Spring 5-15-2020

Effects Of Ketamine On Treatment-Resistant Depression

Aaron J. Stanley
University of North Dakota, aaron.stanley@und.edu

EFFECTS OF KETAMINE ON TREATMENT-RESISTANT DEPRESSION

By

Aaron J. Stanley

Bachelor of Science in Nursing, Union College, 2013

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

Grand Forks, North Dakota

April

2020

PERMISSION

Title Effects of Ketamine on Treatment-Resistant Depression

Department Nursing

Degree Master of Science

In presenting this independent study in partial fulfillment of the requirements for a graduate degree from the University of North Dakota, I agree that the College of Nursing and Professional Disciplines of this University shall make it freely available for inspection. I further agree that permission for extensive copying or electronic access for scholarly purposes may be granted by the professor who supervised my independent study work or, in his absence, by the chairperson of the department or the dean of the School of Graduate Studies. It is understood that any copying or publication or other use of this independent study or part thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of North Dakota in any scholarly use which may be made of any material in my independent study.

Signature Aaron Stanley

Date 04/13/2020

Abstract

Treatment-resistant depression (TRD) is diagnosed after at least two trials of failed monotherapy of antidepressants. The patient in the case report of this paper is seen for major depressive disorder for a couple years and is trialed on multiple medications. After psychopharmacology trials of monotherapy, combinations, augmentations, and electroconvulsive therapy (ECT), the patient is trialed on low dose ketamine. Patient's response includes decreased negative symptoms, such as improved emotional flattening, brighter affect, psychomotor stability, and decreased feelings of hopelessness. Based on a review of literature on ketamine on treatment-resistant depression, an analysis of the responses demonstrated that ketamine can help improve treatment-resistant depression symptoms based on popular depression scoring tools. This paper aims to determine the usefulness of ketamine on treatment-resistant depression and suicidal thought through literature reviews, and to provide some implications for future use with the medication that has seen an increase in its use in the field of mental health.

Keywords: Ketamine; Depression; Treatment-Resistant Depression

Background

Mental illness is a topic that has been getting more attention over recent years. People from all walks of life have been stepping up and sharing their struggles with one of the debilitating illnesses. Over the last few years, celebrities, like actors and professional sports players, have been using their platform to share their experiences on living with a mental illness. This is done with the hopes that more people will pay attention to the signs of mental illness and will be willing to seek help. Hopefully with the increase in attention to such a sensitive topic, more research will be done to provide more treatment options. One of these mental illnesses that has a big impact in people's lives is depression.

Depression has multiple presentations, timeframes, and diagnostic criteria. The National Institute of Mental Health (2019) states that "Major depression is one of the most common mental disorders in the United States" (n.p.). In 2017, almost 17.5 million adults (18 years and older) in the United States suffered from a major depressive episode (National Institute of Mental Health, 2019). This is just over 7% of the adult U.S. population. The American Psychiatric Association's (2013) *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5) defines major depressive disorder as five or more symptoms (one at least being depressed mood or loss of interest) over a 2-week period and "cause clinically significant distress or impairment in social, occupational, or other important areas of functioning" (p. 161). The symptoms mentioned include sleep disturbance, significant weight changes, sleep pattern disturbance, psychomotor changes, fatigue, feelings of worthlessness, impaired concentration, and recurrent thoughts of death (APA, 2013). Treatment of this disorder is typically done with the pharmacological use of antidepressants. Even with all of the types of medications available for depression, sometimes there are people who are unresponsive to them. These are the patients that

have what is termed “treatment-resistant” depression, which Hartberg et al. (2017) defined as “having previously failed at least two separate, evidence-based pharmacological treatments for depression” (p. 393). Roughly 30% of patients with major depressive disorder develop treatment-resistant depression (Haroon et al., 2018). “Many clinical factors have been related to treatment non-response including psychiatric co-morbidities such as anxiety disorders, personality disorders, and bipolar disorder as well as obesity and a history of childhood maltreatment” (Haroon et al., 2018 p. 43). Other physical conditions like cancer, cardiovascular disease, and diabetes could also play a part in poor treatment response, thus leading to treatment-resistant depression. Haroon et al. (2018) did a study that found that patients with treatment-resistant depression had higher plasma levels of inflammatory markers, which could lead to further developments and treatments when targeting treatment-resistant depression.

Treatment-resistant depression poses additional challenges in finding the right intervention. By researching and discovering new, novel treatment options, providers will be better equipped in managing challenging cases like these. The following is a patient case scenario who has treatment-resistant depression and the interventions tried before using ketamine infusions, along with the patient response to the trialed ketamine. This paper focuses on the research done with ketamine for the use of treatment-resistant depression. Having another option available for patients suffering from treatment-resistant depression could help people finally have stability from their debilitating illness that they have struggled with for so long.

Case Report

Patient was a 21-year-old female who had a long standing mental health history. Patient was from another country and was adopted before she was two-years old and was brought to the United States. Due to the patient being adopted, her family medical history and family

psychiatric history was unknown. As far as pertinent medical history, the patient had a delay in speech and milestones, with a perceptual reasoning IQ of 73 and a verbal IQ of 93. This had led some people to, at times, overestimate her intellectual capacities. Patient's adopted father had passed away just a little over two years after being adopted, which was hard on her. Previous diagnoses included major depressive disorder, generalized anxiety disorder, reactive attachment disorder, and attention deficit hyperactivity disorder (ADHD). She was a nonsmoker, denied any alcohol use, caffeinated beverages, or any illicit drug use. Patient came to this hospital's clinic initially as a referral for an ECT consult.

Patient presented to the clinic for reports of depressed mood. Stated in the last couple months she endorsed dysphoria, hypersomnolence, anhedonia, feelings of guilt and worthlessness, decreased energy, decreased concentration, decreased appetite, and psychomotor slowing. She denied thoughts of suicide, but had been recently hospitalized one month prior for suicidal thoughts and thoughts of cutting herself with a knife. Patient also had some "creepy thoughts of cutting my mother". Patient was diagnosed with major depressive episode, single episode, severe, with psychotic features. Patient also had endorsed depression that had been consistent over the last 3 years, but those last 6 weeks had been worse. She had also been diagnosed with persistent depressive disorder.

Patient also endorsed "years" of excessive, bothersome, daily worries. She worried something was always going to happen to her. She also endorsed fatigue, restlessness, irritability, decreased concentration, muscle tension in her neck, and initial insomnia due to the constant worry. Patient was diagnosed with generalized anxiety disorder.

Patient had a history of 3 previous psychiatric hospitalizations, which all happened in a recent two year span. She had attempted suicide twice in the past, once by hanging and another

time by attempted overdose. She had endorsed a history of violence towards others. No head trauma with loss of consciousness or seizure disorder was endorsed. Previous psychotropic medications included, but were not limited to, adderall, clonidine, vyvanse, wellbutrin, lamictal, latuda, abilify, cymbalta, lexapro, celexa, zoloft, lithium, effexor, viibryd. Patient had individual counseling, group counseling, services such as assertive community treatment (ACT), and dialectical behavior therapy (DBT) sessions were attempted, but the patient wasn't in the best cognitive state for that at that time. Patient and mother had reviewed the risks, benefits, and side effects of ECT and decided to proceed with it. A standard preop physical was done the included an electrocardiogram and labs that consisted of thyroid stimulating hormone (TSH), complete blood count (CBC), and a comprehensive metabolic panel (CMP). Patient also was prescribed Reglan and Ranitidine to take the night before the treatments. She had 10 sessions of ECT completed. She reported some overall improvement in mood, but went back to down in her mood after 3 months. Given the different treatments that were used and patient still had not had successful responses to treatment, patient had been reported as having treatment-resistant depression.

This young female was finally referred by the psychiatrist who performed ECT to another doctor who had been using ketamine to help treat depression. Upon arrival to the hospital for ketamine infusions, patient was scored a 13/15 on the Maudsley scale. "The Maudsley Staging Method (MSM) is the first multidimensional model developed to define and stage treatment-resistance in 'unipolar depression'" (Fekadu et al., 2018 p. 1). A score between 11-15 is considered severe treatment-resistant depression. Over the course of the hospital stay, the patient received 6 intravenous (IV) ketamine treatments, which started at 0.5 mg/kg and with the last 4 treatments being 0.75 mg/kg. Patient's Beck Depression Inventory (BDI) score went from 47 on

admission to 10, which was a score classified of having minimal depressive symptoms. She had also denied any suicidal thoughts.

Patient continued to receive ketamine after discharge. She started by going in three times in the first week after discharge, with a dose of 1 mg/kg. She had some decline in mood in between treatments initially but was able to recover from those episodes. Eventually, patient was able to improve to where she would only go in one time a week, or longer, and received doses of 1.1 mg/kg. Her BDI score had continued to be less than 10 on subsequent visits. The BDI is "One of the most commonly used instruments to measure depression symptom severity in clinical settings" (Reis et al., 2019 p. 1). A score between 0-13 is considered having minimal depressive symptoms at that time, so patient was responding well.

This patient case shows the reason for the purpose of this paper. Ketamine has shown some promise as a viable alternative option for the treatment of treatment-resistant depression. Ketamine has recently been FDA approved for the treatment of depression. There are clinics that advertise ketamine infusions for the treatment of depression, at a price of $500 per treatment ("Ketamine Therapy", 2020). This paper explores the literature on ketamine as a novel treatment for depression.

Literature Review

A review of literature was completed using the Ebscohost search program through the University of North Dakota. The databases used in the search were Academic Search Premier, CINAHL Complete, MEDLINE Complete, PsyARTICLES, and PsycINFO. The keywords used in the search were ketamine, depression, and treatment-resistant depression. The limiters included articles published within 8 years and only articles that were available as full text

articles, which yielded in 1,030 articles. The search was then further refined to only literature reviews as a methodology, which yielded 28 total articles. Using the library services provided by Essentia Health for employees, the same keywords and limiters were used except for not limiting it to just literature reviews. This resulted in 84 total articles, some of which were duplicates from the first search. The primary articles selected for this paper included literature reviews and meta-analyses, as they are compilations from multiple studies and are the highest levels of evidence.

In one systematic review (Xu et al., 2016), 9 randomized trials were found that examined either low-dose ketamine and very low-dose ketamine administrations. Low-dose ketamine infusions is considered 0.5mg/kg and very lose-dose ketamine is 0.1-0.4mg/kg. Amongst all the trials, it was concluded that low dose ketamine infusions provided better results than the very low-dose ketamine infusions. During these 9 studies, the main results that were looked at were "depression scale scores at days 1, 3, and 7, remission, response, suicidality, safety, and tolerability" (Xu et al., 2016 p. 1). From day 3 and on, the overall response, depression scores, and remission rates were much more in favor for the use of low-dose ketamine compared to very low-dose ketamine. For benefits on depressive symptoms and scaling scores, "A large reduction in depression severity was evident within 4 hours…and treatment effects were largest at day 1" (Xu et al., 2016 p. 4). While the day 1 depression scores were close between groups, "the reduction in overall severity appeared smaller and shorter lived" (Xu et al., 2016 p. 4) was evident compared to low-dose trials. Response and remission rates were almost four times higher in the ketamine groups versus the placebo groups. As predicted, the low-dose ketamine groups showed greater response and remission, even up to day 7, than the very low-dose group. As far as suicidal thought is concerned, scores were improved on days 1 and 3 after ketamine infusions, but not at day 7. While it shows some limitation in chronic improvement in suicidal thoughts, it

is promising to see that ketamine could make for an emergency medication that could be administered in crisis situations where patients may be having increasingly strong suicidal urges.

Depression response in a review by Bobo et al. (2016) also shows the immediate impact ketamine can have. “Those who benefitted from ketamine experienced rapid (within hours) onset of clinical antidepressive response” (p. 698). This clinical review by Bobo et al. (2016) had shown that “positive benefit from ketamine persisted for 3-14 days on average after single infusions” (p. 698). This is one of the highest response rates in terms of days that was found throughout the articles. This may be due to the fact that most articles did not have follow ups that went past two weeks since final infusion. As with the rest of the literature, Bobo et al. (2016) found through the studies of nine meta-analyses, that “the efficacy advantage of ketamine was most consistently observed within hours of initiating ketamine therapy through post-administration day 7, with peak effects occurring at 24 hours in most cases” (p. 699). This continued theme of immediate efficacy helps in building a case for the use of ketamine as a potential short-acting medication. Response and remission rates were shown to be beneficial in the short-term for the use of ketamine. One study in the article by Bobo et al. (2016), had shown a longer improvement in depressive symptoms for 12-14 days.

Wilkinson et al. (2019) did a systematic review that focused on studies that did only single dose, IV ketamine treatments. Compared to the reviews and studies that were done with multiple treatments, the single use treatments of ketamine had shown similar results in efficacy. Participants in studies that Wilkinson et al. (2019) included had either passive suicidal ideation or active suicidal thoughts. After administration of ketamine, participants had reports of improved suicidal thought compared to controls. These improved suicidal scores started at day 1 and lasted up until day 7 post administration (Wilkinson et al., 2019). Studies in the Wilkinson et

al. (2019) review included clinician-reported suicidal assessments as well as participant self-reported scores. No matter the report (clinician-administered or self-reported), suicidal scores carried this overall improvement after ketamine administration.

Depressive symptoms showed similar improvement in single use administration trials. Depressive symptoms not only improved but "changes in suicidal ideation and overall severity of depressive symptoms were strongly correlated at all time points" (Wilkinson et al., 2019 p. 6). The correlation occurred from day 1 and lasted until day 7. This correlation occurred with both clinician-administered assessments and self-reported symptoms. This review by Wilkinson et al. (2019) continues to support the idea that ketamine's symptom improvement appears to be dose-related.

A smaller study of participants was shown to have similar response to ketamine after single infusions. Bratsos and Saleh (2019) reported similar findings of ketamine scoring improved treatment-resistant depression scores and response to treatment. These improved scores started after 24 hours. "Ketamine's benefits were maintained for up to seven days post-infusion, at which point significant differences in MADRS (Montgomery-Asberg Depression Rating Scale) compared to midazolam were no longer observed" (Bratsos & Saleh, 2019 p. 2). Just one infusion has been shown to be effective for at least 7 days.

Single infusion studies seem to show similar results, even given the varying differences in depression rating scales, controls, and other variables and exceptions for each study. Molero et al. (2018) reported on 4, single infusion studies that all had similar results. The benefits of ketamine, compared to placebos of saline, riluzole and midazolam, were greater after 24 hours and, in most studies, lasted up to one week. These results agreed with the overall results of 17 single dose trials that were analyzed by Coyle and Laws (2015). "Turning to single infusion

studies, large effects emerged at 4 hours and at 24 hours, confirming the reported rapid reduction in depressive symptoms, and also at 7 days" (Coyle & Laws, 2015 p. 154). Ibrahim et al. (2012) had almost 60% of their participants remain with a positive response after 1 week of a single ketamine infusion.

Strong and Kabbai (2018) shared their reviews of studies and challenged the idea of ketamine effects being dose-dependent. Ketamine was shown, through depression rating scales, to have sustained remission periods of treatment-resistant depression when ketamine was given in repeated infusions multiple times a week. Not only were the depressive symptoms/scores lower, but "clinical studies have reported a greater number of TRD patients responding to low-dose ketamine…repeated infusions as compared to single infusion paradigms" (Strong & Kabbai, 2018 p. 167). Strong and Kabbai's (2018) claim to this is that "The enhancement of antidepressant efficacy of low-dose ketamine treatment under repeated infusion paradigms could be indicative of behavioral sensitization to ketamine's antidepressant effects" (p. 167). While ketamine does have some short term, positive responses to treatment-resistant depression, reviews like these show that there is potential for moderate to long-term use studies.

Repeated infusions have had some mixed results overall as far as finding the duration and frequency of doses for appropriate efficacy. Bratsos and Saleh (2019) reported on a smaller study where participants received either ketamine or placebo infusions. These infusions were given either twice weekly or three times weekly for four week period. The dosing regime was determined to initially be twice a week for ketamine "Since a significant difference in the MADRS score between the two ketamine frequencies was not found, although the study lacked the power to detect significant differences between the two regimens" (Bratsos & Saleh, 2019 p. 3). Overall, however, the response to treatment for repeated infusions was impressive, as

improved depression scores were noted up until day 15 post-treatment (Bratsos & Saleh, 2019). Molero et al. (2018) shared four studies of repeated infusion trials where response rates were noted to last around a similar time of 12-18 days. There were some participants who had exaggerated response times. In one study, five participants had positive response after 28 days, with another study having two participants with the same response time of four weeks (Molero et al., 2018). The response of repeated infusions is shown to be beneficial, but the challenge lies in finding a standardized dose and frequency of administrations per week.

Currently, the main route of administration for ketamine is by IV infusion, but some studies focused on other routes as well. While the study had a small sample size, Loo et al. (2016) did a pilot study that focused on three routes of administration, IV, intramuscular (IM) and subcutaneous (SC), with increasing titration. While the increase in dose was effective for some, "An important finding is that participants differed in their response to ketamine at specific mg/kg doses, with some attaining response and remission at doses lower than 0.5mg/kg" (Loo et al., 2016 p. 54). A positive correlation to increased dose and response to treatment-resistant depression was noted, but no set dose was discovered to be most effective across the board. While all three routes (IV, IM, and SC) had positive response and remission, the dosing inconsistencies show a need for increased research on proper starting doses and general safe and effective dose ranges. In a study with Hartberg et al. (2018), the route of administration was sublingual. This changed doses to an average dose of 2-3mg/kg. Even with the study focusing on a different administration route, ketamine was still shown to decrease hospital admission rates by 70% on follow up (Hartberg et al., 2018). The one consistent finding with the Loo et al. (2016) study was that "high response and remission rates were seen with all modes of administration, with peak effects occurring 24 hours after treatment, consistent with the reports of earlier

studies" (p. 54). These studies further validate how ketamine can be effective in the short term for emergent patients.

Suicidal ideation was another measurement that was used in gauging the efficacy of ketamine on treatment-resistant depression. All studies that measured suicidal ideation had seen improvement (Fond et al., 2014; Wilkinson, 2016; Molero et al., 2018; Hartberg et al., 2018; Bobo et al., 2016; Xu et al., 2016). However, these results were noted to only be beneficial up to 72 hours. These results still show the immediate benefit that could be provided to a patient in a suicidal crisis. Bobo et al. (2016) shared how one study "showed sustained reductions of suicidal ideations over a 12-14 day period following repeated ketamine infusions that were delivered over a 2-week period" (p. 704). Molero et al. (2018) confirmed similar results of a 12 day response to suicidal ideation in studies of repeated infusions given three times a week. All studies that had reported on suicidal ideation had shown immediate reduction (within 24 hours) after first administration of ketamine, whether it was single infusion studies or repeated infusions.

These articles all show that there is a positive response to ketamine for treatment-resistant depression and suicidal ideation. Some studies, however, did show that ketamine was not as effective in the short-term treatment of bipolar depression as compared to unipolar depression (Xu et al., 2015; Bobo et al., 2016; Coyle & Laws, 2015). Loo et al. (2016) excluded any participants with a bipolar disorder in general, even if was bipolar depression. There were some limitations within the research. Studies were not consistent in the types of controls used. Some used saline as the control, while others used midazolam. Studies also differed with what psychotropic medications the patients were allowed to be on during the trial. Some studies focused on ketamine as monotherapy, while others allowed any psychotropic medications. Some studies included in the review by Fond et al. (2104) also had compared ECT to ketamine

treatment. Scoring tools for depression also varied. While some studies used MADRS, others used the BDI, Hamilton Depression Rating Scale (HAM-D), or Quick Inventory of Depressive Symptomology-Self Report (QIDS-SR). The research was also scattered in terms of single use trials and repeated IV infusions. With the repeat infusions, the time frames also varied. Even with ketamine clinics opening up and currently being used as a late-stage treatment option for treatment-resistant depression, more research needs to be conducted. It would be beneficial for trials to have longer periods of low-dose ketamine infusions to gauge any potential threshold for addiction, exhaustion/plateau of its intended efficacy, and any potential long term side effects.

Implications

Ketamine has been shown to have a relatively short duration of efficacy. This is most likely due to its short half-life and peak times of effect. Given the results from the studies, all of these factors show that ketamine could be a beneficial medication for short-term use. This may include emergency situations, such as a severe crisis or suicidal intent, inpatient treatment for acute stabilization, or possibly as just maintenance therapy in an outpatient setting, like ketamine clinics now are doing.

Given the rough average range of 3-7 days of positive response after treatment, it would be interesting to have studies done in emergency departments where ketamine is used as a one-time dose to prevent hospital admissions. A psychiatric nurse practitioner could do an initial assessment, and if certain criteria is met, that patient could receive the infusion in the emergency department. After criteria is established and a study made, the effect on patient outcomes and admissions could be assessed. If the patient has a follow up appointment with their psychiatric provider within the week, ketamine could perhaps enable that patient to stabilize and return home before that appointment.

Even with some of the limitations discussed in the literature review, there are still good implications of use for ketamine and where it could go as a viable option for treatment-resistant depression for psychiatric nurse practitioners. One implication could be to screen their outpatient clients, perhaps with an updated Maudsley Scale. Referrals could then be made for outpatient ketamine infusions if they scored in the severe category while also being diagnosed with treatment-resistant depression. In subsequent outpatient visits to their psychiatric provider, monitoring the effectiveness of treatments could be done by continuing to administer the Maudsley Scale for depressive symptoms. With one of the limitations of the studies being multiple scoring tools, it would be imperative that a standard scoring tool be used in the screening and evaluations of patients receiving ketamine. While it's limited evidence, nurse practitioners have been shown to be effective at expanding their role and being able to provide safe and effective screening, as well as providing the ketamine services (Svensson et al., 2016). With the growing field of ketamine use for treatment-resistant depression, this shows that nurse practitioners, with the proper training and certification, could help carry some of the increasing demand for ketamine services that may be seen in the future.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.)

Bobo, W. V., Vande Voort, J. L., Croarkin, P. E., Leung, J. G., Tye, S. J., & Frye, M. A. (2016). Ketamine for treatment-resistant unipolar and bipolar major depression: Critical review and implications for clinical practice. *Depression and Anxiety, 33*(8), 698-710. https://doi-org.ezproxylr.med.und.edu/10.1002/da.22505

Brastos, S., & Saleh, S. N. (2019). Clinical efficacy of ketamine for treatment-resistant depression. *Cureus, 11*(7), e5189. doi:10.7759/cureus.5189

Coyle, C. M., & Laws, K. R. (2015). The use of ketamine as an antidepressant: A systematic review and meta-analysis. *Human Psychopharmacology: Clinical and Experimental, 30*(3), 152-163. https://doi-org.ezproxylr.med.und.edu/10.1002/hup.2475

Fekadu, A., Donocik, J. G., & Cleare, A. J. (2018). Standardisation framework for the Maudsley staging method for treatment resistance in depression. *BMC Psychiatry, 18*(1), 100. https://doi-org.ezproxylr.med.und.edu/10.1186/s12888-018-1679-x

Fond, G., Loundou, A., Rabu, C., Macgregor, A., Lancon, C., Brittner, M., … Boyer, L. (2014). Ketamine administration in depressive disorders: A systematic review and meta-analysis. *Psychopharmacology, 231*(18), 3663-3676. https://doi-org.ezproxylr.med.und.edu/10.1007/s00213-014-3664-5

Haroon, E., Daguanno, A. W., Woolwine, B. J., Goldsmith, D. R., Baer, W. M., Wommack, E. C., Felger, J. C., & Miller, A. H. (2018). Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder. *Psychoneuroendocrinology, 95*, 43-49. https://doi-org.ezproxylr.med.und.edu/10.1016/

j.psyneuen.2018.05.026

Hartberg, J., Garrett-Walcott, S., & De Gioannis, A. (2018). Impact of oral ketamine augmentation on hospital admissions in treatment-resistant depression and PTSD: A retrospective study. *Psychopharmacology*, *235*(2), 393-398. https://doi-org.ezproxylr.med.und.edu/10.1007/s00213-017-4786-3

Ibrahim, L., Diazgranados, N., Franco-Chaves, J., Brutsche, N., Henter, I. D., Kronstein, P., … Zarate, C. A., Jr. (2012). Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 37*(6), 1526-1533. https://doi-org.ezproxylr.med.und.edu/10.1038/npp.2011.338

Loo, C. K., Galves, V., O'Keefe, E., Mitchell, P. B., Hadzi, P. D., Leyden, J., … Glue, P. (2016). Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatrica Scandinavia, 134*(1), 48-56. https://doi-org.ezproxylr.med.und.edu/10.1111/acps.12572

Molero, P., Ramos-Quiroga, J. A., Martin-Santos, R., Calvo-Sanchez, E., Gutierrez-Rojas, L., & Meana, J. J. (2018). Antidepressant efficacy and tolerability of ketamine and esketamine: a critical review. *CNS Drugs, 32*:411-420. https://doi.org/10.1007/s40263-018-0519-3

National Institute of Mental Health. (2019). *Major Depression.* https://nimh.nih.gov/health/statistics/major-depression.shtml

Reis, D. J., Namekata, M. S., Oehlert, M. E., & King, N. (2019). A preliminary review of the Beck Depression Inventory-II (BDI-II) in veterans: Are new norms and cut scores needed? *Psychological Services.* https://doi-org.ezproxylr.med.und.edu/10.1037/

ser0000342.supp

Strong, C. E., & Kabbai, M. (2018). On the safety of repeated ketamine infusions for the treatment of depression: Effects of sex and developmental periods. *Neurobiology of Stress, 9*, 166-175. https://doi-org.ezproxylr.med.und.edu/10.1016/j.ynstr.2018.09.001

Svensson, T. K., Miller, L., & Huurd, C. (2016). Expanding the nurse practitioner role in resistant major depression. *Journal of Hospital & Medical Management, 2*(1:4), 1-7. https://hospital-medical-management.imedpub.com/expanding-the-nurse-practitioner-role-in-treatment-resistant-major-depression.pdf

Wilkinson, S. T., & Sanacora, G. (2016). Ketamine: A potential rapid-acting antisuicidal agent? *Depression and Anxiety, 33*(8), 711-717. https://doi-org.ezproxylr.med.und.edu/10.1002/da.22498

Xu, Y., Hackett, M., Carter, G., Loo, C., Galvez, V., Glozier, N., … Rodgers, A. (2016). Effects of low-dose and very low-dose ketamine among patients with major depression: A systematic review and meta-analysis. *International Journal of Neuropsychopharmacology, 19*(4), 1-15. https://search-ebscohostcom.ezproxylr.med.und.edu/login.aspx?direct=true&db=psyh&AN=2016-28970-008&site=ehost-live