# **Hi Pamela!**

# **The introduction, methods and results are now more or less done, and i’ll try to write the discussion tonight. Please add, criticise, comment, edit etc. as much as you can!**

# **Unfortunately the word-count so far is 3200, and the requested size for the total paper is 2000-3000, so we will have to cut it down quite a bit. I have some ideas about that, but let me know what you think!**

# 

# **Introduction 1505 words**

**Intro 1: Gravity of depression (300)**

**Intro 2: Existing treatments (275)**

**Intro 3: Introduction to ketamine (400)**

**Intro 4: Introduction to meta-analysis in general (250)**

**Intro 5: Introduction to this meta-analysis (280)**

# **Methods 750 words**

**Methods 1: Search strategy and criteria for selection**

**Methods 2: Data extraction**

**Methods 3: Statistical analyses**

**Results 950 words**

**Results 1: First Model**

**Results 2: Subgroup Analysis**

**Results 3: Publication Bias**

**Results 4: Meta Regression / Covariates**

**Results 5: Multilevel Analysis (non-existent)**

**Discussion (non-existent) i think approx 500 is required (must cut ~700)**

# **I will reduce the introduction part**

# **Introduction**

**Part 1: Gravity of depression**

Cities and societies around the world today face many modern and unprecedented challenges. Many people, from all backgrounds, struggle to adapt to aspects of reality regarding their social, professional, or philosophical situations, and these struggles can often manifest themselves in a variety of different ways, such as stress, anxiety and depression. Depression, the treatment of which is the subject of this paper, is a leading cause of disability worldwide, and major contributor to the overall global burden of disease (World Health Organisation, 2020). 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.

Not only is the prevalence of depression a clear indicator of this disability’s importance, its cost, both in an economical sense as well as phenomenological, is also critical. Many adults today have either experienced depression, or know someone who has, and the experience is nothing to take lightly. Indeed, while there is no clear definition of what it is we are supposed to strive for in life in general, most definitions revolve in some way around the concept of happiness, which is situated at the opposite end of the abstract continuum of wellbeing as “depression”. But depression is much more than “unhappiness”. An author well-acquainted with the subject writes, *depression is actually much more complex, nuanced and dark than unhappiness – more like an implosion of self. In a serious state of depression, you become a sort of half-living ghost* (Lott, 2016)*.* This dire, and in fact terrifying, account of such a condition only serves to emphasise the importance of determining effective treatments for what is, essentially, a treatable disorder.

**Part 2: Existing treatments**

For these reasons, many treatments for depression are already in practice, with varying measures of success. These treatments can involve pharmaceutical treatments (antidepressants, such as SSRIs or tricyclic treatments), psychotherapy (such as CBT or mindfulness therapy), brain stimulation therapy (such as ECT or transcranial magnetic stimulation), among many others (Mayo Clinic, 2019). While a full discussion of these treatment options is outside the scope of this paper, one of the key factors that is often concluded by healthcare practitioners is that there is a huge range of treatments that operate through a huge range of mechanisms. Some of these treatments may seem like a miracle cure for some individuals, but do nothing for others. 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 form 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). When a patient is experiencing a major depressive episode, and is in danger of taking their own life or at risk of engaging in self-destructive or dangerous behaviour, these issues become unacceptable; a delay of weeks or months for improvement is entirely too slow to be clinically sufficient. Historically, this has necessitated hospitalisation or sectioning, neither of which are desirable for anyone involved. The importance of a treatment that could offer immediate or fast acting relief to depression is thus paramount.

**Part 3: Introduction to ketamine**

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 anesthetic, with publications coming from all over the world (including North-American, German, Italian, Brazilian, Japanese and Danish research teams) (Mion, 2017), often discussing it favourably as providing sufficiently potent analgesia for surgery, but less potent and of considerably shorter duration of action than alternatives, meaning it was safer and easier to control. Because of these properties, it was administered as a field anaesthetic to american soldiers during the Vietnam war.

The drug was quite popular, until practitioners became quite concerned over people abusing the drug for its psychadelic effects. In the nineties, this led to the drug becoming a controlled substance, which, alongside the appearance of newer anesthetics without these complications, led to it falling out of regular use as a human anesthetic. Its recreational use and abuse, however, led researchers to acknowledge the drug’s euphoric and psychedelic properties, leading to initial investigations into the drug’s suitability for palliative care (Jansen, 2001). This 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. 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 effectiveness, by aggregating the results of a sample of clinical trials on Ketamine.

**Part 4: Introduction to meta-analysis in general**

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 than 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).

However, the process does involve some input from the researcher that can potentially invite bias into the analysis. The choices of the researcher can affect the results, in that they determine how studies are sourced, which studies are included, and what analytical model is applied. These aspects of the meta analysis must therefore be consciously defined and clearly specified.

An important distinction to make is between the assumptions underlying the fixed effects model and those underlying the random effects model. The fixed effects model assumes the existence of a true effect size, and so the meta-analysis aggregates the individual studies’ estimates of this effect size to derive a new, higher powered estimate. The random effects model, on the other hand, assumes a distribution of different true effects due to differences between the studies. The objective of the meta-analysis is therefore to derive a mean effect size.

**Part 5: Introduction to this meta-analysis**

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.

As discussed above, an important implication of these differences between the studies being investigated is that the “true” effect size being measured by the different clinical trials will vary, and so a random effects model is more appropriate to this meta-analysis.

*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 depression, major depressive disorder, and bipolar depression. 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 |

Other methods to address these differences between trials exist, which can involve including these variables as factors in a multilevel meta-analyses, 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.

# **Methods**

**Methods 1: Search strategy and criteria for selection**

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 to be used in the meta-analysis according to a selection criteria. The selection criteria was 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 with 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

The last two criteria are the most subjective, and relate to the specific question being asked of the data. For this reason, each will be briefly discussed.

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.[[1]](#footnote-0))

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 Appendix A.

**Methods 2: Data extraction**

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 in Appendix A.

**Methods 3: Statistical analyses**

To perform the meta-analysis, these studies were first analysed all together, using a random effects model, and the results and heterogeneity of this model were 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.

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 (), but that there is another source of variance introduced by the fact that the studies do not stem from one single population (), 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
* Higgin’s & Thompson’s measures the the percentage of variability in the effect sizes due to this heterogeneity (as opposed to chance or sampling error)
* Tau-squared (), which is a measure for the between-study variance in our meta-analysis, and can reflect the variance of the true effect sizes

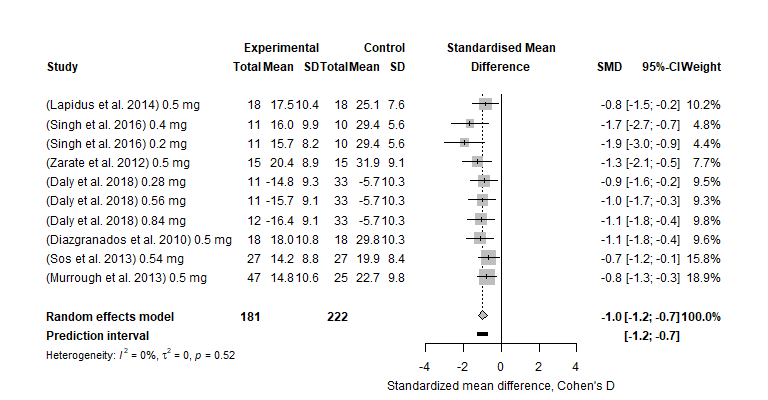
**Results**

Seven different studies were included in the analysis, two of which include multiple experimental groups (with different doses of ketamine; these were [Singh et al. 2016](https://www.zotero.org/google-docs/?Lb4GNe) and [Daly et al. 2018.)](https://www.zotero.org/google-docs/?y5YlOr) Of the seven studies, four had a crossover design [(Lapidus et al. 2014](https://www.zotero.org/google-docs/?FkqFtf), [Zarate et al. 2012](https://www.zotero.org/google-docs/?Ntnn11), [Diazgranados et al. 2010](https://www.zotero.org/google-docs/?7il3Xd), and [Sos et al. 2013)](https://www.zotero.org/google-docs/?4nHGfh), meaning that the participants acted as their own control (after a washout period). Conversely, the remaining three studies [(Singh et al. 2016](https://www.zotero.org/google-docs/?qwYjtH), [Daly et al. 2018,](https://www.zotero.org/google-docs/?a0Td8L) and [Murrough et al. 2013)](https://www.zotero.org/google-docs/?bLck0j) use 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 Appendix A. In total, one hundred and eighty one participants received ketamine or esketamine, and two hundred twenty two received placebo.

**Results 1: First Model**

Standardised effect sizes (as shown in Appendix A) 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

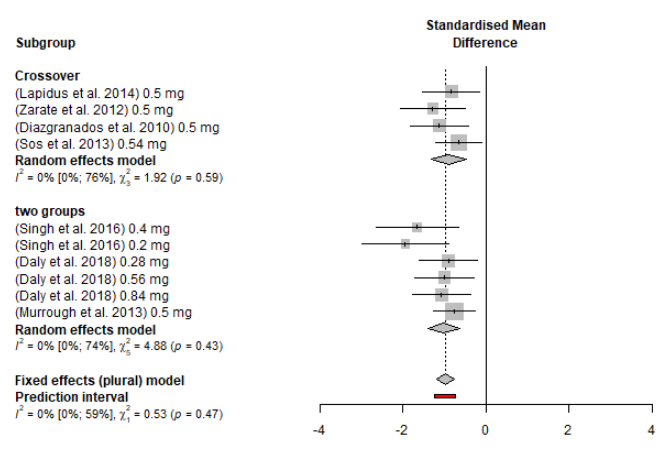


We see in Figure 1 that, for our sample of studies, there was not much variation in either the effect size nor the variance of the effect-size. The implication of this is that, despite the different calculation for the weights between the fixed and random effects model, the results are very similar, 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 24hours 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 Higgin’s & Thompson’s and 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.

**Results 2: Subgroup Analysis**

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

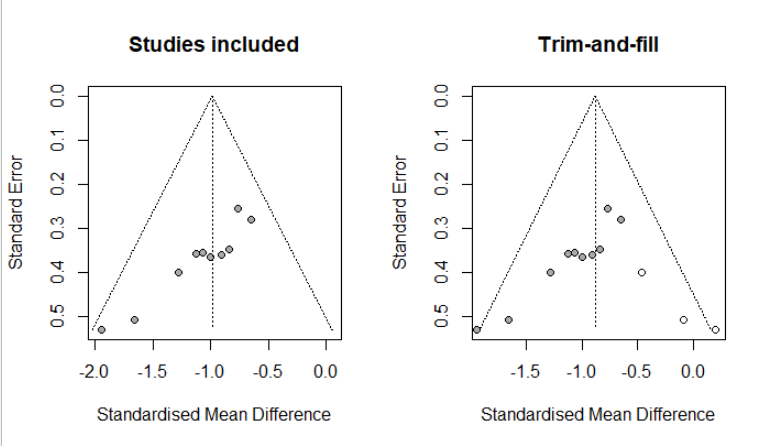


**Results 3: Publication Bias**

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 (Taylor 1998, Duval 2000). 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 remain significant after adjustment for bias, using trim and fill method for estimating numbers and outcomes of missing studies in a meta-analysis (SMD = -0.9; 95% CI: [-1.2;-0.6]) and heterogeneity indicator increase to 29%, which is still considerate as low heterogeneity. The funnel plot is shown in Figure 3, where we can see two studies 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

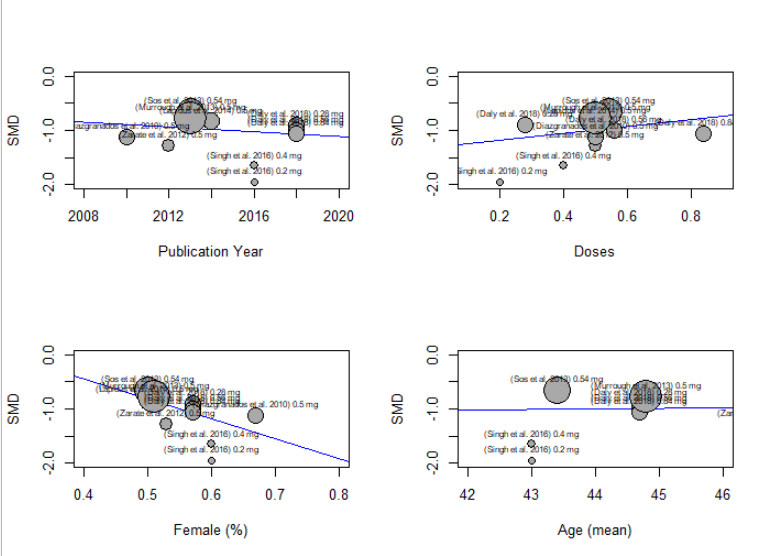
* 

**Results 4: Meta Regression / Covariates**

As discussed in the introduction, previous research has indicated that the effect of ketamine may be modified by age and sex. For our studies, while we found a positive relation between the standardized mean difference and the percentage of females in the studies, we did not find any significant covariates in a meta regression. This is likely due to the baseline sample characteristics of our studies being quite similar; for the most part, they worked with population samples of similar mean ages and sexes. If there were extreme differences between the study populations in the covariate in question, its effect would be much more pronounced. Likewise, we found no significant relation between the standardized mean difference and the publication year, nor the amount of ketamine doses in the intervention of each study. These meta-regressions are visualised in Figure 4.

A more sensitive analysis of these covariates would involve splitting each individual study according the covariate in question, then pooling the subgroups across the studies (all the females from all the studies compared to all the males from all the studies). However, the reported data in our sample of studies was too often pooled across sex and age, so it was not possible generate a standardised effect for each study across these potential covariates.

Figure 4: Visualisations of Covariates Analysed in Meta Regression



**Results 5: Multilevel Analysis**

The Random-Effects Model was chosen to conduct this analysis using the effect size, and a dispersion (variance) estimate for each study, of which the inverse is taken (Borenstein et al. [2011](https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/pool.html#ref-borenstein2011)).

The inverse variance is calculated considering .

In addition, prediction intervals are calculated that will give a range for which we can expect the effects of future studies to fall based on our present evidence in the meta-analysis.

Heterogeneity is also addressed by conducting a subgroup analysis which consists of two parts;

1. pooling the effect of each subgroup, and
2. comparing the effects of the subgroups (Borenstein and Higgins [2013](https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/subgroup.html#ref-borenstein2013meta)).

# 

# **Discussion/Conclusion**

**Points to discuss;**

* Possibility of publication bias; only including trials that were published (funnel plot?)

**Discussion 1: Efficacy of ketamine as rapid acting treatment**

* Significance of a new rapidly-acting treatment for depression
  + ECT also serves this purpose, but with severe side effects and mixed results
* Can potentially function with other therapies
  + Ketamine for immediate relief, traditional pharmaceuticals for mid-term relief, behavioural therapy for long-term relief
* Each treatments as one of many tools in a toolbox

**Discussion 2: Steps to make this a full meta-analysis**

* From the assignment description; You can show that you reached the attainment targets of the course by doing a metaanalysis on a convenience sample of studies (for instance 5-10 studies), but explaining what additional steps should have been taken in order to make it a systematic review.

**The paper should include about 2000-3000 words of text (which is about 4-6 pages) besides tables, graphs and the reference list**

Good concluding comments from this article [*https://www.yalemedicine.org/stories/ketamine-depression/*](https://www.yalemedicine.org/stories/ketamine-depression/)

*Most important for people to know, however, is that ketamine needs to be part of a more comprehensive treatment plan for depression. “Patients will call me up and say they don’t want any other medication or psychotherapy, they just want ketamine, and I have to explain to them that it is very unlikely that a single dose, or even several doses of ketamine alone, will cure their depression,” says Dr. Sanacora. Instead, he explains, “I tell them it may provide rapid benefits that can be sustained with comprehensive treatment plans that could include ongoing treatments with ketamine. Additionally, it appears to help facilitate the creation new neural pathways that can help them develop resiliency and protect against the return of the depression.”*

*This is why Dr. Sanacora believes that ketamine may be most effective when combined with cognitive behavioral therapy (CBT). CBT is a type of psychotherapy that helps patients learn more productive attitudes and behaviors. Ongoing research, including clinical trials, addressing this idea are currently underway here at Yale.*

*But like any new drug, this one comes with its cautions. Side effects, including dizziness, a rise in blood pressure, and feelings of detachment or disconnection from reality may arise. In addition, the research is still relatively new. Studies have only followed patients for one year, which means doctors don’t yet know how it might affect patients over longer periods of time. Others worry that since ketamine is sometimes abused (as a club drug called Special K), there may be a downside to making it more readily available—it might increase the likelihood that it will end up in the wrong hands.*

*In the end, though, the FDA approval of esketamine gives doctors another valuable tool in their arsenal against depression—and offers new hope for patients no one had been able to help before.*

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[Zarate, Carlos A., Nancy E. Brutsche, Lobna Ibrahim, Jose Franco-Chaves, Nancy Diazgranados, Anibal Cravchik, Jessica Selter, Craig A. Marquardt, Victoria Liberty, and David A. Luckenbaugh. 2012. ‘Replication of Ketamine’s Antidepressant Efficacy in Bipolar Depression: A Randomized Controlled Add-On Trial’. *Biological Psychiatry* 71(11):939–46.](https://www.zotero.org/google-docs/?ploOFy)

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**Part 1: Gravity of depression**

Impact of depression on society

* Philosophical definition, and importance of striving for happiness
* Increasing prevalence / effect on society; increasing global burden of depression
* Importance of effective and manageable treatments

**Part 2: Existing treatments**

* Limited options for treatment (CBT, benzos, ECT)
  + Too slow (weeks or months to see improvement)
  + Often ineffective (increase of TR depression)
  + Side effects (often severe with benzos and ECT)
* Risk of suicide, destructive behaviour before treatment takes effect
  + Importance of new, faster acting treatments

**Part 3: Introduction to ketamine**

Ketamine as a new and novel treatment

* Historically as horse tranquiliser, then general anesthetic
  + Brief history of use, and discovery as potential, fast-acting depression treatment
* Brief history of clinical investigations, existing meta-analyses
  + Ketamine as first new treatment of depression in long time
* Importance of vigorous testing to avoid dangerous or ineffective treatments

**Part 4: Introduction to meta-analysis in general**

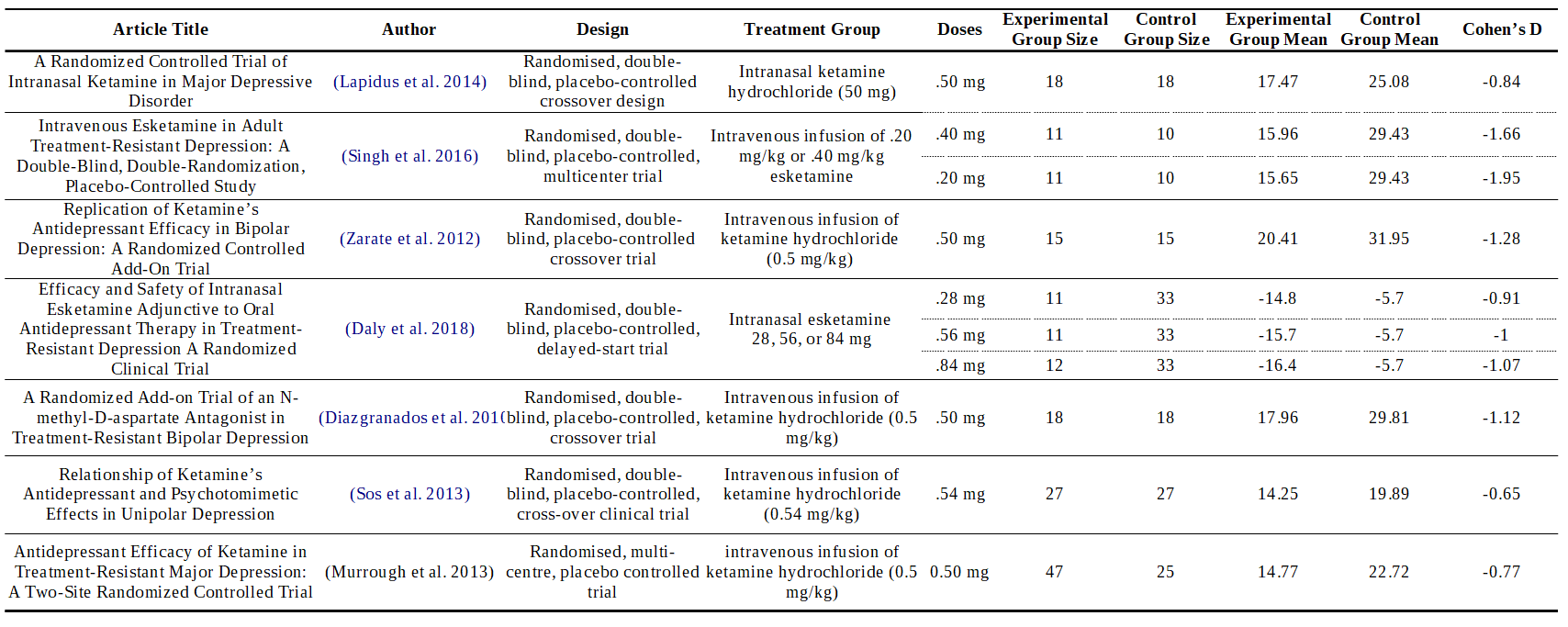
Means of aggregating existing data

* Techniques used in general
  + Fixed effects / random effects
* Techniques used in this analysis
* Strengths and limitations of the techniques (in general)

**Part 5: Introduction to this meta-analysis**

* Differences between ketamine trials
  + Study design (independent groups or crossover), measurement time differences, types of control group (alternative treatment or placebo)
  + types of participants (random; age, sex, SES, and other other characteristics) as well as non-random (history of depression / treatments, presence of other treatments, commorbidities)
  + types of depression diagnoses (MDD, TRD, BP), types of depression metrics
  + types of ketamine (drug type and means of administration), dose differences,,

.Appendix A: Articles included in meta-analysis



1. Fava, et al., (2004) Double-Blind, Placebo-Controlled, Dose-Ranging Trial of Intravenous Ketamine as Adjunctive Therapy in Treatment-Resistant Depression [↑](#footnote-ref-0)