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Identifying Patients with Major Depression who Benefit from Ketamine Therapy

Jessi Riel
University of the Pacific, jessiriel8@gmail.com

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Jessi Riel

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INTRODUCTION:

Major depression is a serious psychiatric illness that has continued to increase in prevalence. In 2017, an estimated 11 million U.S. adults aged 18 or older had at least one major depressive episode with severe impairment.[1] According to the Centers for Disease Control, depression is addressed in 9.3% physician office visits and 10% of emergency room visits.[2] The management of major depression not only impacts the healthcare system but also poses an economic burden as it costs the US $210.5 billion per year.[3] The most common form of treatment for major depressive disorder has been oral antidepressants. These drugs treat depression through mechanism of targeting the central neurotransmitter system, primarily serotonergic, noradrenergic and dopaminergic pathways and have been successful in managing depressive symptoms in many patients. Approximately 30% of individuals continue to suffer from major depression despite one or more adequate trials of antidepressants, thus identifying these patients with a diagnosis of Treatment-Resistant Depression (TRD).[4,5,6,7] Patients with TRD experience increased chronicity of depression, functional disability, and overall morbidity, resulting in greater therapeutic challenges.[4]

Over the last few years, ketamine has been studied as a possible treatment option for Major Depressive Disorder (MDD)[a] and TRD. Ketamine is an NMDA receptor antagonist that targets the glutaminergic system and produces rapid antidepressant effects from mechanisms that are still incompletely defined.[5] In March 2019, the FDA approved intranasal esketamine, an enantiomer of ketamine, as a treatment for those who have failed at least two antidepressant medications.[6]The approval of esketamine as a treatment option for major depressive disorder is considered a significant

breakthrough in psychiatric medicine and provides promise for the future of depression management. Nonetheless, the effects from treating TRD with ketamine are not fully characterized or known. For that reason, identifying patients and other factors associated with an increased likelihood of success with esketamine would not only expand the knowledge base, but also limit potential adverse effects from treating persons who are not likely to benefit. These factors might include age, symptom severity, comorbid psychiatric disorders, route of drug administration, drug formulation et cetera. Moreover, examining the different TRD patient populations who experience benefits from esketamine/ketamine therapy would aid in determining who are most likely to benefit from it.

DISCUSSION:

To date, research on ketamine's effects on MDD has included only adult participants most of whom ranged in age from 18-64 years.[4,5] Fortuitously, ketamine has been studied in both men and women who failed previous antidepressant medications. Otherwise investigations focused on different populations of depressed patients and monitored different outcomes.

Suicidal ideation in major depression can increase the risk of mortality MDD alone causes disability. A double-blind**,** placebo-controlled trial by Ionescu et al. explored the short and long-term antidepressant efficacy of repeated dose (0.5mg/kg) IV ketamine in comparison with placebo in medicated, TRD outpatients with chronic suicidal ideation.[6] The participants included 24 adults of both sexes between ages of 18-65 years-old with MDD as their primary diagnosis and with distressing suicidal ideation for at least three months. Individuals in need of immediate hospitalization were

excluded from this outpatient study. Other exclusion criteria included a diagnosis of bipolar depression, current pregnancy, unstable medical illness, psychotic features, a history of multiple adverse drug reactions, any history of substance use disorder, a positive urine toxicology screen, and any history of recreational ketamine abuse. Participants completed three initial visits prior to ketamine treatment (pre-infusion phase) and received a total of six 45- minute infusions of IV ketamine or placebo over the course of three weeks (active phase). They were followed every other week for an additional three months following the active phase of the trial (follow-up phase). The primary outcome was depression experienced over the past week as rated by the Hamilton Rating Scale for Depression (HRSD or HAM-D).[b] A positive response was defined as a 50% or greater improvement in the HRSD score. An HRSD score of 7 or less met criteria for remission of depression. The presence of suicidal ideation (SI) was the secondary outcome and was assessed by Columbia Suicide Severity Rating Scale (C-SSRS)[c] score based on a five- point scale with “0” being the absence of SI. Overall, depression decreased significantly across infusions, whereas SI did not.[6] During the active phase, 25% of the subjects in the ketamine group and 35% subjects in the placebo group experienced antidepressant responses. When examining remission rates, 17% of the ketamine subjects met criteria for remission while only 8% did ~~so~~ in the placebo group. During the follow up phase, 22% of the ketamine group met criteria for antidepressant response and remission, while 27% of placebo subjects had an antidepressant response and 18% met criteria for remission. The was no significant difference between responders or remitters between the placebo and ketamine groups.[6] When examining SI, only five patients met criteria for the absence of SI with the final

ketamine infusion, four of these subjects continued to experience lack of SI in the beginning of the follow-up phase; however, only one subject maintained absence of SI at the end of the three month follow up phase. Among the placebo group, two patients met criteria for absence of SI at the end of the follow- up phase. In conclusion, IV ketamine infusions did not outperform placebo in terms of short or long-term antidepressant and anti-suicidal efficacy.[6] Nonetheless, participants in the study reported decreased suicidal ideation within hours of administration of ketamine, suggesting its effects may be transient and dose dependent. Several limitations to this study as well as significant strengths may have influenced the outcomes. The first limitation was a small sample size due to difficulty with recruitment and retention of participants as only 14 of the 26 participants completed the study. The low retention of participants was due to the lack of compensation and the unfounded (or unrealistic) expectation that severely depressed patients would be able to comply with extended research.[6] The small sample size may have affected the evaluation of true differences between the groups.[6] Secondly, the participants were maintained on their other psychiatric medications during the infusion phase of the study; thus any effects due to those medications could not be distinguished from effects due to ketamine. Third, the study was conducted with outpatient participants only and excluded those with acute SI who met criteria for hospital admission. The inclusion of only outpatient participants may have contributed to a lack of significant difference in depression and SI pre-and post-infusion with ketamine since the participants' baseline SIs were already low.[6] Lastly, no 24-48-hour post-infusion evaluation was performed. The short duration of the four-hour post-infusion evaluation potentially excluded identification of the acute effects of

ketamine.[6] Strengths of the study included the inclusion of participants with TRD experiencing both chronic and current SI, the double-blind placebo controlled trial study design, and extended three month follow up phase which observed the prolonged effectiveness of ketamine.[6]

A review of clinical trials by Kraus et al**.** investigated the efficacy and tolerability of ketamine in patients with unipolar or bipolar MDD (as defined by DSM criteria), a population that was excluded in the above trial. This review included meta-analyses and Cochrane reviews from peer-reviewed journals and excluded trials with individuals who had other primary psychiatric diagnoses.[8] The outcome of depression was assessed solely with rating scales, including the HAM-D/HRSD, Montgomery-Asberg Rating Scale (MADRS)[d], and Beck Inventory (BDI).[e] The antidepressant effects were evaluated at 24 hours post ketamine treatment in most of the studies for which reason it was chosen as the main outcome. This review included a total of 12 clinical trials that had participants with unipolar MDD as the primary diagnosis and 7 clinical trials that had participants with bipolar MDD as the primary diagnosis for a total sample size of 226 participants .[8] Studies using either intranasal (IN) or IV ketamine infusions were included. Significant response was defined as reduction in baseline depression scores in all studies of 50% or higher.[8] Twenty-four hours post-treatment, ketamine, without exception, was superior to placebo as evidenced by a significant response rate of 59%. Specifically, depression rating scores decreased in the ketamine treatment groups an average of 10.91 in HAM-D/HDRS scores, 15.7 in BDI scores, and 20.8 in MADRS scores.[9] Overall the most significant antidepressant affects were noted on the first day of ketamine treatment with prolonged effects lasting an average of 7-14 days. In conclusion, IV and IN ketamine

were highly effective at producing rapid antidepressant effects in patients with bipolar and unipolar MDD. Response rates up to 88% after the first 24 hours of ketamine treatment were observed with an average duration of 1-2 weeks.[8] Relapse rates after treatment with ketamine were high and up to 90% in some trials. The latter findings exposed the transient effects of ketamine and hence, the need for further research on means to prolong its antidepressant effects. Nonetheless, ketamine may be a potentially useful in the acute suicidal crises and highly resistant depression.[8] Furthermore, an individual's initial response to ketamine may be an indicator of further responses.[8] Study limitations were the inclusion of clinical trials utilizing different IV doses of ketamine thus lacking the a uniform dose regimen among all trials. An additional limitation was the inclusion of trials that used ketamine as an add-on treatment to medication, ECT, et. cetera for depression as well as trials where ketamine was used as the primary treatment. A strength was the large sample size of 12 clinical trials. Additionally, all the trials used scores from standardized depression rating scales as instruments for the measuring primary outcomes.

Besides population, another factor for choosing successful outcomes with this therapy might include the presence or absence of ketamine-induced dissociative symptoms as predictors of ketamine's antidepressant efficacy. A secondary study by Niciu et al. investigated whether an increase in dissociative symptoms after initial ketamine treatment would predict improvement in depressive symptom scores.[9] Findings from three trials that included adult participants ages 18-65 years, 84 with MDD and 42 with bipolar depression (BD) were analyzed in this study.[f] Prior to treatment, all participants were experiencing a major depressive episode without

psychotic features for a duration of at least two weeks. Individuals with MDD were medication-free for at least two weeks prior to the first ketamine or placebo infusion and persons with BD were maintained on lithium or valproate. The HAM-D scale was used to measure antidepressant response and Clinician Administered Dissociative States Scale (CADSS) was used to evaluate dissociation effects. Both scores were calculated at 60 minutes prior to infusion and 40 minutes post-infusion. The CADSS scale was further characterized into different subscales such as derealization, depersonalization, and amnesia.[9] A significant association between depersonalization symptoms and greater antidepressant responses across all time points and studies, suggested that depersonalization effects may be the best predictor antidepressant response in individuals treated with ketamine.[9] Study limitations were the inclusion of participants with bipolar depression and major depressive disorder and possible type 1 error because the study was a secondary analysis.[9]

ROUTE OF ADMINISTRATION:

In the last 10 years, many studies examined the use of intravenous ketamine for TRD. More recent studies have examined intranasal esketamine. The only FDA approved use of ketamine in the treatment of depression is the intranasal form, esketamine, approved in March 2019.[4] Although more research on intravenous ketamine compared with intranasal esketamine is available, obstacles to the IV route remain. For example, a universal induction and tapering dose for IV ketamine has yet to be determined. Additionally, the IV route for ketamine is not acceptable for all patients because they are either unwilling to receive IV treatment or cannot tolerate it for other reasons. In contrast, the benefits of intranasal ketamine include fixed dosage, user

tolerability, and ease of administration. Intranasal ketamine can be administered in an outpatient setting; nonetheless, patients need to be monitored by a physician for 1-2 hours following administration. The potential for abuse of either form of this drug is obviated somewhat by the need for clinical supervision of dosing.

RECOMMENDATIONS FOR FURTHER RESEARCH:

Ketamine and esketamine have evidence for efficacy in the treatment of severe major depressive disorders; rapid antidepressant effects occur within 24 hours of administration.[7,10] Further research is necessary to determine how much ketamine or esketamine would provide an effective dose for severe depression and what doses would be standard treatment. Additionally, the efficacy of ketamine/esketamine in conjunction with other treatment modalities such as electroconvulsive therapy, cognitive behavioral therapy, or pharmacotherapy should be explored. Lastly, the long-term side effects of ketamine and esketamine are unknown because research follow-up has been relatively short in duration.[11]

CONCLUSION:

Severe depression is a crippling disorder that plagues the lives of many people and negatively effects mental and physical well-being. The introduction of TRD treatment with ketamine, which works by a different mechanism of action compared to traditional antidepressants, has provided an alternative for these patients. A rapid decrease in depressive symptoms occurs within hours after treatment with ketamine. The total duration of antidepressant effects is transient and is still open for further investigation. Nonetheless, ketamine as a potential treatment option for severe

depression should not be overlooked due to its transient nature, as it may have potential for treatment in critical situations. Furthermore, the rapid onset of the antidepressant effects of ketamine may provide effective treatment for acute severe depression which may present in emergency settings. In addition, ketamine's antidepressant effects have been demonstrated in adults with a primary diagnosis of MDD, specifically TRD. It is also effective in bipolar disorders with depression. More information is needed about the long-term effects of ketamine therapy. Nonetheless, ketamine and esketamine are potential treatments for individuals with severe depression who have failed one or more traditional antidepressant medications.

REFERENCES:

1. National Institute of Mental Health. Major Depression. https://www.nimh.nih.gov/health/statistics/major-depression.shtml. Accessed November 9, 2019.
2. Centers for Disease Control and Prevention. Depression. https://www.cdc.gov/nchs/fastats/depression.html. Accessed November 9,2019.
3. Center for Workplace Health. Quantifying the Cost of Depression. http://www.workplacementalhealth.org/Mental-Health-Topics/Depression/Quantifying-the-Cost-of-Depression. Accessed December 20, 2019.
4. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients with Treatment-Resistant Depression. *JAMA Psychiatry*. 2019. doi:10.1001/jamapsychiatry.2019.1189.
5. Singh JB, Fedgchin M, Daly E, et al. Intravenous Esketamine in Adult Treatment-Resistant Depression: A Double-Blind, Double-Randomization, Placebo-Controlled Study. *Biological Psychiatry*. 2016;80(6):424-431. doi:10.1016/j.biopsych.2015.10.018.
6. Ionescu DF, Bentley KH, Eikermann M, et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: A randomized, double blind, placebo controlled trial. *Journal of Affective Disorders.* 2019;243:516-524. doi:10.1016/j.jad.2018.09.037.

7. Lapidus KA, Levitch CF, Perez AM, et al. A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder. *Biological Psychiatry.* 2014;76(12):970-976. doi:10.1016/j.biopsych.2014.03.026.

8. Kraus C, Rabl U, Vanicek T, et al. Administration of ketamine for unipolar and bipolar depression. *International Journal of Psychiatry in Clinical Practice.* 2017;21(1):2-12. doi:10.1080/13651501.2016.1254802.

9. Niciu MJ, Shovestul BJ, Jaso BA, et al. Features of dissociation differentially predict antidepressant response to ketamine in treatment-resistant depression. *Journal of Affective Disorders*. 2018;232:310-315. doi:10.1016/j.jad.2018.02.049.

10. Feifel D, Malcolm B, Boggie D, Lee K. Low-dose ketamine for treatment resistant depression in an academic clinical practice setting. *Journal of Affective Disorders.*

11. Sanacora G, Frye MA, McDonald W, et al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. *JAMA Psychiatry*. 2017;74(4):399–405.doi:10.1001/jamapsychiatry.2017.0080.

[a] Major Depressive Disorder (MDD) Criteria- at least 5 of the following symptoms have to be present during the same 2-week period (and at least 1 of the symptoms must be diminished interest/pleasure or depressed mood): depressed mood, diminished interest or loss of pleasure in almost all activities (anhedonia), significant weight change or appetite disturbance, sleep disturbance, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, diminished ability to think or concentrate; indecisiveness, recurrent thoughts of death, recurrent suicidal ideation without specific plan, or suicide attempt or specific plan for committing suicide. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Washington, DC: American Psychiatric Association; 2013.

[b] Hamilton Rating Scale for Depression (HRSD/HAM-D)- Stratifies the severity of depression based on depressed mood, feelings of guilt, suicide, insomnia, work/interests, retardation, agitation, psychiatric anxiety, somatic anxiety, GI somatic symptoms, general somatic symptoms, genital symptoms, hypochondriasis, weight loss, and insight. The original HAM-D has 21 items, but scoring is based on only the first 17. Hamilton, M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62. doi:10.1136/jnnp.23.1.56

[c] Columbia-Suicide Severity Rating Scale (C-SSRS)- screens for suicidal ideation and behavior. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266–1277. doi:10.1176/appi.ajp.2011.10111704

[d] Montgomery Asberg Rating Scale (MADRS)-stratifies severity of depressive episodes in adults based on apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulty, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. Montgomery, S., & Åsberg, M. (1979). A New

Depression Scale Designed to be Sensitive to Change. *British Journal of Psychiatry, 134*(4), 382-389. doi:10.1192/bjp.134.4.382

[e] Beck Inventory (BDI)- 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression. https://www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/beck-depression.

[f] Bipolar Depression- a mental illness characterized by periods of deep, prolonged and profound depression that alternate with periods of an excessively elevated or irritable mood known as mania. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Washington, DC: American Psychiatric Association; 2013.