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The Use of Ketamine to Decrease Depressive Symptoms in Adults With Major Depressive Disorder

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Abstract

Background: Mental Health Conditions including Major Depressive Disorders cause many emergency department visits and hospital admissions with few acute treatment options. The use of N-methyl-D-aspartate antagonist drugs such as Ketamine show promise in treatment of these patients.

Method: Exhaustive search of medical literature using MEDLINE, CINAHL, PsychInfo, and EBM multifiles was conducted, using search terms Ketamine, Major Depressive Disorder, N-methyl-D-aspartate Antagonist, Excitatory Amino Acid Antagonist. Articles that were not randomized control trials or were duplicates were excluded.

Results: Two studies fit inclusion, exclusion criteria. The studies found were of low quality using the GRADE approach. Patients that received Ketamine when compared to placebo were found to have a decrease in depressive symptoms.

Conclusion: The current research shows a connection between N-methyl-D-aspartate antagonists like Ketamine and decrease depressive symptoms. Although due to the low quality of the studies the use of Ketamine in treating Major Depressive Disorders should not be adopted without further examination.

Keywords: Ketamine, Major Depressive Disorder, N-methyl-D-aspartate Antagonist, Excitatory Amino Acid Antagonist.

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Annjanette Sommers PA-C, MS

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: Ketamine, Major Depressive Disorder, N-methyl-D-aspartate Antagonist, Excitatory Amino Acid Antagonist

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Jessica Otis

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

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Faculty Advisor: Dr. Robert Rosenow
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

Jessica Otis is originally from Pittsburgh, Pennsylvania where she obtained her undergraduate degree in Biology. After completing her degree, she moved to southern California where she met her husband. Six years ago they fell in love with the Pacific Northwest, and moved to Portland. Jessica worked at Providence Portland Medical Center as an ER tech prior to attending PA school at Pacific University, and plans to work in surgery post graduation.

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Acknowledgements

This is dedicated to my sister, thank you for reading every paper I have ever written, and expecting something better. You have been my rock when everything felt like it was crumbling around me, a friend even when I wasn't a good one, and one of the few constants in my life. You knew what I could do long before I ever did, and have continued to push me to success. Thank you.

To my mom, thank you for your continued support and unconditional love even when I wasn't a success. Your friendship and support means the world to me!

To my husband, thank you for your love, support, and PATIENCE. I don't think at the start of this either one of us knew what to expect, but at the end of it I realize it was your strength that made us persevere.

I love you all!

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Becks Depression Inventory—BDI
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The Use of Ketamine to Decrease Depressive Symptoms in Adults With Major Depressive Disorder

BACKGROUND

In 2007 there were 4.1 million visits to the Emergency Department that listed a mental health condition as their primary diagnosis of which 41% resulted in the patient being admitted.[1] When a patient is seen in the ED with depressive symptoms, it often requires admission to allow for time for medication to take effect. With the number of patients being seen in the ED for mental health issues on the rise over the past decade,[2] the need for a fast acting, effective antidepressant is quickly becoming apparent.

The pathophysiology of depression is widely accepted as a regional reduction in brain volume, although the precise etiology is still not fully understood. Current antidepressant therapy works by increasing synaptic serotonin or norepinephrine, which can take weeks or months to work. The delayed response is suggestive of a cascade effect. A growing body of data points to the glutamatergic modulating system as a proximal player in the suspected pathway to neuronal plasticity and cellular resilience, thought to be directly correlated with severe mood disorders. [3,4]

In addition to the decreased time to onset of therapy, the glutamatergic modulating system shows promise in treating refractory patients. Current antidepressant therapies, such as the popular SSRIs, have a better side effect profile when compared to older medications, but have changed very little in their mechanism of action. This raises concern about our current therapy as there is a large population of patients that are refractory to these medications. Finding a medication that works more proximally in the

chain of biochemical events leading to depression, may help this subpopulation of depressed patients suffering from prolonged illness.[3]

Glutamate is an excitatory neurotransmitter that regulates many different activities of the central nervous system (CNS), and has a crucial role in many aspects of normal brain function. Glutamate, a mainly intracellular neurotransmitter, is released into the synaptic cleft, and binds to one of the 3 identified receptors: N-methyl-D-aspartate (NMDA) , AMPA/kainite, or the metabotropic receptor. Among their many functions, activation of these receptors is responsible for brain cell production, elimination, and differentiation, along with proliferation and destruction of neuronal communication. Following the interaction of the chemical receptor, excess extracellular glutamate binds to, the glutamate uptake pump, and is transported back into the cell. To assure the maintenance of low extracellular glutamate, astroglial cells patrol the extracellular fluid converting excess glutamate to inactive glutamine.[4-6] Increased extracellular glutamate causes inflammation at the amygdala, the area of the brain that controls fear and anger, reducing its control. The act of internalizing these excess feelings of fear and anger is thought to lead to depression.[7]

A proposed theory behind the use of Ketamine is that blocking glutamate at the NMDA receptor will decrease dysfunction in brain plasticity.[7,8] This review addresses the efficacy of Ketamine in decreasing symptoms in adult patients with Major Depressive Disorder.

METHODS

Data Search

A systematic search of electronic databases, and bibliographies was conducted to find all studies that discuss the use of N-methyl-D-aspartate antagonists in Major Depressive Disorders. MEDLINE, CINAHL, and PsychInfo were the databases used in the comprehensive search. A methodical approach of combining Mesh terms was used to elicit the most pertinent articles. Mesh terms included: *Major Depressive Disorder* and *N-methyl-D-aspartate antagonists or Excitatory Amino Acid Antagonist* or *Ketamine* or *Memantine*. The bibliographies of all studies obtained were then searched for eligible studies. All studies obtained were reviewed for relevance using preset inclusion, and exclusion criteria.

Inclusion/Exclusion

All studies that looked at the use of Ketamine in decreasing depressive symptoms in patients with DSM IV criteria for Major Depressive Disorder were included, regardless of the date of the study, language, or publication status. Studies that used the Hamilton Rating Scale for Depression, as at least one determinant of outcome, were included. Studies were excluded if they were an open-label studies, or looked at NMDA antagonist drugs other than Ketamine in the treatment of Major Depressive Disorder.

Quality Assessment

Article that met the inclusion criteria were reviewed for validity using a standardized form. The articles were then analyzed using the Cochrane GRADE method, to assess limitations of methodology, inconsistent results, indirectness of evidence, publication bias, or lack of precision.[9] GRADE criteria was then applied to rate the quality of the study as high, moderate, low, or very low.

RESULTS

The systematic literature search identified 223 relevant references (Figure I). After screening abstracts 209 of the articles were either not relevant articles, or repeats. Full text articles were printed of the remaining 14 articles for formal review. After reviewing the 14 articles, 12 were excluded because they were open-label studies, or looked at other glutamate antagonists other than Ketamine. Bibliographies from the studies were also reviewed for relevant studies. Only 2 additional studies were found that were not a repeat of studies already obtained, but they did not meet inclusion/exclusion criteria. No more studies were added. Table I gives an outline of the 2 studies that met all inclusion and exclusion criteria with formal GRADE[9].

Zarate et al

This study[10] enrolled 18 patients with the DSM-IV criteria for Major Depressive Disorder. All patients went through a 2 week drug holiday prior to starting the study. They were then randomly assigned to either receive 0.5mg/kg of Ketamine or placebo on week 1 and switched and received the opposite treatment on week 2, in a crossover double-blinded fashion. Patients were interviewed 60 minutes prior to the administration

of Ketamine or placebo and at 40, 80, 110, and 230 minutes post administration, along with 1,2,3 and 7 days post infusion using the Hamilton Depression Rating Scale (HDRS)[11] as the primary endpoint. The Becks Depression Inventory (BDI),[12] Brief Psychiatric Rating Scale (BPRS),[13] and Young Mania Rating Scale (YMRS)[14] were secondary endpoints. Response was defined by a 50% decrease in the HDRS, and remission was defined by a score of 7 or below. Of the 18 patients, 9 patients received Ketamine on week 1, but only 4 went on to receive placebo on week 2, due to "improved mood" from phase one. In the placebo group, 1 patient did not complete the second phase due to unrelated medical problems.[10]

Zarate et al[10] performed both an intent-to-treat analysis and an analysis of those actually completing both phases of treatment. The analysis looked at the HDRS survey to assess drug efficacy.[10]

Patients completing both phases--The mean HDRS score when looking at the Ketamine group versus the placebo group showed a large effect ($F=58.24$) with a small probability of a type one error ($p<.001$). When effects of Ketamine were examined at different time intervals there was a significant effect ($F=9.48$; $p<.001$). When they analyzed Ketamine versus placebo at the different time intervals, there was a lower effect ($F=4.15$), but it was still statistically significant ($p<.001$). The effect size showed a large effect size $d=1.46$ at 24 hours (95% confidence interval 0.91-2.0). At 1 week the effect size was considered moderate $d=0.68$ (95% confidence interval 0.13-1.23).[10]

Intent-to-treat—The intent-to-treat group had similar effects as the completers. There was a significant effect when analyzing the mean HDRS for Ketamine when compared to

placebo (F=34.08; p<.001), Ketamine at different time intervals (F=8.92; p<.001), and Ketamine versus placebo across the time intervals (F=5.29;p<.001).[10]

The study[10] also examined "responders" and "remitters" which are shown in figure 3. Of the patients treated with Ketamine 12 of the 17 had a 50% decrease in their HDRS[11] after 24 hours, placing them in the responders category, while 5 of the 17 met remissions criteria with a score less than 7. Of the 12 patients who met response criteria 6 maintained response criteria for 1 week and 2 maintained response for 2 weeks. None of the patients receiving placebo met response or remission criteria, at any point within the study.[10]

The results of the secondary outcomes supported the findings of the primary outcome and can be examined in Figure III. BPRS positive symptoms scores show no correlation to the decreased depressive symptoms seen by the increased HDRS scores.

Berman et al

The Berman et al[5] study only enrolled 9 patients who fulfilled the DSM-IV criteria for Major Depressive Disorder. All patients had a 2 week drug holiday prior to the start of the study. Patients were then randomly assigned to either receive Ketamine 0.5mg/kg or placebo on week 1 then switching, and those who received Ketamine on week 1 received placebo on the second week, in a double-blinded crossover fashion. Two patients stopped the study after the first phase, one from each group drug and placebo, to seek antidepressant therapy. Patients were interviewed at baseline as well at 80 minutes, 230 minutes, 24 hours, 48 hours, and 72 hours post infusion using the Hamilton

Depression Rating Scale (HDRS) as a primary endpoint. Secondary endpoints included BDI, BPRS, and Visual Analog Scale score for intoxication.

The HDRS score was then analyzed on the patients completing both phases of treatment, examining Ketamine versus placebo, Ketamine versus time, and Ketamine versus placebo with respects to time. Ketamine versus placebo and Ketamine versus time were not statistically significant (F=0.157 p=.71; F=2.62 p=.09, respectively), but Ketamine versus placebo with respect to time showed statistical significance with an F=3.97 and p=.02. Figure IV depicts the mean change in HDRS scores from baseline.[5]

Berman et al[5] had 4 of the 8 patients receiving Ketamine have a 50% or greater reduction in HDRS score. Only 1 of the 8 in the placebo group had that large a decrease in score. Patient's scores all returned to baseline +/- 5 points within 1-2 weeks of Ketamine infusion. BPRS scores were also analyzed, but were not statistically significant and did not correlate with the HDRS scores.[5]

Adverse events

The most significant adverse event seen with the use of Ketamine was a feeling of euphoria, confusion, perceptual disturbances, elevated blood pressure, dizziness, and increased libido. The Zarate et al[10] study showed a significant worsening of BPRS scores in the Ketamine group over the placebo group at 40 minutes only (drug, F=4.23 P=.04; time, F=9.31 P<.001; drug x time, F=6.89 P<.001). Berman et al[5] found Ketamine to produce significantly greater BPRS scores, especially the positive symptoms, but returned to baseline at 120 minutes (Figure II and Figure IV).

DISCUSSION

This systematic review of literature showed that low dose Ketamine does decrease depressive symptoms when compared to placebo. Zarate et al[10] and Berman et al[5] both showed a significant decrease in HDRS scores over time when compared to placebo. When Zarate et al[10] examined the HDRS results they showed a large F value (a statistical figure found by calculating the difference in the means of the Ketamine versus the placebo divided by the standard deviation) with a significant p value from 110 minutes through 7 days. The Berman et al[5] study revealed a significant mean change in HDRS scores from 240 minutes through three days.

Zarate et al[10] and Berman et al[5] studies were both downgraded to low quality according to the GRADE approach, due to small sample size and the psychotomimetic effects of the medication introducing bias in a crossover style study. Although the Ketamine dose was low, patients may be able to discern drug versus placebo based on perceptual disturbances with administration of Ketamine, which would subsequently limit blinding and potentiate confounding results. With that being said, the time of onset, and peak antidepressant results were similar for all patients, receiving Ketimine, in both studies. This pattern seen across the board is suggestive of a relationship between NMDA blockade and antidepressant effects.

Misinterpretation between positive change in mood and the side effect of euphoria is of concern when studying the efficacy of Ketamine, a known euphorigenic drug, in treating depression. This paired with the subjectivity of the rating scales could potentially decrease the validity of the results. To combat this Zarate et al[10] and Berman et al[5] both used the BPRS positive symptoms scores to illustrate any connection between

the immediate side effects of the medication and the longer antidepressant effects. In both studies the improvement in depressive symptoms seen did not correlate to the Ketamine induced "high," this is illustrated in Figure II and IV. The BPRS score peaked at around 40 minutes in the Zarate et al[10] study and at around 60 minutes in the Berman et al[5] study and abruptly dropped to baseline shortly thereafter, whereas the HDRS scores in both studies continued to decrease over the following days.

In future studies it will be important to us multiple doses and infusion rates to determine if there is a dose related effect and the role, if any, of the opiate induced "high" felt with Ketamine infusion. It would be of great benefit to use a placebo that has similar side effects to those of Ketamine. Utilization of a dopamine agonist as the placebo, may be fraught with ethical issues, but would be optimal to decrease bias. Employing a drug with similar psychotomimetic effects would also help reduce loss to follow-up due to the decrease awareness of placebo versus control.

Although the results seen in both studies were robust, there are some serious limitations in methodology and precision of the studies making utilization of this information clinically of little use without further investigation. The adverse psychotomimetic effects and abuse potential of Ketamine also limit the use of this drug as a mainstay therapy for treating depression. With a large number of NMDA antagonist medications on the market, it would also be clinically beneficial to study other similar medications that have less perceptual disturbances and are more selective for the NMDA receptor.

CONCLUSION

Although current studies are small the results are promising that there is a role for these drugs in treating Major Depressive Disorder. Time will need to be taken, in the future, to develop a study that eliminates the confounders and enrolls a larger number of participants. As more large randomized control trials are done the use of Ketamine and other N-methyl-D-aspartate antagonists will become more apparent.

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14. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* 1978;133:429-435.

Table I. Characteristics of Reviewed Studies

Quality Assessment								
Designs	Limitations	Inconsistancy	Indirectness	Imprecision	Other considerations	Quality	# Participants at Start	# Completed Study
Zarate et al[10]: A Randomized Trial of an NMDA Antagonist in Treatment Resistant Major Depression								
RCT	concealment *	None	None	None	None	Low	18	12**
Berman et al[5]: Antidepressant Effects of Ketamine in Depressed Patients								
RCT	concealment *	None	None	None	None	Low	9	7***

*Not fully concealed due to side effects of Ketamine versus placebo
** 5 lost from therapy group after phase 1, 1 lost from placebo group after phase 1
*** 1 lost from both placebo and therapy after phase 1

Figures I: Review of Literature

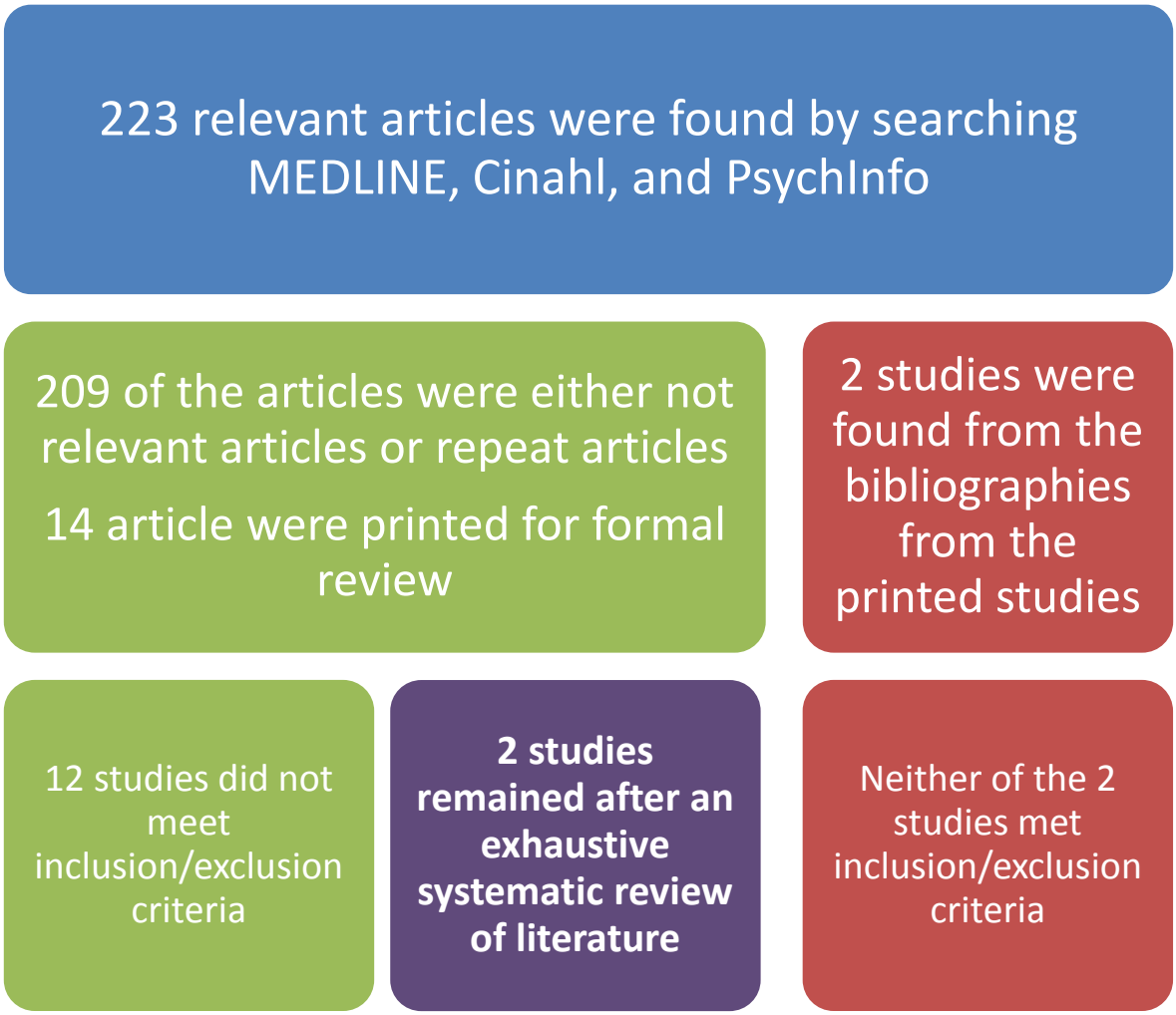


Figure II: Zarate et al Ketamine vs Placebo

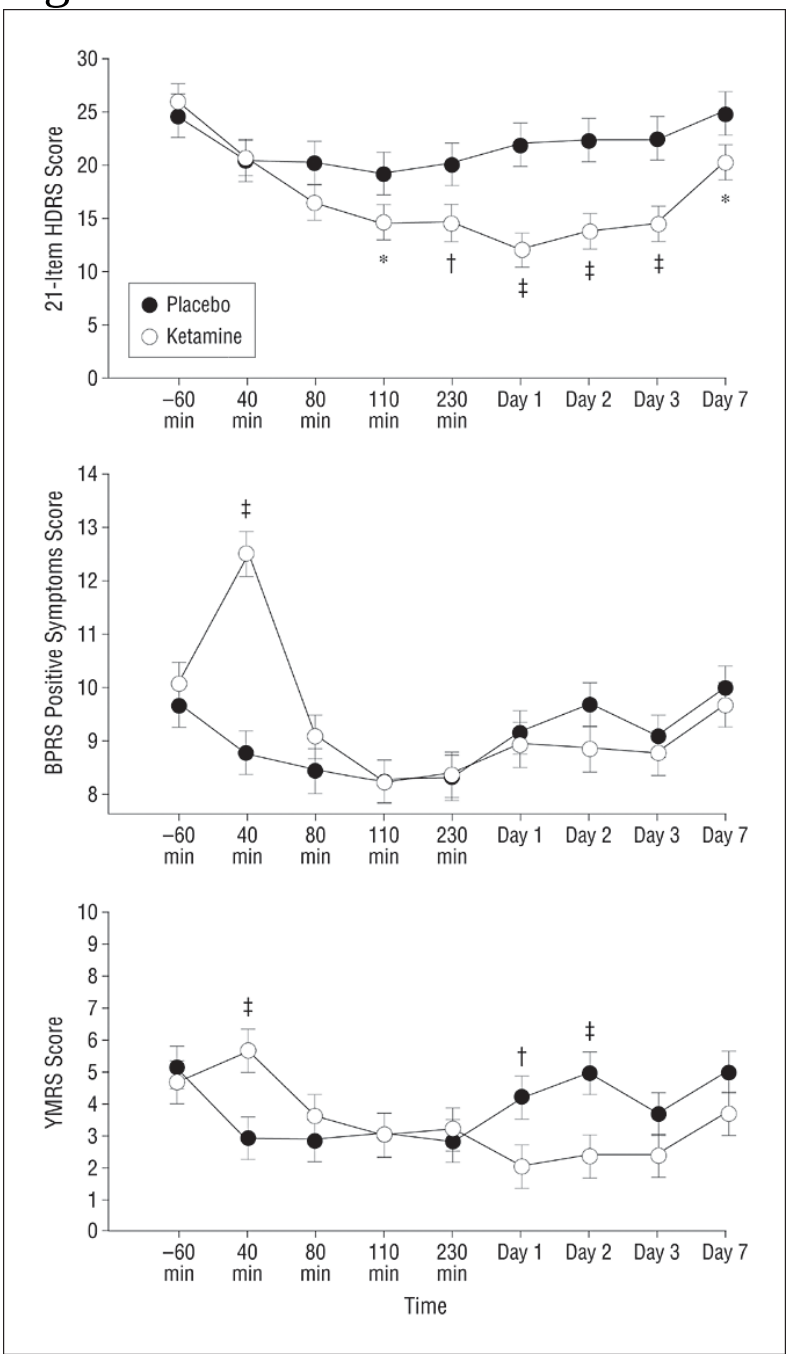


Figure II: Shows the curve that best describes the relationship between the expected and observed outcome, using least square means of the completers using 3 of the depression scales. ***indicates** $p<.05$; †, $p<.01$; ‡, $p<.001$

Figure III: Zarate et al Responders and Remitters

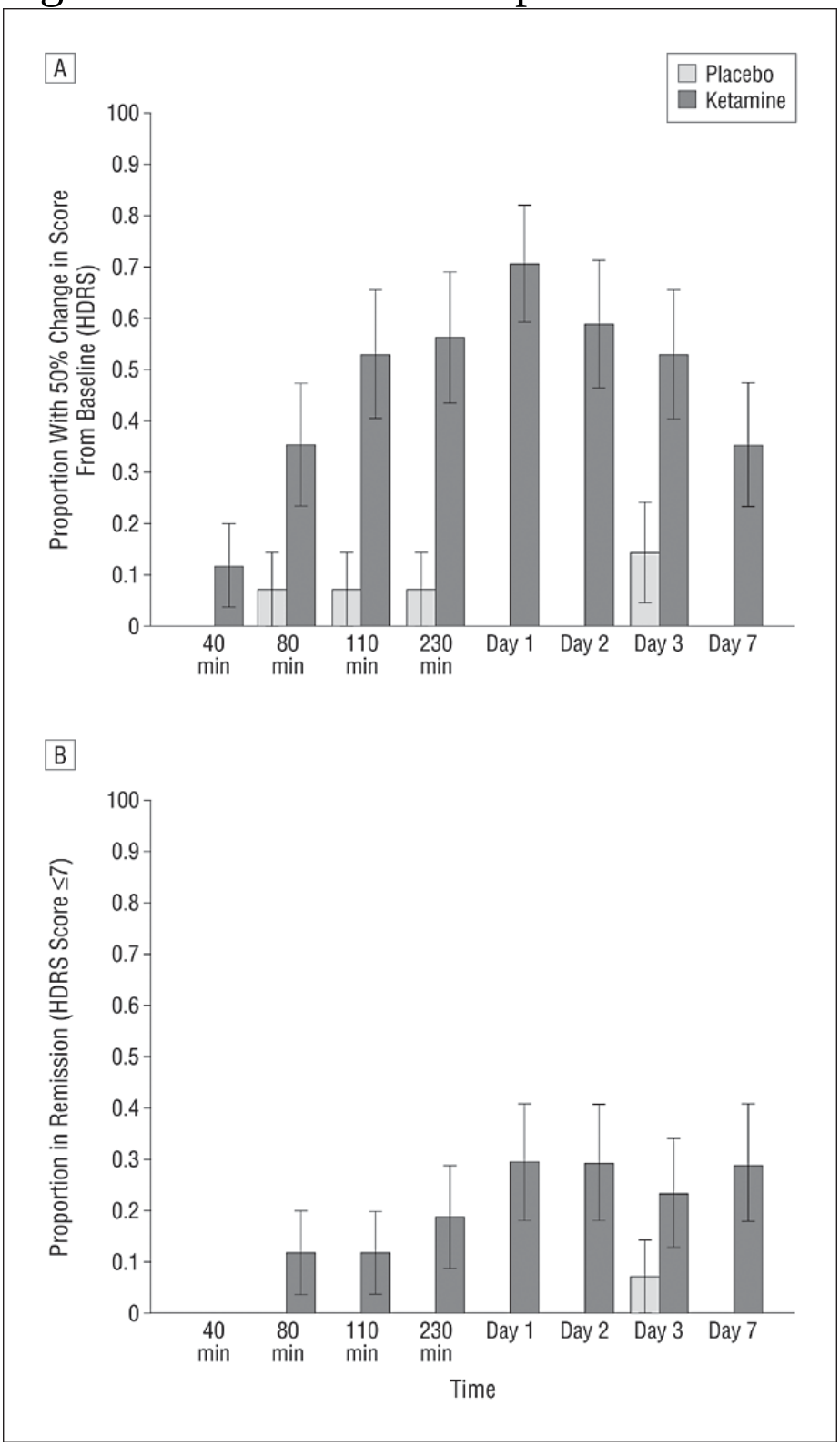
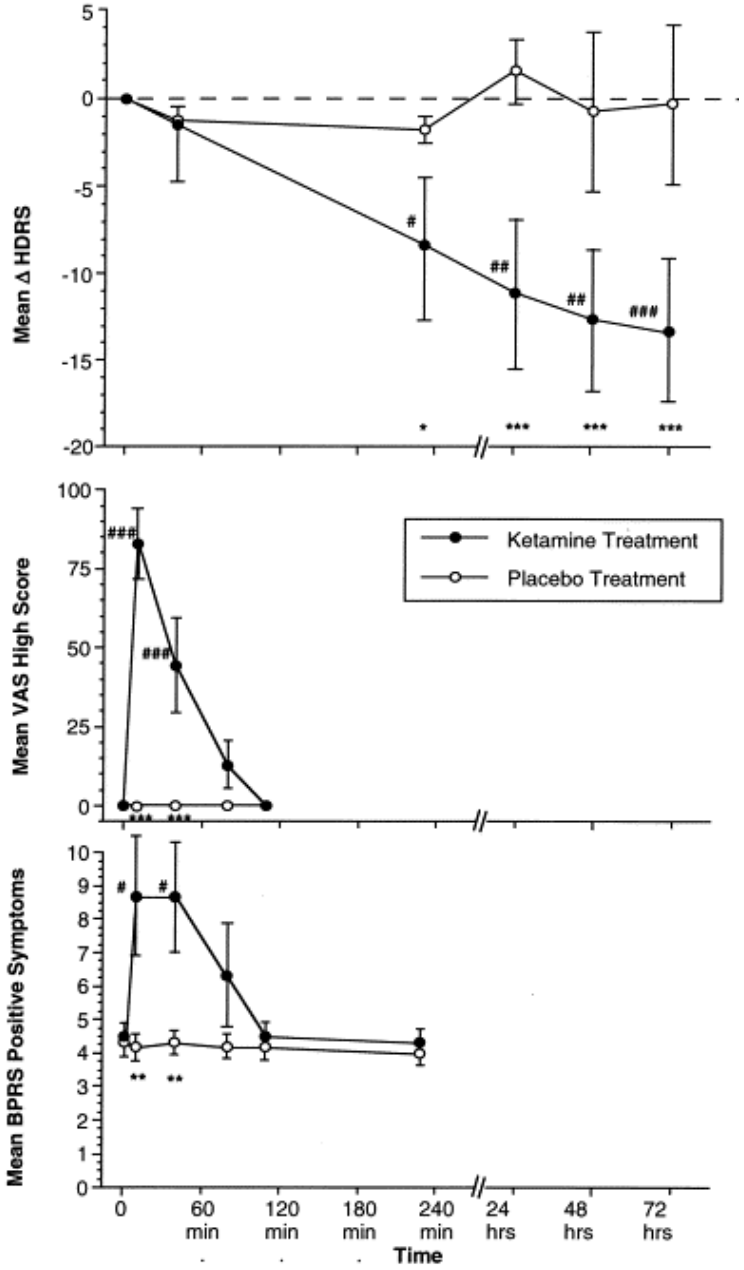


Figure IV: Berman et al Ketamine vs Placebo



Mean changes (± SEM) from baseline in the 25-item Hamilton Depression Rating Scale scores (ΔHDRS), the mean Visual Analog Scale "high" scores (VAS-high), and mean positive symptom scores of the Brief Psychiatric Rating Scale (BPRS-positive) after ketamine (.5 mg/kg over 40 min) and saline infusions in seven subjects completing both treatment conditions. Omission of error bars signifies lack of variance. Post hoc contrasts represent comparison to baseline (# signifies $p < .05$; *##,* $p \leq .01$; *###,* $p \leq .001$*) or between groups (∗,* $p < .05$; *∗∗,* $p \leq .01$; *∗∗∗*$p \leq .001$*). The former statistic utilized absolute HDRS scores for the top panel. These contrasts were performed with Huyn-Felt adjustments for lack of sphericity. Treatment-by-*

*time effects on the repeated measures analysis of variance were significant for HDRS (*p = *.02) and VAS scores (*p < *.001), but not for BPRS-positive symptoms scores (*p = *.07).*

Appendix A
Hamilton Depression Rating Scale

[Measure redacted from online copy of manuscript]

REFERENCE
Br. J. Soc. Clin. Psychol. 6 : 278-296 (1967)

Appendix B
Young Mania Rating Scale

[Measure redacted from online copy of manuscript]

REFERENCES

Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429-435.

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Appendix C
Beck's Depression Inventory

[Measure redacted from online copy of manuscript]

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Beck, AT, CH Ward, M Mendelson, J Mock, and J Erbaugh. 1961. An inventory for measuring depression. Arch Gen Psychiatry 4: 561-571.

Beck, AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. J Clin Psychol. 1984 Nov; 40(6):1365-7

Appendix D
Brief Psychiatric Rating Scale (BPRS)

[Measure redacted from online copy of manuscript]

REFERENCES

Overall JE, Gorham DR (1962). The brief psychiatric rating scale. Psychological Reports 1962 vol. 10, pp799-812