
# Meta-Analysis of fast-acting efficacy of ketamine as a treatment for depression

Master in Statistics

Meta-Analysis [G0B75a]

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**Introduction**

This document includes an improvement of the paper delivered in the first examination period, in this version results from Meta-regression and Multilevel models are added.

Nowadays, cities and societies around the world face many modern and unprecedented challenges. Many people, from all backgrounds, struggle to adapt to aspects of reality regarding their social, professional, or family situations, and these struggles can often manifest themselves in a variety of different ways, such as stress, anxiety and depression. The cause of depression, as specified by the World Health Organisation, is a complex interaction of social, psychological, and biological factors. This complexity extends to treatment, with cases of depression often being chronic, resistant to treatment, and comorbid with other disabilities, adding further complications.

Many treatments for depression are already in practice, with varying measures of success. These treatments can involve pharmaceutical treatments (such as antidepressants), psychotherapy (such as mindfulness therapy), brain stimulation therapy (such as transcranial magnetic stimulation), among many others (Mayo Clinic, 2019). Due to varying rates of success and complex interactions, new patients often need to experiment with several treatments in turn before finding something that works for them.

As well as this issue of mixed results for different individuals (those suffering from what is termed treatment-resistant (TR) depression), there are two other key issues with those treatments listed above. They are slow (often taking weeks, months or even years to take effect), and they often incur side effects, ranging from mild to life-threatening (which can cause discontinuation of treatment before clinical improvements). The importance of a treatment that could offer immediate or fast acting relief to depression is thus paramount.

In 2019, the FDA approved the first truly new medication for major depression in decades; an anaesthetic drug called Ketamine (Chen, 2019). The chemical has been known for a long time and has had quite a turbulent history. The first commercial use began in Belgium, who patented the drug in 1963 as a veterinary anaesthetic (or horse tranquiliser). Shortly after, researchers from all over the world began exploring the drug in the sixties and seventies as a general anaesthetic, with publications coming from all over the world (Mion, 2017). For this reason, it was administered as a field anaesthetic to American soldiers during the Vietnam war.

Its recreational use and abuse, however, led to it becoming a controlled substance, decreasing the drug's availability, but also to researchers acknowledging the drug's euphoric and psychedelic properties. Due to this, investigations into the drug's suitability for palliative care began (Jansen, 2001). This eventually led to the first trials of Ketamine as a treatment for depression (Berman et al. 2000).

Since 2001, there has been an abundance of clinical trials assessing how ketamine performs as a treatment for depression, specifically, for treatment resistant depression and for those at risk for suicide. The reason for this is that the biological mechanism underlying the therapeutic effect of ketamine is both very fast acting, and unique from other treatments, meaning patients who have not benefited from existing treatments could benefit from Ketamine (Zarate & Niciu, 2015), especially if they are an immediate danger to themselves and need immediate relief. Many of these trials report very positive results, inciting a media response and general excitement, which introduces a risk of hype and bias. This makes the importance of vigorous testing (to avoid dangerous or ineffective treatments) even more important. The objective of this paper is to perform a meta-analysis on ketamine's rapid-acting effectiveness, by aggregating the results of a sample of clinical trials.

**Meta-analysis**

Meta-analysis is a statistical method for aggregating existing results from multiple studies. The benefit of such an endeavour is to produce a global result with greater statistical power than that derived from any individual study. Such a method is appropriate when there are multiple scientific studies addressing the topic in question, where each study can be seen as estimating a true effect (or range of effects) with a certain degree of error. The meta-analysis will derive a pooled estimate that will theoretically be closer to the true effect (or represent the mean of effects in question).

Numerous clinical trials have been conducted on the safety and efficacy of Ketamine as a rapidly acting treatment for depression. These trials vary in many important ways that affect their results and make a simple comparison of trials complicated. The most important ways in which these trials can vary are listed in Table 1.

*Table 1: Ways in which clinical trials on ketamine can vary*

| | |
|---|---|
| Design | Study designs vary widely; these may involve how the subjects are organised (independent groups or case crossover), when they are measured (hourly, daily), and who they are compared to (placebo or active treatment) |
| Participants | Baseline characteristics may vary between studies (such as nationality, age, sex, SES) as well as selective characteristics, depending on the nature of the trial (history of depression and previous treatments, other ongoing treatments) |
| Depression | Trials have typically focussed on treatment resistant (TR) depression, major depressive disorder (MDD), and bipolar depression (BD). These are defined and measured with different psychological metrics. |
| Ketamine | Ketamine has a few molecular variations (esketamine, ketamine hydrochloride), can be administered differently (orally, nasally, intravenously), and in different doses |

Multiple methods exist to address these differences between trials, which can involve including these variables as factors in a multilevel meta-analysis, or covariates in a regression meta-analysis. Indeed, previous research has indicated that ketamine affects males and females different, as well as there being an age effect and even an interaction between age and sex (Derntl et al, 2019). These variables are therefore interesting candidates as regression parameters.

To begin the analysis, academic articles were searched for online via the KU Leuven university database (Limo) as well as Google Scholar. Generic keywords were used to find all articles resembling clinical trials on ketamine, giving a list of 20 articles.

These articles were reviewed, and a sample kept for use in the meta-analysis according to a selection criterion. The selection criteria were defined such that those studies included in the analysis would form a coherent and comparable group; each asking a relatively similar question of the data and using relatively similar tools to do so. The selection criteria were as follows;

- Study is a randomised, placebo-controlled clinical trial
- The experimental group is administered at least one dose of ketamine
- All subjects are diagnosed with either major depressive disorder (MDD) or bipolar depression (BP)
- The study uses the Montgomery–Åsberg Depression Rating Scale (MADRS) as a metric for depression
- Depression is measured 24 hours after ketamine is administered

Using only studies that use the MADRS is a matter of convenience; this is the metric used by the vast majority of trials concerning depression and having a uniform metric in our meta-analysis simplifies things immensely. In addition, this criterion only eliminates one study that would otherwise be included (eliminated study; Fava et al. 2018).

Using only studies that have a measurement 24 hours after ketamine administration relates to the question being investigated. We are primarily interested in whether ketamine could be beneficial for patients who require immediate relief from their depressive episode and cannot wait for the slower effects of traditional treatments or therapies. The trials reviewed contained measurements ranging from hourly to weekly, but 24 hours suits our research question and was a commonly measured time point. When these selection criteria were applied to the 20 articles found in the online search, all but 7 were filtered out. The 7 remaining articles were clinical trials conforming to the selection criteria outlined above, the key features of which are summarised in *Table 2*.

In order to pool the data from the different trials to calculate an overall effect, the results of each individual trial must be standardised. This was done by collecting the sample sizes and means for the control and experimental groups in each study and using these data to calculate a standardised effect size (Cohen's D) for each trial. Two trials included in this meta-analysis (Singh et al. 2016, and Daly et al. 2018) contained multiple experimental groups, each with different doses of ketamine. These are included as levels within the meta-analysis. Cohen's D for each experimental group is included in the *Table 2*.

To perform the meta-analysis, these studies were first analysed all together, using a random effects model, and the results and heterogeneity assessed. We considered the possibility of publication bias in our sample of selected studies via an analysis of funnel plots. We then looked at more advanced analyses; subgroup analyses, a regression model to include the effect of covariates and a multilevel model to account for dependency within the data. Finally, we discuss measures of the power of the analysis.

*Table 2: Articles included in meta-analysis*

| Article Title | Author | Design | Treatment Group | Doses | Experimental Group Size | Control Group Size | Experimental Group Mean | Control Group Mean | Cohen's D |
|---|---|---|---|---|---|---|---|---|---|
| A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder | (Lapidus et al. 2014) | Randomised, double-blind, placebo-controlled crossover design | Intranasal ketamine hydrochloride (50 mg) | .50 mg | 18 | 18 | 17.47 | 25.08 | -0.84 |
| Intravenous Esketamine in Adult Treatment-Resistant Depression: A Double-Blind, Double-Randomization, Placebo-Controlled Study | (Singh et al. 2016) | Randomised, double-blind, placebo-controlled, multicenter trial | Intravenous infusion of .20 mg/kg or .40 mg/kg esketamine | .40 mg | 11 | 10 | 15.96 | 29.43 | -1.66 |
| | | | | .20 mg | 11 | 10 | 15.65 | 29.43 | -1.95 |
| Replication of Ketamine's Antidepressant Efficacy in Bipolar Depression: A Randomized Controlled Add-On Trial | (Zarate et al. 2012) | Randomised, double-blind, placebo-controlled crossover trial | Intravenous infusion of ketamine hydrochloride (0.5 mg/kg) | .50 mg | 15 | 15 | 20.41 | 31.95 | -1.28 |
| Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression A Randomized Clinical Trial | (Daly et al. 2018) | Randomised, double-blind, placebo-controlled, delayed-start trial | Intranasal esketamine 28, 56, or 84 mg | .28 mg | 11 | 33 | -14.8 | -5.7 | -0.91 |
| | | | | .56 mg | 11 | 33 | -15.7 | -5.7 | -1 |
| | | | | .84 mg | 12 | 33 | -16.4 | -5.7 | -1.07 |
| A Randomized Add-on Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Bipolar Depression | (Diazgranados et al. 201 | Randomised, double-blind, placebo-controlled, crossover trial | Intravenous infusion of ketamine hydrochloride (0.5 mg/kg) | .50 mg | 18 | 18 | 17.96 | 29.81 | -1.12 |
| Relationship of Ketamine's Antidepressant and Psychotomimetic Effects in Unipolar Depression | (Sos et al. 2013) | Randomised, double-blind, placebo-controlled, cross-over clinical trial | Intravenous infusion of ketamine hydrochloride (0.54 mg/kg) | .54 mg | 27 | 27 | 14.25 | 19.89 | -0.65 |
| Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial | (Murrough et al. 2013) | Randomised, multi-centre, placebo controlled trial | intravenous infusion of ketamine hydrochloride (0.5 mg/kg) | 0.50 mg | 47 | 25 | 14.77 | 22.72 | -0.77 |

In a random-effects model meta-analyses, it is not only assumed that effects of individual studies deviate from a true effect size due to sampling variance ($se^2$), but that there is another source of variance introduced by the fact that the studies do not stem from one single population ($\hat{\tau}$), but are drawn from a "universe" of populations. We can use the heterogeneity of our studies to estimate the variance of this universe of populations. Heterogeneity is addressed by examining the following.

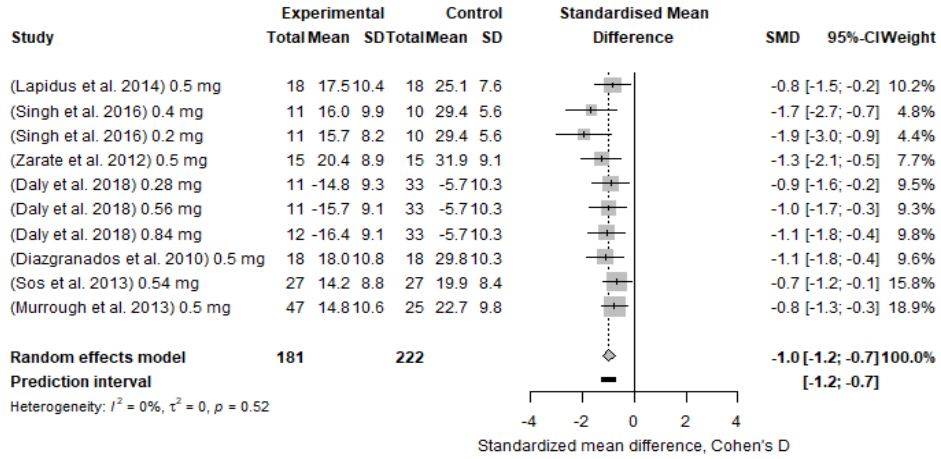
- *Clinical baseline heterogeneity*, which can be defined as the differences in participant characteristics, types or timing of outcome measurements and intervention characteristics between different studies
- *Statistical heterogeneity* in the collected effect size is calculated with Cochran's *Q*-statistic, which is the difference between the observed effect sizes and the fixed-effect model estimate of the effect size, which is then squared, weighted and summed
- Higgins & Thompson's $I^2$ measures the percentage of variability in the effect sizes due to this heterogeneity (as opposed to chance or sampling error)
- Tau-squared ($\tau^2$), which is a measure for the between-study variance in our meta-analysis, and can reflect the variance of the true effect sizes

**Random effect model**

Seven different studies were included in the analysis, two of which included multiple experimental groups (with different doses of ketamine; these were Singh et al. 2016 and Daly et al. 2018.) Of the seven studies, four had a crossover design (Lapidus et al. 2014, Zarate et al. 2012, Diazgranados et al. 2010, and Sos et al. 2013), meaning that the participants acted as their own control (after a washout period). Conversely, the remaining three studies (Singh et al. 2016, Daly et al. 2018, and Murrough et al. 2013) used two independent groups of participants for the treatment and control. Intravenous infusion or intranasal interventions of ketamine hydrochloride or esketamine are used in the studies as detailed in *Table 2*. In total, 181 participants received ketamine or esketamine, and 222 received placebo.

Standardised effect sizes (as shown in *Table 2*) were worked with in R using the package 'meta' to conduct the meta-analysis with a random effects model. All the calculated effect sizes were negative, meaning that the studies were all in agreement; depression measurements in the ketamine groups were lower than the control groups (greater feelings of depression mean high MADRS score). A forest plot was generated which clearly shows the similar results found in the sample of selected studies, which is shown in *Figure 1*.

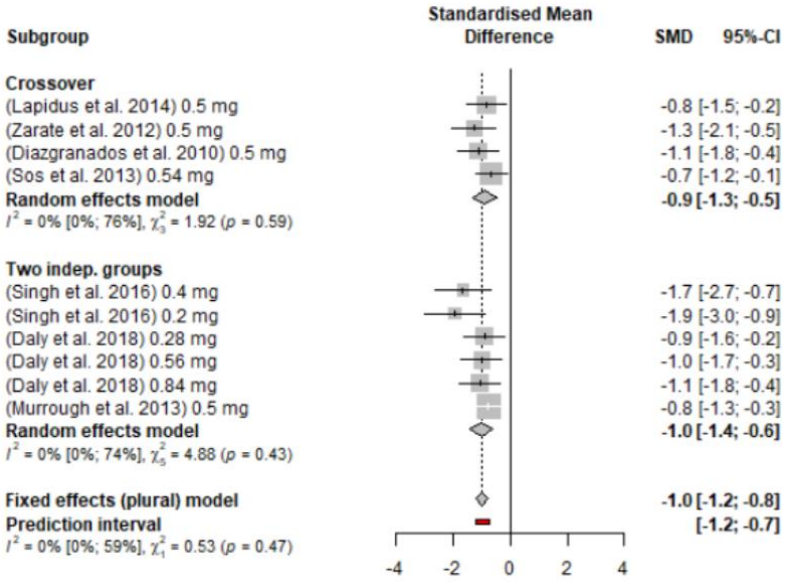
*Figure 1: Forest plot for meta-analysis*




We see in Figure 1 that, for our sample of studies, there was not much variation in either the effect size or the variance of the effect-size. The implication of this is that, despite the different calculation for the weights between the fixed and random effects model, the results are very similar, as the variation between the studies can largely be attributed to sampling variance (that is, our studies do not appear to have heterogeneity). This is corroborated statistically, in that we can observe that the global effect of ketamine on the depression scores at 24 hours post-treatment was significantly improved in patients receiving ketamine compared to controls (SMD = -1.0; 95% CI: [-1.2;-0.7]). No heterogeneity in the studies is found, as indicators Higgins & Thompson's $I^2$ and $\tau^2$ are equal to 0. It is important to note, however, that this first model is not taking into account any of the details discussed above, such as the fact that there are multiple groups belonging to the same studies, or any covariates.

We then proceeded to a subgroup analysis and compared those studies with independent groups with the crossover trials. This yielded very similar results; the ketamine treatment was deemed equally effective in studies with a crossover design (SMD = -0.9; 95% CI: [-1.3;-0.5]) than studies with two independent groups (SMD = -1.0; 95% CI: [-1.4;-0.6]). These results are shown in the forest plot in *Figure 2*.

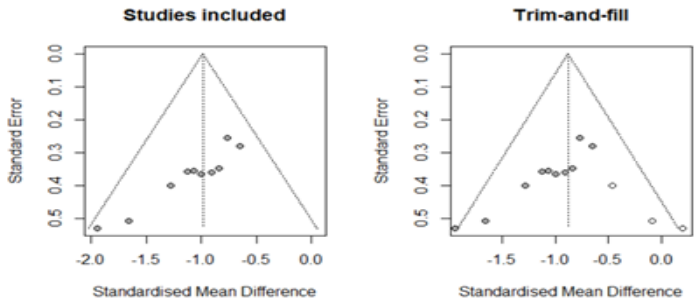
*Figure 2: Subgroups; Crossover design and Independent Groups*




An additional consideration taken in this analysis involves the possibility of the results being affected by publication bias. As all the studies used in this meta-analysis come from published trials with significant results, there is a possibility that unpublished trials with conflicting results may exist, while not being included in this analysis. The 'trim and fill' method is used to identify and correct for asymmetry that can be seen in a funnel plot, arising from publication bias. The basis of this method is to remove the smaller studies causing funnel plot asymmetry, and to use the trimmed funnel plot to estimate the true 'centre' of the funnel, then replace the omitted studies and their missing 'counterparts' around the centre. As well as providing an estimate of the number of missing studies, an adjusted intervention effect is derived by performing a meta-analysis including the filled studies.

Results are unchanged after adjustment for bias when using the 'trim and fill' method for estimating outcomes with missing studies in the meta-analysis (SMD = -0.9; 95% CI: [-1.2;-0.6]) The heterogeneity indicator $I^2$ increased to 29%, which is still considered as low heterogeneity. The funnel plots are shown in Figure 3, where we can see how two studies were added to provide symmetry. The effects of this adjustment on the overall results is negligible, indicating that publication bias does not seem likely to be a large influence.

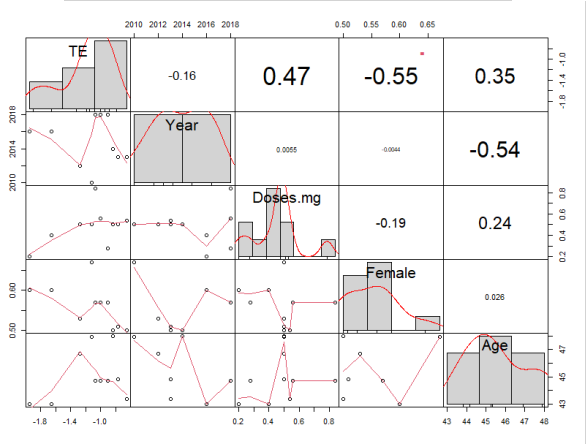
*Figure 3: Funnel plots*



**Meta-regression and multilevel model**

As discussed in the introduction, previous research (Derntl et al, 2019) has indicated that the effect of ketamine may be modified by age and sex. For the analysed studies, a multiple Meta regression model was conducted, not only modelling additive relationships but also modelling so-called interactions. Interactions means that the relationship between one predictor variable and the estimated effect size changes for different values of another predictor variable.

*Figure 4: Intercorrelations between covariates*




In order to decide which variable to include in the multiple meta regression model, multicollinearity was checked, in Figure 4 can be observed that standardized effect of Ketamine (TE) has a strong relationship with the percentage of Female participants in the studies, and in opposite but strongly correlated too with the average age of the participants and the dosage used in each study. Even though Year is not highly correlated with TE, there is a relationship with covariate Age that we want to review. For these reasons, these variables were included in the model and results of the meta-regression can be seen in Figure 5.

*Figure 5: Meta-regression coefficients*

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Mixed-Effects Model (k = 10; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
  0.0087   -0.0174   13.9826    9.6866  125.9826

tau^2 (estimated amount of residual heterogeneity):     0 (SE = 0.0801)
tau (square root of estimated tau^2 value):             0
I^2 (residual heterogeneity / unaccounted variability): 0.00%
H^2 (unaccounted variability / sampling variability):   1.00
R^2 (amount of heterogeneity accounted for):            100.00%

Test for Residual Heterogeneity:
QE(df = 4) = 0.5780, p-val = 0.9655

Test of Moderators (coefficients 2:6):
F(df1 = 5, df2 = 4) = 10.5014, p-val = 0.0204

Model Results:

                  estimate      se      tval    pval     ci.lb    ci.ub
intrcpt            -1.1235  0.0463  -24.2680  <.0001   -1.2520  -0.9949  ***
Year_sc             0.0922  0.0276    3.3398  0.0288    0.0156   0.1688    *
Doses_sc           -0.2489  0.3320   -0.7495  0.4952   -1.1708   0.6730
Female_sc          -8.6498  1.2891   -6.7098  0.0026  -12.2290  -5.0706   **
Age_sc              0.1249  0.0358    3.4832  0.0253    0.0253   0.2244    *
Female_sc:Age_sc    3.3122  0.6389    5.1845  0.0066    1.5384   5.0859   **

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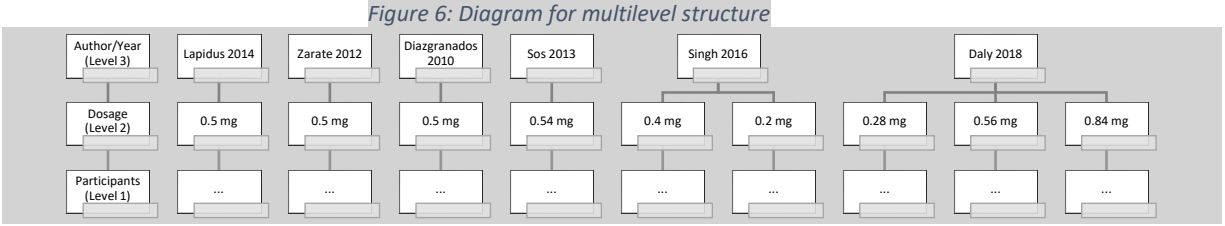
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

It was found a positive significant relationship not only for the standardized mean difference effect (intercept) but also for the percentage of females in the study (remember that greater feelings of depression mean high MADRS score). There is an inverse relationship for publication year, the average Age of participants and the interaction effect of Gender and Age, all these coefficients were statistically significative at 1% (α=0.01). These results can be interpreted as the treatment with Ketamine reduce the MADRS score in 1.12 points in average. There is a decrease in effect sizes in favour of Ketamine in recent years, effects are better in younger

people but with higher results in female participants. Even though the dosage showed high correlation with the effect size, the covariate is not significant in the model. It is important to mention that Gender and Age effect and consequently the interaction term are highly affected by year variable, as their significance increase after controlling by this variable. The significance of the model was validated by performing a permutation test to confirm the robustness of the model results.

In order to assess the nested structure of the different dosage applied within studies, a multilevel model was fit, where participants and dosages are "nested" within studies (authors). This means that participants are on level 1 in a "pooled" form (mean and standard deviation of the studied sample instead of the raw data), on level 2 the dosage used in the participants in the study and on level 3, the study level (Author and Year) as the following diagram show.

*Figure 6: Diagram for multilevel structure*




The null model using this multilevel structure indicate in Figure 7, that there is variance to be explained only between authors (0.013) but not between doses within authors (0.000). This means that there is no variation in the results if different dosages are applied in the participants in a same study. Now, that is controlled by this characteristic of the effects, we can test the impact that moderators has on the results. In this case, after controlling for year of publication, which now is not significant, Female covariate is significant at 5% (α=0.05), meanwhile, the effect of the interaction between Female and Age is only significant to 10% (α=0.1), in this model Age is not significant as it was in the meta-regression.

*Figure 7: Multilevel null model (1) Multilevel model with moderators (2)*

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Multivariate Meta-Analysis Model (k = 10; method: REML)

  logLik  Deviance       AIC       BIC      AICc
 -3.3689    6.7377   12.7377   13.3294   17.5377

Variance Components:

            estim    sqrt  nlvls  fixed       factor
sigma^2.1  0.0130  0.1139      7     no       Author
sigma^2.2  0.0000  0.0000     10     no  Author/dose

Test for Heterogeneity:
Q(df = 9) = 8.1656, p-val = 0.5175

Model Results:

estimate      se     tval    pval    ci.lb    ci.ub
 -0.9963  0.1207  -8.2539  <.0001  -1.2693  -0.7232  ***
```

(1)

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Multivariate Meta-Analysis Model (k = 10; method: REML)

  logLik  Deviance       AIC       BIC      AICc
  0.0445   -0.0890    9.9110    7.9582   69.9110

Variance Components:

            estim    sqrt  nlvls  fixed       factor
sigma^2.1  0.0000  0.0000      7    yes       Author
sigma^2.2  0.0000  0.0000     10    yes  Author/dose

Test for Residual Heterogeneity:
QE(df = 5) = 0.6592, p-val = 0.9851

Test of Moderators (coefficients 2:5):
F(df1 = 4, df2 = 5) = 1.8766, p-val = 0.2527

Model Results:

                estimate      se     tval    pval     ci.lb    ci.ub
intrcpt          -1.1232  0.1218  -9.2235  0.0003   -1.4363  -0.8102  ***
Year_sc           0.0837  0.0662   1.2639  0.2620   -0.0865   0.2540
Female_sc        -8.2455  3.0801  -2.6770  0.0440  -16.1633  -0.3278    *
Age_sc            0.1151  0.0878   1.3102  0.2471   -0.1107   0.3409
Female_sc:Age_sc  3.1042  1.5138   2.0506  0.0956   -0.7871   6.9955    .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(2)

Considering these outputs, it is possible to suggest that there is a dependency of the results of each study with different dosage to the Author that carry out the study and to the year of publication. If this relation is not introduced correctly in the model and not taken into account, some relations could be inflated or result in spurious. In this case is necessary to use multilevel models for test moderators.

**Discussion and conclusion**

This meta-analysis, based on the data reported in seven clinical trials, supported the evidence that ketamine, as compared with placebo, was significantly effective in reducing depressive symptoms within 24 hours of treatment.

A limitation of this meta-analysis was the limited number of trials and data included in the analysis. This small sample of studies meant that analyses involving more factors (such as measurements at multiple time points or dose sizes) was not possible. Indeed, of the 7 included trials, only four doses were used (0.2, 0.4, 0.5, 0.8 mg/kg), so it was not possible to analyse a dose effect. A lack of available data to work with may be responsible for this meta-analysis not detecting significant relationships between demographic characteristics and ketamine's efficacy. Having the raw data of each trial would open up many possibilities for exploring covariates.

Extrapolation must also be cautioned against; patients with alcohol dependence and substance abuse were excluded in most of the studies, as well as those with a history of psychotic episodes. 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 as a transient side effects of ketamine.

Further studies could focus on how ketamine interacts with other treatment types. As a rapidly acting treatment, if combined with traditional treatments known to have slower but longer-term benefits, the true value of ketamine as a treatment for depression may be appreciated, and offer new hope to patients who need both immediate and long term help with their disorder.

To be able to analyse these results, it is necessary to account for the relationship between dosages in a same study, as they may be influenced by the author performance and this could lead to distorted conclusions, multilevel model is highly recommended.

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