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

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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.

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

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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, 2012; Diazgranados et al., 2010; 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 (Fig. 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.

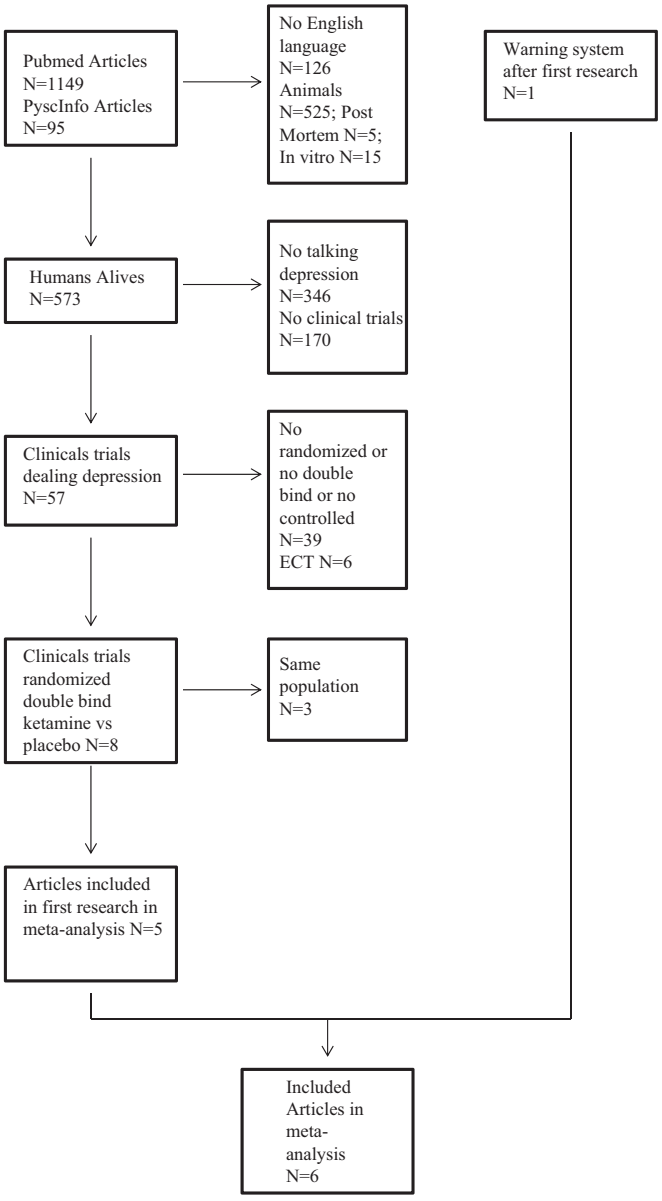

Fig. 1. Article identification process of randomized, double-blind and placebo-controlled trials of ketamine in major depression.

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 and 4, day 7 and day