. (2006)	Y	Y	Y	Y	Y	Y	Y	Class I	Y	Y	Y	Y	Low risk of bias
Zarate et al. (2012)	Y	Y	Y	Y	Y	Y	Y	Class I	Y	Y	Y	Y	Low risk of bias

Y yes, N no, U unclear, R randomization, MOA masked or objective outcome assessment, BE baseline equivalent characteristics or appropriate adjustment, CA concealed allocation, PO primary outcome clearly defined, EID exclusion/inclusion clearly defined, D dropouts <20 %, SG sequence generation, AC allocation concealment, B blinding, COD complete outcome data

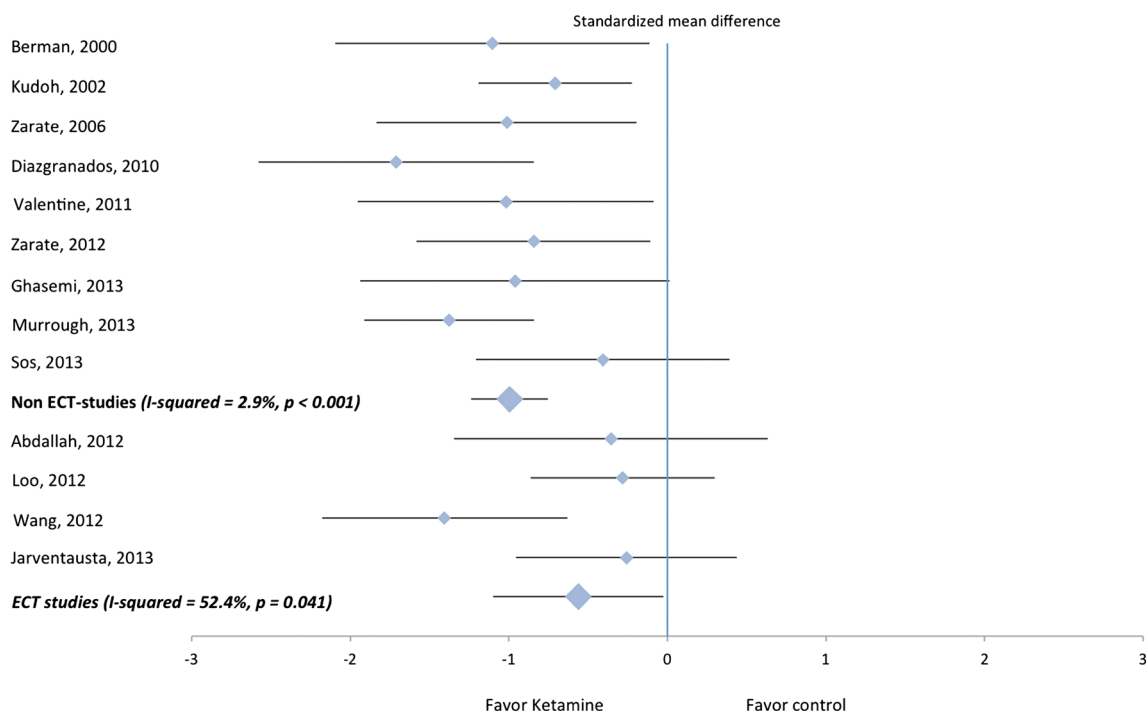


Fig. 2 Global ketamine's efficacy on depressive symptomatology in non-ECT and ECT studies. All depression assessments were made 24 h after administration in non-ECT studies

-0.99; 95 % CI -1.23, -0.75; $p < 0.001$; $I^2 = 2.9$ %) (Fig. 2). The efficacy of ketamine remained significant (SMD=-1.10; 95 % CI -1.39, -0.81; $p < 0.01$; $I^2 = 6.3$ %) after excluding the two studies with high risk of bias (as defined in Table 3 (Kudoh et al. 2002; Valentine et al. 2011)). The associated funnel plot was reasonably symmetrical, although the limited number of studies does not allow the exclusion of publication bias (Appendix). The p value of the Egger's regression intercept was 0.76, and the asymmetry is considered to be statistically non-significant. The Rosenthal's fail-safe N value was 138. Given that we identified nine studies that looked at ketamine and depression, it is highly unlikely that nearly 140 studies were missed.

Subgroup analyses: ketamine in MDD versus bipolar depression

Six studies included patients with only MDD (Ghasemi et al. 2014; Kudoh et al. 2002; Murrough et al. 2013; Sos et al. 2013; Valentine et al. 2011; Zarate et al. 2006), two included patients with only bipolar depression (Diazgranados et al. 2010; Zarate et al. 2012), and the remaining study included patients with either MDD (eight) or bipolar depression (one) (Berman et al. 2000) (Fig. 3).

Overall, depression scores were significantly improved in the 127 MDD cases compared to the 112 MDD controls (SMD=-0.91; 95 % CI -1.19, -0.64; $p < 0.01$; $I^2 = 4.4$ %). Depression scores were also significantly improved in the 27

bipolar cases compared to those in the 27 bipolar controls (SMD=-1.34; 95 % CI -1.94, -0.75; $p < 0.01$, $I^2 = 24.1$ %).

Sensitivity analyses

Study design: drug-free patients versus patients under antidepressant or mood-stabilizing treatment Only four studies included in their protocol at least 2-week withdrawal of any antidepressant or mood-stabilizing treatment (Fig. 4) (Berman et al. 2000; Murrough et al. 2013; Valentine et al. 2011; Zarate et al. 2006). Ketamine was effective in both drug-free and non-drug-free studies (SMD=-1.15; 95 % CI -1.52, -0.79; $p < 0.01$; $I^2 = 0.0$ % vs SMD=-0.87; 95 % CI -1.19, -0.55; $p < 0.01$; $I^2 = 27.1$ %).

Effect of ketamine in studies including pharmacological resistance to antidepressants or mood stabilizers in inclusion criteria Overall, five studies included pharmacological-resistant patients (Diazgranados et al. 2010; Murrough et al. 2013; Sos et al. 2013; Zarate et al. 2012; Zarate et al. 2006) and the other four studies included patients with depression, independently of the resistance to a previous treatment (Fig. 5). Resistance was not always defined as an inclusion criterion, but some studies included patients that were under medication with persistent depressive symptomatology, who may therefore be defined as resistant to pharmacological treatment. For example, resistance was defined by a MADRS score ≥ 20 after 3 weeks of stable

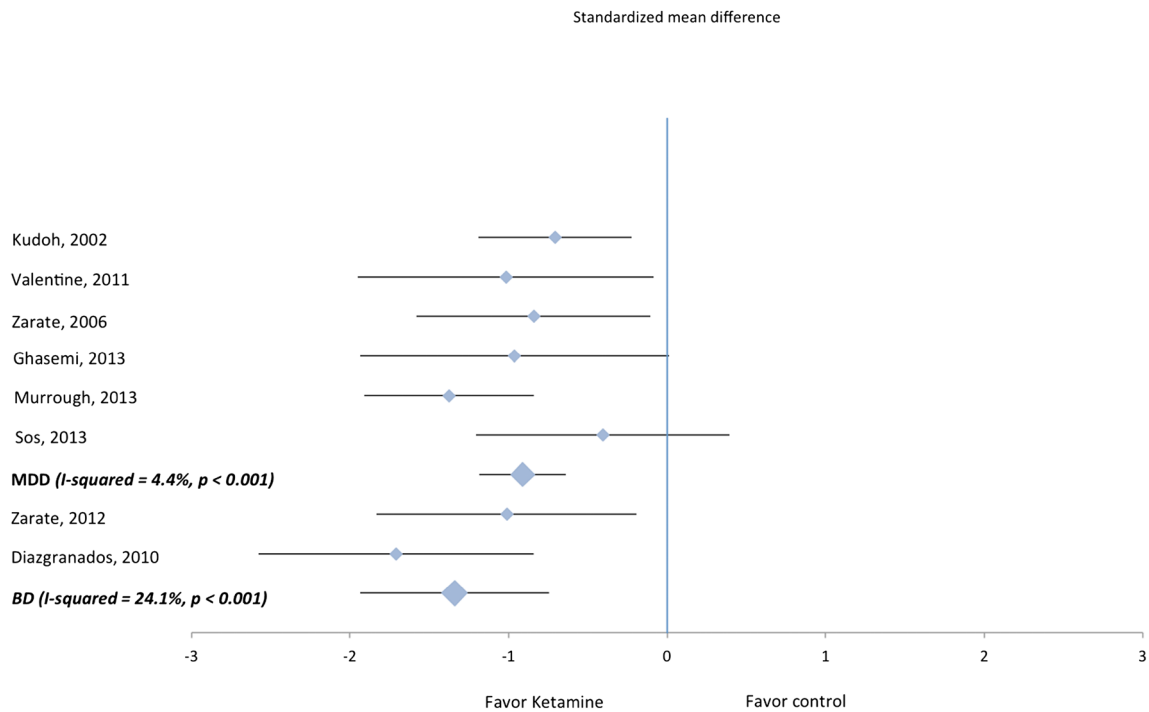


Fig. 3 Subgroup analysis: ketamine’s efficacy in major depressive disorder (MDD) and bipolar depression (BD)

antidepressant treatment in one study (Sos et al. 2013). In Zarate et al. study, resistance was defined by a HDRS score ≥ 20 after at least two well-conducted antidepressant trials (Zarate et al. 2006). For patients with bipolar depression, resistance was defined by non-response to open treatment with lithium or valproate (Diazgranados et al. 2010; Zarate et al. 2012). In Murrough et al study, resistance was defined by non-response to three well-conducted antidepressant trials (Murrough et al. 2013).

Ketamine was also effective when only patients with resistant depression were included (SMD=-1.11; 95 % CI -1.43, -0.79; $p < 0.01$; $I^2 = 36.7\%$ for resistant depression studies vs SMD=-0.84; 95 % CI -1.21, -0.48; $p < 0.01$; $I^2 = 0.0\%$ for other studies).

Controls’ treatment: placebo versus non-placebo studies Ketamine was effective in studies in which the control group received placebo (six studies, SMD=-0.99; 95 % CI -1.33, -0.64; $p < 0.01$; $I^2 = 0.0\%$)

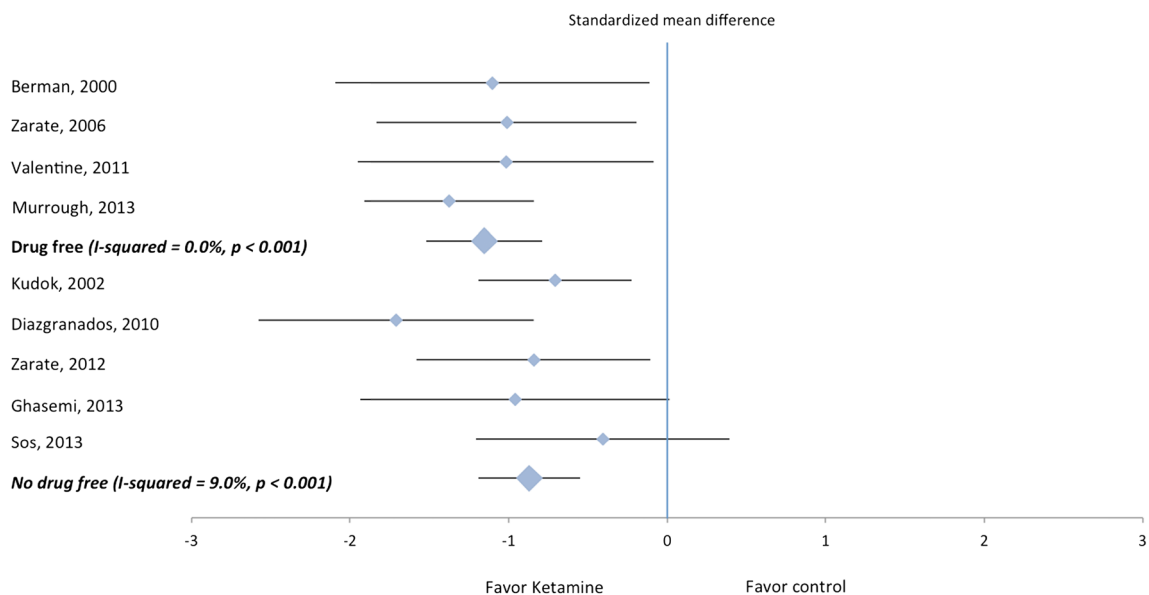


Fig. 4 Sensitivity analysis: ketamine’s efficacy in drug-free patients versus patients taking antidepressants or mood-stabilizing agents

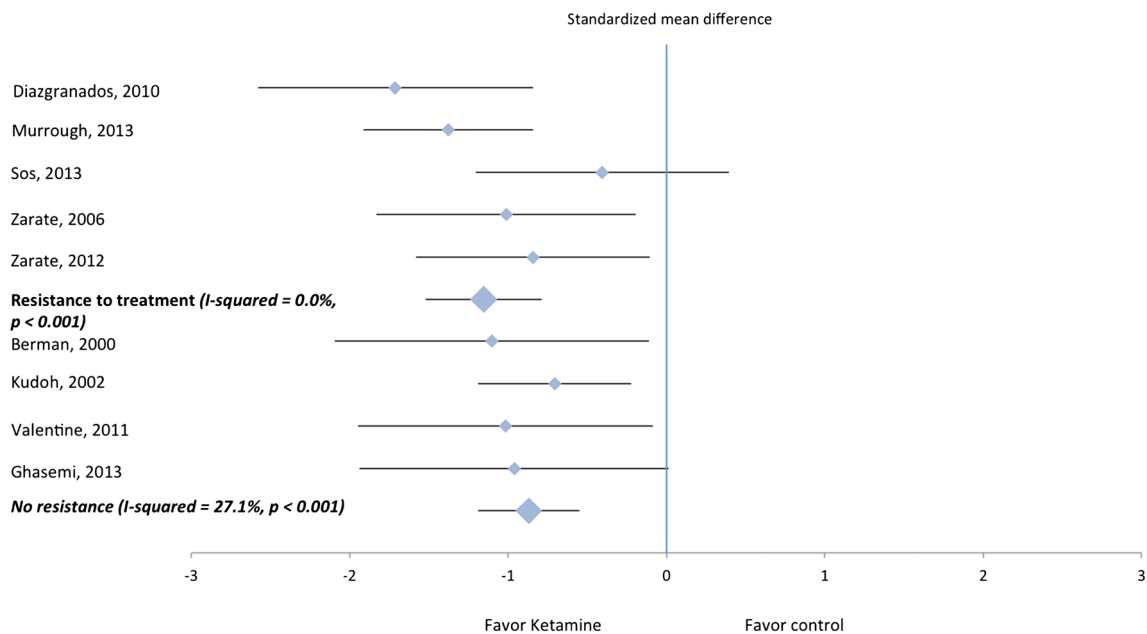


Fig. 5 Sensitivity analysis: ketamine's efficacy in trials including resistance to pharmacological treatments in inclusion criteria versus others (resistance was defined by resistance to two or three previous pharmacological treatments)

(Berman et al. 2000; Diazgranados et al. 2010; Sos et al. 2013; Valentine et al. 2011; Zarate et al. 2012; Zarate et al. 2006) as well as in other studies (Fig. 6; SMD=-1.00; 95 % CI -1.34, -0.67; $p < 0.01$, $I^2 = 40.1$ %) (Ghasemi et al. 2014; Kudoh et al. 2002; Murrough et al. 2013).

Study design: crossover versus non-crossover studies Considering that the study design may have an impact on efficacy, we performed a sensitivity analysis confirming the significant efficacy of ketamine after

removing the four crossover studies (SMD=-1.01; 95 % CI -1.32, -0.71; $p < 0.01$; $I^2 = 0.0$ %) (Diazgranados et al. 2010; Sos et al. 2013; Zarate et al. 2012; Zarate et al. 2006).

ECT studies

Study characteristics

Overall, 118 patients (58 cases and 60 controls) were included in four ECT studies (Abdallah et al. 2012; Jarventausta et al.

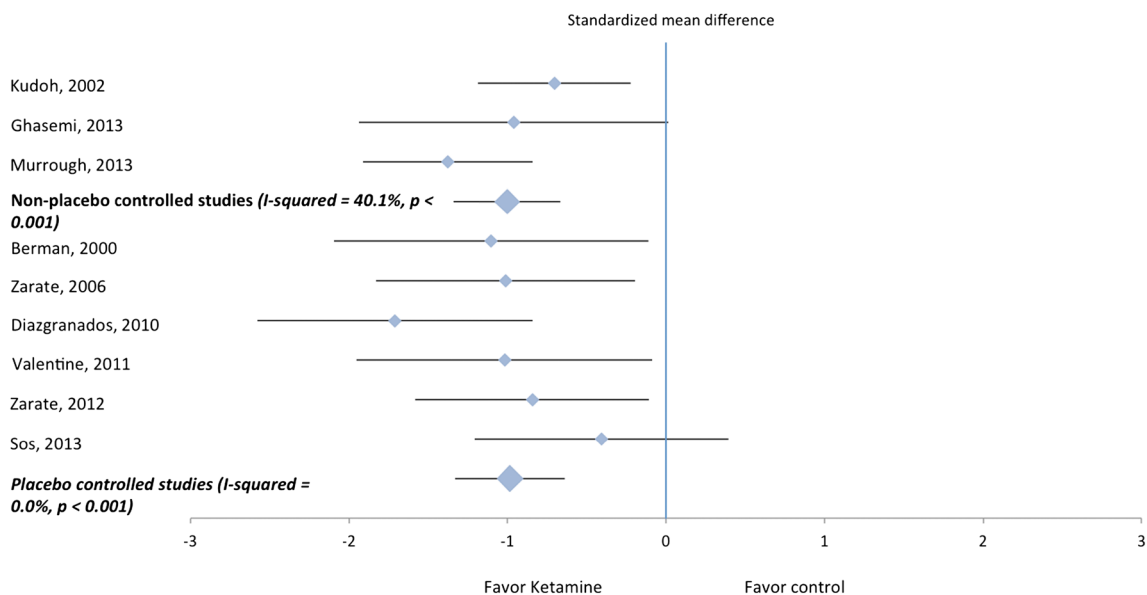


Fig. 6 Sensitivity analysis: ketamine's efficacy in placebo-controlled trials versus non-placebo controlled trials (in these trials, patients received miscellaneous treatments: midazolam, electroconvulsive therapy + thiopental or propofol + fentanyl)

2013; Loo et al. 2012; Wang et al. 2012) (Tables 1 and 2). One hundred and three patients were diagnosed with MDD and 15 with bipolar depression. Thirty-two cases received a combination of ketamine hydrochloride 0.5 mg/kg and thiopental (Abdallah et al. 2012; Loo et al. 2012), 12 received ketamine hydrochloride 0.8 mg/kg alone (Wang et al. 2012), and 16 cases received S-ketamine 0.4 mg/kg in combination with propofol (Jarventausta et al. 2013). Thirty-two controls received thiopental (Abdallah et al. 2012; Loo et al. 2012) and 28 propofol (Jarventausta et al. 2013; Wang et al. 2012). All patients were on pharmaceutical antidepressant or mood-stabilizing treatment during the whole protocol. Delays between ketamine administration (before the first ECT session) and first mood evaluation were highly heterogeneous 24 h (Wang et al. 2012), 24 to 72 h (Abdallah et al. 2012), after three ECT sessions (Jarventausta et al. 2013), and 1 week (Loo et al. 2012).

Global effect of ketamine in ECT studies

Overall, depression scores were significantly improved in the 58 patients with major depression receiving ketamine in ECT anesthesia induction compared to those in the 60 patients receiving thiopental or propofol (SMD=-0.56; 95 % CI -1.10, -0.02; $p=0.04$, $I^2=52.4$ %) (Fig. 2).

Qualitative analyses

Suicidal ideations

To date, the quantity and quality of the available literature on ketamine for reducing suicidal ideations and suicide risk is relatively low. Suicidality or suicidal ideations were assessed in five randomized controlled trials (RCTs) included in our quantitative analysis (Berman et al. 2000; Diazgranados et al. 2010; Kudoh et al. 2002; Murrough et al. 2013; Zarate et al. 2012). The effect of ketamine administration on suicidal thoughts was mostly measured by the suicide item of the depression scales in the non-ECT studies. In the study by Murrough et al., patients at serious and imminent suicidal risk were excluded, but those only presenting suicidal ideations were not. The presence of suicidal ideations or suicidal risk was not exclusion criteria in the other studies.

Three studies reported significant decrease of suicidal thoughts in depressed patients after ketamine administration compared to controls (Berman et al. 2000; Kudoh et al. 2002; Zarate et al. 2012). In the study by Zarate et al. 2012, repeated assessments showed that patients who received ketamine had lower suicidal ideation scores from the 40th minute to day 2 and at day 10. However, one other study in bipolar depression found no significant effect of ketamine on this item contrary to other depressive symptoms (Diazgranados et al. 2010).

Duration of ketamine efficacy and dose effects

Repeated ratings of depression scores over time in non-ECT studies showed that depressive symptoms were significantly improved compared to controls as early as 40 min after injection. This difference could be maintained during 2 to 3 days (Diazgranados et al. 2010). As a 0.5 mg/kg dose was used in most studies, the calculation of a dose effect was not possible.

Adverse events

In non-ECT studies, common side effects of ketamine administration included dry mouth, tachycardia, increased blood pressure, and dissociation. These adverse events were transient and benign. More severe cardiovascular events (mostly tachycardia/hypertension requiring treatment) associated with higher doses of ketamine (0.8–1 mg/kg) during anesthesia were also described (Table 4).

In ECT studies, cardiovascular events (severe hypertension, diastole blood pressure >100 mmHg) were described only when 0.8 mg/kg ketamine hydrochloride was administered (Wang et al. 2012). Studies using lower doses (0.4 or 0.5 mg/kg) described transient disorientation and restlessness. One drug-induced agitation was described with a combination of 0.4 mg/kg ketamine hydrochloride and propofol (Jarventausta et al. 2013). Of the nine bipolar participants included in Loo et al. study, one became hypomanic and one developed rapid cycling manic symptoms (Loo et al. 2012).

Discussion

Non-ECT studies

Overall, depression scores were significantly improved in ketamine groups compared to those in controls. The results remained significant in all our subgroups and sensitivity analyses.

Ketamine was found to be effective in MDD as well as in bipolar depression (Figs. 2 and 3). However, only two studies, conducted by the same research center but classified as “low risk of bias”, were carried out in bipolar depression. Significant positive effects of ketamine were reported in both studies (Diazgranados et al. 2010; Zarate et al. 2012). Overall, both bipolar I ($N=8+9$) and bipolar II ($N=10+6$) patients were included, but it was not possible to determine if ketamine was more effective in a specific type of bipolar disorder. While rapid cycling (>4 mood episodes within 12 months, based on *DSM-IV* criteria) was not an exclusion criterion, no rapid cyclers were included, and hence, results cannot be extrapolated to this subgroup. In the study by Diazgranados et al. (2010), four patients receiving ketamine dropped out of

Table 4 Reported adverse events in ketamine groups

Author	Ketamine type, dose (mg/kg), and number of administration	Control treatment	Reported adverse events
Non-ECT studies			
Berman et al. (2000)	Ketamine hydrochloride, 0.5 mg/kg, once	Placebo	No serious adverse event occurred during the study
Kudoh et al. (2000)	Ketamine, 1 mg/kg, once, + 1.5 mg/kg propofol, + 2 µg/kg fentanyl; tracheal intubation was then facilitated by vecuronium 0.1 mg/kg, IV	Propofol	One patient (3 %) of 35 in ketamine group and two patients (6 %) of 35 in propofol group developed ventricular ectopic rhythm and returned to sinus rhythm without any treatment. Hemodynamic changes immediately after the induction of anesthesia was observed in both groups. Two patients (6 %) of 35 in ketamine group and two patients (6 %) of 35 in propofol group had episodes of hypotension <70 mm Hg in systolic blood pressure during the induction. Ephedrine and the infusion of acetate Ringer's solution were effective for all patients who developed hypotension. Postoperative confusion occurred in five patients (14 %) of ketamine group and in eight patients (23 %) of propofol group (differences were not significant)
Diazgranados et al. (2010)	Ketamine hydrochloride, 0.5 mg/kg, once	Placebo	No serious adverse events occurred during the study. Adverse events occurring during the infusion in 10 % or more of subjects receiving ketamine or placebo included feeling woozy or loopy, feeling lethargic or drowsy, cognitive impairment, fear or anxiety, nausea, dizziness, odd sensations, blurred vision, and headache. Adverse events associated only with ketamine (>10 % of subjects) included dissociation; feeling strange, weird, or bizarre; dry mouth; tachycardia; and increased blood pressure. The two subjects who experienced increased blood pressure and tachycardia returned to normal within minutes after the infusion. No adverse event was significantly different from placebo at 80 min or thereafter. No significant changes occurred in electrocardiography, respiratory, or laboratory values during the study
Ghasemi et al. (2014)	Ketamine hydrochloride, 0.5 mg/kg, once, + thiopental	ECT+ thiopental	Both ketamine treatment and ECT were well tolerated in all patients. Overall, there was no significant change in hemodynamic parameters including heart rate and blood pressure in both groups. There was only increase in systolic blood pressure as well as heart rate in three patients after the second and the third doses of ketamine which was temporary, and this rise was not clinically significant
Murrough et al. (2013)	Ketamine hydrochloride, 0.5 mg/kg, once	Midazolam	The most common adverse events in the ketamine group for up to 4 h after infusion were dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, poor concentration, and restlessness. Within this same time period, the most common adverse events in the midazolam group were general malaise, dizziness, headache, restlessness, nausea or vomiting, dry mouth, decreased energy, and poor coordination. Eight of the 47 patients receiving ketamine (17 %) had significant dissociative symptoms (i.e., feeling outside of one's body or perceiving that time is moving more slowly or more quickly than normal) immediately after the ketamine infusion; these symptoms resolved by 2 h postinfusion. No severe psychotic symptoms (paranoia, hallucinations, delusions, or thought disorder) occurred in any patient. On average, mild transient changes in blood pressure were observed on the infusion day. The infusion was discontinued for two patients in the ketamine group because of hemodynamic changes. In one case, a blood pressure elevation (peak, 187/91 mm Hg) unresponsive to beta-blocker therapy resulted in infusion termination after 30 min. The blood pressure normalized within 10 min of infusion cessation. In the other case, there was transient but pronounced hypotension and bradycardia that resolved without sequelae and was followed by overnight observation in the hospital
Sos et al. (2013)	Ketamine hydrochloride, 0.5 mg/kg, once	Placebo	Ketamine was well tolerated and no serious adverse or side effects (other than the expected acute psychotomimetic effect) occurred during the study. Typical effects occurring at subanesthetic doses of ketamine were dissociation/perceptual disturbances, confusion, mild increases

Table 4 (continued)

Author	Ketamine type, dose (mg/kg), and number of administration	Control treatment	Reported adverse events
Valentine et al. (2011)	Ketamine hydrochloride, 0.5 mg/kg, once	Placebo	in blood pressure, emotional blunting, and euphoria. The majority of these effects ceased within 30 min after the ketamine infusion No serious adverse events occurred during the study
Zarate et al. (2006)	Ketamine hydrochloride, 0.5 mg/kg, once	Placebo	No serious adverse events occurred during the study. Adverse effects occurring more commonly in participants taking ketamine than those taking placebo were perceptual disturbances, confusion, elevations in blood pressure, euphoria, dizziness, and increased libido
Zarate et al. (2012)	Ketamine hydrochloride, 0.5 mg/kg, once	Placebo	No serious adverse events occurred during the study. Adverse events occurring during the infusion in 10 % or more of the subjects receiving ketamine or placebo included feeling woozy or loopy, feeling lethargic or drowsy, cognitive impairment, fear or anxiety, nausea, dizziness, odd sensations, blurred vision, and headache. No adverse event was significantly different from placebo at 80 min or thereafter. Headaches, drowsiness or sedation, early morning awakening, and difficulty falling asleep were reported in >10 % of the sample in both the ketamine and placebo phases. Dry mouth, dizziness or faintness, difficulty falling asleep, and flatulence were reported for ketamine only. No significant changes occurred in electrocardiogram, respiratory, or laboratory values during the study
ECT studies			
Abdallah et al. (2012)	Ketamine, 0.5 mg/kg, before each of the six ECT sessions, + 3.5 mg/kg thiopental	Thiopental	No major adverse effects were observed in this cohort during the 2 weeks of ECT treatment. Minimal transient side effects reported by both groups included nausea, headaches, disorientation, and muscle pain
Loo et al. (2012)	Ketamine, 0.5 mg/kg, + thiopental	Thiopental	No psychomimetic effects were reported after ketamine administration, and ketamine did not significantly increase posttreatment agitation or confusion. Of the nine bipolar participants, one became hypomanic and one developed rapid cycling manic symptoms. Both were in the ECT-ketamine group and were on lithium at therapeutic serum levels during the course of ECT
Jarventausta et al. (2013)	S-ketamine, 0.4 mg/kg, + propofol	Propofol	The posttreatment disorientation and restlessness seemed to be more common in the S-ketamine group. In the S-ketamine group, there was one serious adverse event (agitation, hyperventilation, sense of fear, raise of blood pressure, and heart rate)
Wang et al. (2012)	Ketamine, 0.8 mg/kg, once	Propofol	There were five cardiovascular events (severe hypertension, diastole blood pressure >100 mm Hg) during ECT in ketamine group requiring 25 mg urapidil (intravenous). Headache occurred in six patients (50 %), nausea in three (25 %) patients, brief delirium (within 2 h) in two patients, prolonged delirium (>2 h) in one patient, and sense of fear upon awakening from anesthesia in three (25 %) patients. Only hypertension was only significantly enhanced in ketamine group compared to controls ($p=0.037$)

ECT electroconvulsive therapy

the study due to anxiety. No manic or hypomanic switches were reported. Further studies are warranted to confirm ketamine's efficacy in bipolar depression.

Ketamine was effective in drug-free studies, as well as in studies in which patients were under active treatment (antidepressants or mood-stabilizing agents). As it does not seem reasonable to recommend a complete withdrawal of antidepressant or mood-stabilizing treatment for 2 weeks in clinical practice and as ketamine remained significantly effective in patients who were administered an active treatment, ketamine

seems recommended as adjunctive treatment in patients treated by antidepressants or mood-stabilizing agents with partial/incomplete response or with the need of a faster response.

Ketamine was also effective when resistance to previous pharmacological treatment figured in inclusion criteria (Fig. 5). Nevertheless, all patients received at least one antidepressant or mood-stabilizing treatment before inclusion in the protocol and may therefore all be considered as resistant to pharmacological treatment. This suggests that ketamine may be recommended in patients that did not respond to previous

conventional treatments. However, while standardized criteria to establish resistance are available for MDD, the same is not true for bipolar depression, given the lack of effective treatments in this condition.

Promising results were found for suicidal ideation, but they should be confirmed in future studies because of the high degree of heterogeneity of current protocols and assessments of suicidal ideations. Moreover, suicidal ideation improvement was not adjusted by global depression improvement; it is therefore not possible to conclude to a specific effect of ketamine on suicidal ideations.

ECT studies

Ketamine has been used in ECT anesthesia for decades, with preliminary evidence suggesting that ketamine anesthesia in ECT may improve seizure duration relative to other anesthetic agents that are commonly used and minimize side effects, particularly cognitive impairment (Brewer et al. 1972; Green 1973; Krystal et al. 2003; McDaniel et al. 2006). Only four studies were included in our quantitative analysis (Table 3). Overall, ketamine administration was found to significantly improve depressive symptomatology ($p=0.04$) (Fig. 2). However, this result should be considered with caution due to the high heterogeneity of studies' designs: (1) depression score was assessed after 24 h in Wang et al. study, after 24–72 h in Abdallah et al. study, and after 1 week in Loo et al. study. The delay was unclear in Jarventausta et al. study (“after 3 ECT sessions”). (2) Two of the three studies that found non-significant results administered thiopental (a barbiturate anesthetic) with a 0.5 mg/kg dose of ketamine hydrochloride (Abdallah et al. 2012; Loo et al. 2012), while the other one used a 0.4 mg/kg dose with propofol (Jarventausta et al. 2013). On the other hand, Wang et al. administered a 0.8 mg/kg dose alone (Wang et al. 2012). The negative results may therefore be explained by a lower dose of ketamine in Abdallah et al., Loo et al., and Jarventausta et al. studies (0.4–0.5 vs 0.8 mg/kg in Wang et al. study). (3) Controls received thiopental alone in Abdallah et al. and Loo et al. studies and propofol alone in Wang et al. and Jarventausta et al. studies. (4) Wang et al. study used a bitemporal electric stimulation, Loo et al. study a unitemporal stimulation, and Abdallah et al. and Jarventausta et al. studies both unilateral or bilateral stimulation as was appropriate. Further trials with standardized protocols are warranted to confirm these results.

Adverse events

The cardiovascular events described in the studies (requiring higher antihypertensive agent dosages) should be considered

as a warning that caution is always required in patients with cardiovascular disease (e.g., patients with ischemic heart disease or hypertension). This may be due to a systemic release of catecholamines and an inhibition of norepinephrine re-uptake at peripheral nerves and non-neuronal tissues such as the myocardium induced by ketamine administration (Kitagawa et al. 2001). Besides cardiovascular side effects, dissociative symptoms can appear even with doses between 0.5 and 1 mg/kg. All patients should have a physical examination, routine hematologic and biochemical tests, urine toxicology measurements, and an electrocardiogram (ECG) to detect unstable medical illness or substance use before ketamine administration. In regard of the data presented in this work, it does not seem possible to determine if the presence of an anesthesiologist is necessary during ketamine administration in a psychiatric ward.

Limitations

Despite a comprehensive review of the literature, the use of stringent inclusion criteria, and the examination of potential publication bias, only 13 RCTs were included in this meta-analysis. However, 10 of 13 studies were classified as low risk of bias. As only four doses were used (0.4, 0.5, 0.8, and 1 mg/kg), it was not possible to carry out a correlation to highlight a dose effect. Included patients were overall middle-aged (group mean ages between 37.6 ± 15 and 65 ± 15 years) with a long history of mood disorders for most of them, even in studies that had no criteria of resistance at inclusion. Thus, these results cannot be extrapolated to date to early onset bipolar disorders, for example, or to mood disorders in the elderly for whom the cardiovascular risk of ketamine administration may outweigh the benefit. Studies in these specific populations should be carried out, as treatments for bipolar depression and MDD in the elderly remain unsatisfactory at times. As in other trials assessing new innovative treatments, patients with alcohol dependence and substance abuse were excluded in most of the studies, as well as those with a history of psychotic episode. These results can therefore not be extrapolated to patients with psychotic features, especially in regard to the risk of dissociation and derealization that is described in the transient side effects of ketamine. In the study by Kudoh et al. (Kudoh et al. 2002), ketamine was administered as an anesthetic agent for orthopedic surgery in depressed patients, and haloperidol 5 mg was administered for treatment of the postoperative confusion, which may have masked psychotic

symptomatology due to ketamine administration. It is thus unclear to date if ketamine may trigger the onset of persistent psychotic symptomatology in vulnerable patients.

Perspectives

Further studies should focus on ketamine's efficacy in bipolar depression and on the long-term efficacy of repeated doses (perhaps every 2–3 days) to assess whether or not ketamine maintains its effect over time and if no undesirable long-term adverse effects appear. Another form of administration (intramuscular administration) has recently been used and may improve the treatment feasibility in daily practice (Cusin et al. 2012; Harihar et al. 2013).

Conclusion

The present meta-analysis confirmed ketamine's efficacy in depressive disorders in both the nine non-ECT studies and the

four ECT studies, but designs in ECT studies were highly heterogeneous. Further non-ECT studies in bipolar depression and ECT studies are warranted. Promising preliminary results were found for suicidal ideations, but it is unclear whether ketamine improves suicidal ideations independently of global depression improvement or not. The use of ketamine should remain cautious for patients with cardiovascular history. Middle- and long-term efficacy and side effects are still not known to date.

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Appendix

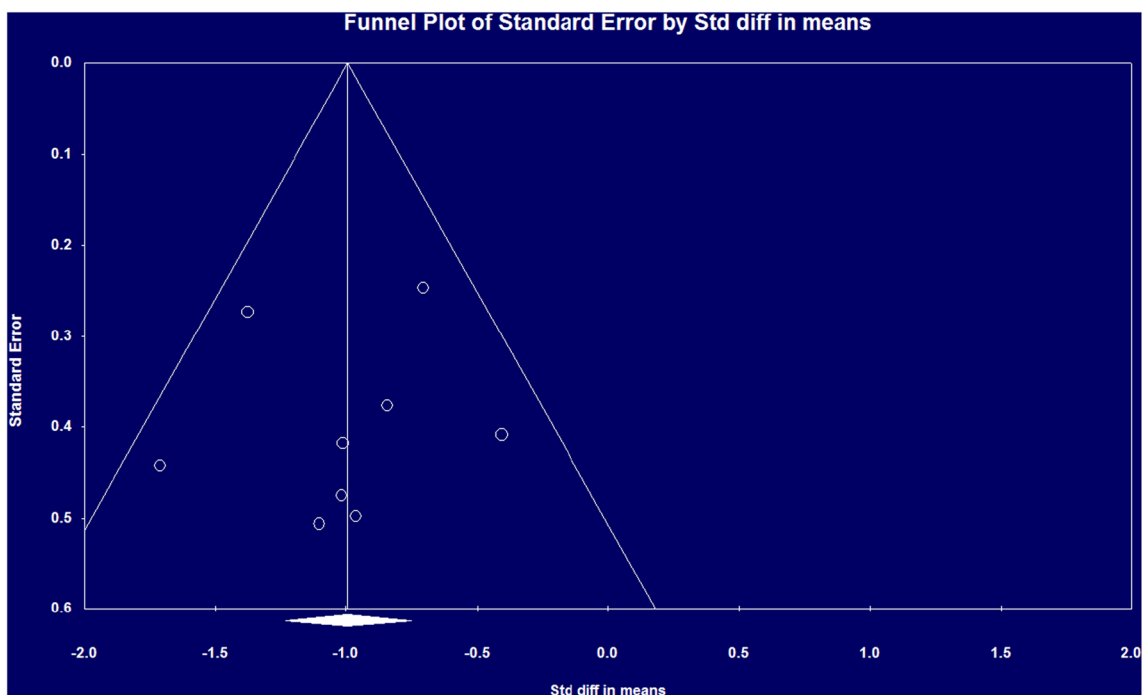


Fig. 7 Funnel plot

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