General Hospital Psychiatry 37 (2015) 178–184

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: http://www.ghpjournal.com

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

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ARTICLE INFO

Article history:
Received 9 September 2014
Revised 29 December 2014
Accepted 8 January 2015

Keywords:
Ketamine
Depression
Therapy
Meta-analysis

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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http://dx.doi.org/10.1016/j.genhosppsych.2015.01.003
0163-8343/

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