2020

Is Ketamine Effective in Reducing Depressive Symptoms in Adults with Treatment-resistant Major Depressive Disorder?

Andrew J. Suplicki
Philadelphia College of Osteopathic Medicine

Is ketamine effective in reducing depressive symptoms in adults with treatment-resistant major depressive disorder?

Andrew J. Suplicki, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 13, 2019

Abstract

Objective: The objective of this selective EBM review is to determine whether or not ketamine is effective in reducing depressive symptoms in adults with treatment-resistant major depressive disorder.

Study Design: A systematic review of 3 randomized, double-blind placebo controlled trials performed in or after the year 2016.

Data Sources: All 3 studies published in peer-reviewed journals found on PubMed and Cochrane Collection.

Outcome Measures: The studies utilized quantitative scales, either the Montgomery-Asberg Depression Scale (MADRS) or Hamilton Depression Rating Scales (HAMD) for the POEM, depressive symptoms.

Results: George et al. (*Am J Geriatr Psychiatry*. 2017;25(11):1199-1209. doi: 10.1016/j.jagp.2017.06.007) did show significant reduction in depressive symptoms with 0.2mg/kg ketamine SQ and the severity of the depressive episode downgraded compared to the placebo of midazolam at day 2 and induced remission in some individuals. Chen et al. (*J Affect Disord*. 2018;225:709-714. doi: 10.1016/j.jad.2017.09.008) additionally found a significant change in depressive symptoms from 0.2mg/kg ketamine infusion compared to the placebo. However, Su et al. (*Neuropsychopharmacology*. 2017;42(13):2482-2492. doi: 10.1038/npp.2017.94) results of 0.2mg/kg ketamine displayed near equal reduction between the intervention and placebo of saline solution at day 2.

Conclusion: This EBM shows that more studies need to be performed before one could recommend ketamine as an intervention for treatment resistant MDD. The reductions in the short term were significant and encourage the capability of ketamine as a bridge therapy or short term episodic treatment.

Key words: ketamine, depression

Introduction

Major depressive disorder (MDD) is a debilitating episodic mood disorder that affects the day to day functions of those afflicted. It has a multitude of symptoms that vary in their presentation and effect on normal daily activities, ranging from mild symptoms like change in appetite and loss of energy to the most damaging, suicidal ideation. The condition affects men and women, young and old, and across socioeconomic status. It is treated with combination of psychotherapy and pharmacologic agents, starting with selective serotonin reuptake inhibitors (SSRIs). However, the prevalence of multi-drug resistant MDD has spurred research for novel pharmacologic agents.

Major depressive disorder (MDD) affects 3.7-6.7% of the world population, with increased incidence when considering just depressive symptoms in the general public.[1,2] The diagnosis of MDD requires the presence of 5 out of 9 symptoms of insomnia, depressed mood, guilt, anhedonia, change in appetite, change in cognition, loss of energy, feeling of worthlessness, and suicidal ideation during a 2-week period. After diagnosis patients are treated in primary care, psychiatry and psychology practices, emergency rooms, and many other specialties with a pharmacologic agent, usually an SSRI. Best practice includes a referral for psychotherapy. With the prevalence of MDD and variety of specialties in which physician assistants (PAs) see these patients, it is common for PAs to be asked to initiate medication or continue their prescriptions.

Patients with MDD, and especially treatment resistant MDD, require multiple visits for their care and in turn MDD has a high treatment cost. In 2010, the economic burden in the US for treatment of MDD was estimated at a total of $210.5 billion.[2] The average total cost, including medical visits and the pharmacy payments was $19,626 per treatment-resistant MDD episode. This is per episode, rather than annual cost, meaning that a patient can have an episode

last longer than 365 days or can have recurrent episodes per year in treatment-resistant MDD.[3] Patients with treatment resistant MDD have an increased duration of a depressive episode, more severe symptoms, increased likelihood of suicidal ideations, increased pharmacy costs, and possible hospitalization compared to a newly diagnosed or easily treated MDD depressive episode. Unfortunately, the amount of healthcare visits for MDD are difficult to estimate due to the high incidence of comorbidities that could be the primary diagnosis for healthcare utilization while MDD is also being managed. However, patients suffering from MDD with increased relapse and remission, which falls under treatment-resistant MDD, have a yearly average of 27 outpatient visits, 1 emergency department visit, and 1-day inpatient visit.[3] The increased outpatient visits and potential inpatient management lead to the aforementioned economic burden of treatment-resistant MDD care.[2]

MDD is pervasive and elusive in treating in part because the exact pathophysiology of the disease is unknown. While it has been studied extensively, the exact mechanism of the condition is not fully understood. First, there is the biochemical hypothesis, in which neurotransmitter synthesis, breakdown and receptor sensitivity are altered. These neurotransmitters traditionally targeted by medication are dopamine, norepinephrine, and most often, serotonin. Second is the neuroendocrine hypothesis, in which endocrine axis such as thyroid hormone and cortisol affect neuroprocessing. This hypothesis is supported by the incidence of MDD and depressive symptoms in individuals with endocrine pathologies including Addison's disease and hypothyroidism. Thirdly is the hypothesis that early life stressors affect the development of the brain and its function. This is currently being researched with results displaying a correlation between stressful events in childhood directly relating to mental health diseases later in life.

These hypotheses establish the different forms of therapies, psychiatric or pharmacologic, for MDD. Starting with the gold standard of treatment for MDD is a combination of

psychotherapy performed by a therapist and pharmacologic anti-depressant agents. The first line treatment include SSRIs such as sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), and escitalopram (Lexapro). If those are unsuccessful or the side effects are undesirable, patients can try serotonin norepinephrine reuptake inhibitors like venlafaxine (Effexor), desvenlafaxine (Pristiq), and duloxetine (Cymbalta) that target norepinephrine in addition to serotonin, in case the patient's current depressive episodes are caused by a lack of norepinephrine rather than serotonin alone. If those do not work, there are other tricyclic antidepressants which block the enzymes transporting neurotransmitters and increasing their concentrations in the brain, like amitriptyline (Elavil) or MAO-inhibitors that block the degradation of neurotransmitters such as selegiline (Zelapar), isocarboxazid (Marplan), phenelzine (Nardil). Furthermore, other medications can augment the effectiveness of the aforementioned medications including antipsychotics such as aripiprazole (Abilify). Ultimately, if pharmacologic therapy fails, electroconvulsive therapy can be used to stimulate and reset the brain, aiming to recalibrate the neurotransmitter deficiency.

Despite all the drugs available to address MDD, multi-drug resistant MDD leaves patients suffering with little pharmacologic support. Treatment resistant MDD decreases the patient's quality of life and the current treatments for MDD take weeks to be effective, leaving the patient to struggle. New therapies need to be effective and rapid acting. Ketamine is useful to address this time disparity as it is fast acting. Ketamine is also useful, as it targets a different neurotransmitter than other antidepressants, glutamate. Ketamine acts on the N-methyl-D-aspartate receptor as an antagonist, blocking the efficacy of the excitatory neurotransmitter glutamate in the CNS. The studies evaluated for this review studied the effectiveness this glutamine receptor antagonism has on depressive symptoms in treatment resistant MDD. While new delivery methods are being explored, like the use of nasal spray, the studies evaluated for

the purposes of this paper had ketamine administered SQ or IV and therefore has been given as repeated clinician administered doses in the management of MDD.

Objective

The objective of this selective EBM review is to determine whether or not ketamine is effective in reducing depressive symptoms in adults with treatment-resistant major depressive disorder.

Methods

The studies that were selected had specific populations, interventions, comparisons, outcomes measured and types of study in order to adequately compare the findings for the objective. The population studied were adults of both genders with treatment-resistant MDD. The intervention was 0.2 mg/kg of ketamine infused or injected, compared to placebo: either saline or 0.01 mg/kg midazolam (Versed). The outcomes measured for these interventions were depressive symptoms rated using quantitative scales. And all of these studies that were selected were double-blind random controlled trials.

All of the studies were personally researched by the author on PubMed and Cochrane Collection. They were selected with the inclusion and exclusion criteria of relevance in order to have studies of recent use: published during or after the year 2016 and the treatment studied be applicable to the desired population of adults with treatment-resistant MDD. Thus, the inclusion criteria were studies in or after 2016 and random controlled trials. Conversely, the exclusion criteria were studies in or before 2015 and systematic reviews. Furthermore, the results had to be in patient-oriented evidence that mattered rather than disease-oriented evidence. The key words in the searches were “ketamine” & “depression”. All of the studies selected were in English and published in peer-reviewed journals. The statistics reported or used were the number needed to treat, relative benefit index, absolute benefit index, mean change. More information of studies can be found in Table 1.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# of Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
George[4] (2017)	Double-Blind RCT Crossover	16	65 ± 6	Adults with the dx of MDD or Bipolar Disorder & depressive episode >4week duration. MADRS Score >20 & failure of >1 antidepressant during current episode	Suicide risk requiring urgent management, pregnancy, schizophrenia, psychotic symptoms, drug abuse/dependence in the last 6 months, known hypersensitivity or medical CI to ketamine, & history of ketamine abuse.	3	SQ doses of 0.1 mg/kg 0.2 mg/kg 0.3 mg/kg 0.4 mg/kg 0.5 mg/kg Ketamine HCl
Chen[5] (2018)	Double Blind RCT	24	49	Adult patients (21-65yo) with a dx of MDD, history of failing to respond to at least 3 antidepressants with adequate dosage & treatment duration & of failing ≥1 trial of adequate antidepressant treatment during their current depressive episode.	Major medical or neurologic condition, did not have a history of alcohol or substance abuse.	0	IV infusions of 0.5 mg/kg or 0.2 mg/kg Ketamine HCl
Su[6] (2017)	Double Blind RCT	71	47	Patients met dx of MDD, recurrent without psychotic features & who had failed to respond to ≥2 adequate antidepressant trials.	Bipolar disorder, psychotic symptoms, substance dependence other than nicotine, & mild symptoms (Hamilton Depression Rating Scale Score <18 at screening or <13 before study entry), active medical disease affecting participation in study.	0	IV infusions of 0.5 mg/kg or 0.2 mg/kg Ketamine HCl

Outcomes

The outcomes measured by the selected studies were depressive symptoms such as depressed mood, low energy, anhedonia, insomnia, feelings of guilt, and suicide using quantitative scales: the Montgomery-Asberg Depression Scale (MADRS) & Hamilton Depression Rating Scales (HAMD). Both of these scales are clinician performed with numeric scaling counted by the number of depressive symptoms reported and observed. These scales are useful in the diagnosis of MDD, categorizing its severity, and measuring progress of therapy in downgrading the patient's MDD episode or inducing remission. The MADRS score is calculated from a 10-item assessment. For severity classification, the MADRS score is out of 60 and a score of 9-17 is mild depression, 18-34 is moderate, and >35 is severe. The HAMD score is a 21-item assessment of depressive symptoms with a maximum score of 52. For the scale, 8-13 is classified as mild depression, 14-18 as moderate depression, 19-22 as severe depression, and ≥23 for very severe depression. For the purposes of this paper, only the quantitative score and severity were extrapolated with these scales.

Results

The papers examined had multiple variables and data about the performance of ketamine for MDD. However, for the purposes of this systematic review, we examined the measurement of symptoms at day 2 in assessing the significance of ketamine on depressive symptoms and the data included about ketamine inducing remission. This time frame for analysis will add weight to ketamine's utility as an effective, fast acting anti-depressant.

George et al. was a double blind RCT that presented outcomes as dichotomous data for those achieving remission (MADRS score <10) and continuous data involving subcutaneous injections of ketamine at 0.02 mg/kg compared to the control midazolam.[4] This study used the MADRS score to study the efficacy of the injection. Total, the study had 16 participants at its

start but lost 2 participants due to physical illness and family illness, leaving 14 to receive the dosing.[4] The study did perform an intention-to-treat for those lost in its final results but did not calculate as a "worst-case" analysis.[4] The process for the study was to be assessed with a MADRS rater blind to treatment at multiple intervals: pre-treatment, 4 hours post, and day 2, 4, 7.[4] The results for this study reported a p-value of <0.01.[4] For those receiving 0.02 mg/kg ketamine, the absolute benefit index was 0.045 and the NNT was 23 for remission.[4] This is a considerably high number when evaluating the utility of ketamine for MDD. Looking at continuous data instead of remission, this study's evaluation of ketamine shows a significant reduction in depressive symptoms at day 2. In Table 2, the mean percentage change in MADRS score was 49.7% on day 2 compared to the control of 25.3%.[4] This greater reduction at day 2 is enough to reduce the category of MDD from a baseline of "severe depression" to "mild depression".

Table 2. Mean Changes in MADRS Scores in George et al.[4]

	Baseline MADRS	Day 2 MADRS (Mean Change %)
0.2mg/kg ketamine SQ	34.8	17.5 (49.7%)
Midazolam	34.8	26 (25.3%)

Chen et al. was a double blind RCT that presented outcomes as continuous data involving the IV infusion of 0.2 mg/kg of ketamine compared to the control of normal saline infusion. This study utilized the HAMD score to study the efficacy of this treatment. Total, the study had 24 participants start and complete the treatment.[5] Individuals were assessed by a rater for HAMD scores 40, 80, 120, 240 min after the infusion and on day 2.[5] This study was precise with a p-value of <0.001.[5] For those receiving the 0.02 mg/kg ketamine infusion the day 2 change from baseline was 25.3%, while the control mean change was 11.9%.[5] This change

would down grade individuals from “very severe depression” to “severe depression” in just one day.

Su et al. performed a double blind RCT as well that presented outcomes as continuous data involving the IV infusion of 0.2 mg/kg of ketamine compared to a control of normal saline infusion.[6] Similar to Chen et al., it used the HAMD score to study the efficacy of this treatment and the comparison of these two studies is shown in Table 3. Su et al. had a similar amount of individuals that had 0.2 mg/kg ketamine, with 23 individuals receiving the dose and completing the study.[7] The individuals were assessed for their response to the infusion at multiple intervals: 40, 80, 120, 240 min and then day 2, 3, 4, 5, 6, 7, and 12.[7] For those receiving 0.02 mg/kg ketamine, at day 2 the mean change was 23.3%, while the control group mean change was 22.8%. These both barely downgraded the severity from “very severe depression” to “severe depression”. These results were precise with a p-value of 0.05.[6]

Table 3: Mean Changes in HAMD Score

	Baseline HAMD	Day 2 HAMD (Mean change %)
Chen et al.[5] Saline (control)	24.63	21.8 (11.9%)
Chen et al.[5] 0.2mg/kg ketamine IV	27.13	20.27 (25.3%)
Su et al.[6] Saline (control)	28	21.63 (22.8%)
Su et al.[6] 0.2mg/kg ketamine IV	28	21.47 (23.3%)

Discussion

First, from assessing the data the studies show an immediate short-term effect of ketamine on depressive symptoms, the question at hand is the significance of that short term effect. Downgrading the severity of depression in these individuals is significant, however there were few instances of remission in these studies and at the dose of 0.2mg/kg. Only George et al. had patients achieve remission at that dose of ketamine.[4] More studies have to be considered at

this dose of ketamine and at higher doses to establish if ketamine can be used as a substitute for other anti-depressants, not just augmentation. Furthermore, one has to consider the other factors into receiving care. Ketamine as a SQ injection can be handled by the patient once the patient has been adequately trained but with IV a patient has to go to the doctor's office with capability of setting up an IV in order to receive the medication. There are multiple barriers in getting patients to the office, having the physical capability, the money to ride the bus or drive, the time to have off work in order to receive the medication, and the question of insurance coverage for the treatment.

There were no serious adverse effects reported in the studies performed with a smaller dose of 0.2mg/kg but ketamine does have the adverse effects like dissociation, psychotomimetic effects, and the potential for abuse due to its intoxicating, euphoric sensation at larger doses, particularly the doses used for anesthesia. This is why the studies examined in this paper excluded those with psychotic illnesses and history of substance abuse. Ketamine administration also does not exist independently pharmacologically and can interact with other medications an individual is receiving. It is not recommended for use with other CNS depressants like alcohol, benzodiazepines, or opioids.[8] Additionally, any individual receiving thyroid medication for hypothyroidism is not recommended to use ketamine due to the increased sympathetic effects.[8]

When looking at these studies for areas of improvement and confounding information, they had small sample sizes and treated individuals who were classified with more severe depressive episodes. This data collected shows a transient significant reduction in depressive symptoms but this cannot be extrapolated and generalized to any adult with MDD, nor can these studies make the claim that ketamine at 0.2mg/kg would be useful for treatment-resistant depression with a depressive severity of mild or low moderate on the HAMD or MADRS scales. Further studies have to include individuals with treatment resistant depression with lower

baseline HAMD and MADRS scores. Also, when examining the mean change from baseline between Chen et al. and Su et al., one can appreciate the larger change in Chen.[5] However, this study allowed individuals to continue their current anti-depressant treatment during the course of ketamine treatments. This confounds the data; we cannot confidently say the decrease from mean score is from a combination effect of standard anti-depressant therapy with ketamine added on or is from the ketamine itself.

Conclusion

In answering the question of is 0.2mg/kg ketamine effective in reducing depressive symptoms in treatment resistant MDD compared to placebo or a control medication like midazolam, the answer cannot be identified with the studies analyzed. The evidence from the studies are conflicting and the results are unclear. George et al. had the largest change in depressive symptoms and severity of depression on day 2 compared to the other groups, however it was the smallest sample size of all of the studies.[4] Additionally, Chen and Su et al. were comparable in size and same treatment delivery, however the results were different.[5,6] Chen et al. showed a more significant reduction in depressive symptoms, but it did have the confounding effect of patients continuing their normal anti-depressant medication regimen.[5] Future studies should not only consider an increase in the amount of participants and length of treatment, but also need to evaluate exclusive ketamine use for treatment resistant MDD and should include individuals in a depressive episode with lower HAMD and MADRS scores to ensure ketamine is useful for milder, treatment resistant depression before routine use is recommended to the healthcare community.

References

1. Loosen PT, Shelton RC. Mood disorders. In: Ebert MH, Leckman JF, Petrakis IL, eds. *Current diagnosis & treatment: Psychiatry, 3e.* New York, NY: McGraw-Hill Education; 2019. accessmedicine.mhmedical.com/content.aspx?aid=1158260005. Accessed Sep 29, 2018.

2. Gauthier G, Mucha L, Shi S, Guerin A. Economic burden of relapse/recurrence in patients with major depressive disorder. *Journal of drug assessment*. 2019;8(1):97-103. https://www.ncbi.nlm.nih.gov/pubmed/31192030 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6542183/. doi: 10.1080/21556660.2019.1612410.

3. Qian Cai, John J. Sheehan, Bingcao Wu, Larry Alphs, Nancy Connolly & Carmela Benson (2019) Descriptive analysis of the economic burden of treatment-resistance in a major depressive episode. Current Medical Research and Opinion, doi: 10.1080/03007995.2019.1671087

4. George D, Gálvez V, Martin D, et al. Pilot randomized controlled trial of titrated subcutaneous ketamine in older patients with treatment-resistant depression. *Am J Geriatr Psychiatry*. 2017;25(11):1199-1209. https://www.ncbi.nlm.nih.gov/pubmed/28739263. Accessed Dec 2, 2018. doi: 10.1016/j.jagp.2017.06.007.

5. Chen M, Li C, Lin W, et al. Persistent antidepressant effect of low-dose ketamine and activation in the supplementary motor area and anterior cingulate cortex in treatment-resistant depression: A randomized control study. *J Affect Disord*. 2018;225:709-714. https://www.ncbi.nlm.nih.gov/pubmed/28922734. Accessed Dec 2, 2018. doi: 10.1016/j.jad.2017.09.008.

6. Su T, Chen M, Li C, et al. Dose-related effects of adjunctive ketamine in taiwanese patients with treatment-resistant depression. *Neuropsychopharmacology*. 2017;42(13):2482-2492. https://www.ncbi.nlm.nih.gov/pubmed/28492279. Accessed Dec 2, 2018. doi: 10.1038/npp.2017.94.

7. Li, C., Chen, M., Lin, W., Hong, C., Yang, B., Liu, R., Tu, P. and Su, T. (2016), The effects of low-dose ketamine on the prefrontal cortex and amygdala in treatment-resistant depression: A randomized controlled study. Hum. Brain Mapp., 37: 1080-1090. doi:10.1002/hbm.23085.

8. Ketamine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed December 7, 2019.