The Role of Ketamine in Depression: By Mary Garner

Background: Introduction

The average person has up to 15% lifetime risk for developing depression[13]. Major depressive disorder symptoms can include a depressed mood, such as feeling sad or having more anger than normal, changes in appetite, loss of interest in activities or hobbies, psychomotor agitation or retardation, loss of energy, feelings of worthlessness or guilt, decreased ability to think or concentrate, sleep disturbance, an/or having suicidal thoughts. To make the diagnosis of major depressive disorder, according to the DSM-V, Diagnostic and Statistical Manual of Mental disorders, a person must have at least 5 or more of these 9 symptoms during a continuous two-week period which causes significant impairment in functioning[1]. Depression is treated in a variety of ways including medications and psychotherapy either as monotherapy or in tandem. When a patient has failed 2 or more medication treatments they are considered treatment resistant or as having refractory depression. Treatment resistant depression or refractory depression has several standard therapies, which include combination pharmacotherapy, electroconvulsive therapy, or ECT, transcranial magnetic stimulation, or TMS, vagal nerves stimulation and deep brain stimulation. Current research does support that a novel therapy, such as ketamine infusions, may help patients in the short-term with their depressive symptoms, including suicidal ideation. The focus of this paper is to review the clinical trials involving ketamine use in refractory depression for the alleviation of depressive symptoms, including suicidal ideation, and to examine the benefits, limitations, and future potential for ketamine as a treatment for refractory depression.

Epidemiology:

Depression varies across sex, socioeconomic status, age and race. Many people who seek treatment for depression have a chronic relapsing-remitting course of the illness[6]. The prevalence of depression usually increases during the teenage years throughout early to mid 20s, with an average age of onset in the mid 20s[6]. Adults over the age of 60 have a lower rate of depression than other age demographics[13]. Females have a greater prevalence for depression in all age groups studied by the Centers for Disease Control and Prevention (CDC)[13]. Hispanic and Non-Hispanic black persons have a higher rate of mild to moderate depressive symptoms than Non-Hispanic white persons, who were more likely to have no depressive symptoms[13]. Socioeconomic levels have been shown to have an effect on levels of depression, with people below the poverty line being twice as likely to have depression[13]. In studying refractory depression in primary care settings across Canada there was no significant prevalence difference in men versus women[14]. Patients with refractory depression were more likely to have longer depressive episodes, with higher rates of comorbid illnesses, such as cardiac disease or anxiety or personality disorders[14]. In patients with RD (refractory depression) there is a higher chance of polypharmacy with increased side effects and decreased ability to work, indicating that with RD a patient's life may be more severely affected long-term[14].

Pathophysiology:

Currently, the cause of depression is not fully understood. There are a variety of diverse risk factors that are positively correlated with the diagnosis of depression and may act at different stages of development. Variables may include genetics and environmental factors, psychosocial adversity, anxiety disorders, and substance misuse[5]. Studies have shown through familial, twin and adoptions that there is a strong link in the genetic aspect to depression, with up to 40% directly correlated to genetic factors[3]. The remaining variance may be associated with childhood traumatic events and lifetime adversity[3]. Other theories focus on the hormonal aspects of depression, such as altered hypothalamic-pituitary axis activity, monoamine deficiency, reduced gamma-amino-butyric acid (GABA) activity, dysfunction of the glutamate system or impaired circadian rhythms[3]. For all of the hypotheses surrounding depression, there are both strengths and limitations. Many of the limitations revolve around not having specific genes or evidence in humans. The lack of a unified theory for the pathophysiology of depression is indicative of a very complex and incompletely understood disease.

Diagnosing Depression:

When diagnosing depression, providers are guided by the DSM-V and physiological instruments, such as the PHQ9, which are increasingly utilized in both the diagnosis and management of depressive disorders. The criteria are based on the clinical findings or what the patient is feeling or another person is observing so it is important to get an accurate history and physical examination. Providers must be thorough in order to make the diagnosis of depression taking into account the patient's current life events and medical and mental comorbidities. Depression is often missed in the primary care setting. There are several tools available that providers may use to assess for depression before a clinical visit begins, but a thorough patient interview is necessary as well. A provider must look at the patient's symptoms to assess for depression: depressed mood, loss of interest or pleasure, appetite or weight changes, trouble sleeping or sleeping too much, psychomotor agitation or retardation, loss of energy or excessive fatigue, guilt or feeling worthless, decreased ability to concentrate, and suicidal thoughts or recurrent thoughts of death. Assessing for suicidal risk is crucial during the interview and may determine whether a patient needs inpatient or outpatient treatment.

Table 1. DSM-V criteria for Major Depressive Disorder.

Five or more of the following symptoms, which represents a change from baseline and have been presents for at least a 2-week period; must include either depressed mood or loss of interest or pleasure.	
1.	Depressed mood
2.	Loss of interest or pleasure
3.	Weight change: unintentional weight gain or weight loss or change in appetite
4.	Insomnia or hypersomnia
5.	Psychomotor agitation or retardation
6.	Fatigue or loss of energy
7.	Feelings of worthlessness or inappropriate guilt
8.	Decreased ability to think or concentrate
9.	Recurrent thoughts of death, recurrent suicidal ideation with or without a specific plan
Symptoms cause a clinically significant impairment or distress in everyday functioning	
Symptoms or depressive episode not due to another medical condition or substance use	
The disorder is not better explained by another mental health disorder.	

Differential Diagnosis:

Distinguishing unipolar depression, or depression without mania, from other disorders that manifest similarly helps guide and focus the treatment. Depression may look similar to other psychiatric disorders or may be caused by a medical condition. A generalized workup is necessary to help narrow down the differential. When a patient presents with new onset depressive symptoms a thorough history, physical examination and lab work is required. Taking into context the DSM-V is crucial to help differentiate depression from other psychiatric disorders including but not limited to: Schizophrenia, Bipolar disorder, anxiety or ADHD, Depressive symptoms are not limited to mental illness. Many medical conditions can mimic depression and cloud a practitioner's clinical picture. A thorough physical examination and blood work can help rule out depression due to a medical condition. Examples of medical conditions that may cause depressive symptoms can include the following: substance induced mood disorder, hypothyroidism, hypoglycemia, and chronic fatigue syndrome.

Treatment:

First-line treatment for depression may involve psychotherapy, most specifically Cognitive behavioral therapy, medication, or a combination of psychotherapy and medication. This paper will focus on the pharmacological approaches to depression. Psychotherapy or medication is considered first line in treating depression and psychotherapy may be used as monotherapy or in combination with medication. The first line medication

therapies include: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and the norepinephrine-dopamine reuptake inhibitor (NDRI)[7]. Treatment is chosen based on a continuing assessment of the patient's symptoms and side effects and any previous drug trials the patient has had. Older drug classes, such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), or antipsychotics are generally reserved for patients that do not have a satisfactory response to first-line antidepressants. Patients are usually started at the minimum therapeutic dose and titrated upward over the course of several weeks, depending on the clinician's judgement; a second drug may be added if the patient is having inadequate symptomatic relief with one medication. Patients are told that symptomatic relief may occur within a few weeks or a number of months.

A patient who does not respond to two or more adequate trials of antidepressant (with adequacy determined by medication duration and dose) is considered treatment resistant. Patients who experience refractory depression have a lower quality of life in addition to more medical visits and higher financial burden on the healthcare system. The excess burden and lower quality of life may also contribute to increased anxiety, depression and other comorbid disorders[11].

Current standard of care for patients who are resistant to treatment includes combination pharmacotherapy in which the provider works to optimize the medication the patient is on and augments current treatment by adding additional medication.

Research has been working towards increasing treatment options for patients who fail even the standardized treatment options for resistant depression, and one of the pathways to achieve this is through non-monoaminergic approaches, such as the N-methyl-D-aspartate (NMDA) receptor antagonists, like ketamine.

Ketamine:

Ketamine was initially introduced as an anesthetic, but throughout the years it has been demonstrating effects in a variety of different roles, including analgesia and therapy for treatment-resistant, or refractory, depression. Ketamine is a structural analog for Phencyclidine, a known hallucinogen, and was discovered in 1962[9]. Ketamine was shown to produce quick acting analgesia of short effect and minimal side effects and lack of severe delirium that its parent compound, phencyclidine, produced[9].

Ketamine is an arylcycloakylamine derivative that exists in S(+) and R(-) isomers and is commonly used in medicine as a racemic mixture of both[9]. Ketamine works as a NMDA antagonist, binding to the receptors and causing an anesthetic effect. Ketamine is available in several different forms including intravenous (IV), intramuscular (IM), oral, nasal, rectal, subcutaneous (SQ), and epidural administration. IV ketamine has the highest bioavailability at 100%, with IM following at 93%[9]. Ketamine has a quick onset of action due to its short half- life of 10-15 minutes and lipid solubility[9]. Ketamine has generally been dosed up to 1mg/kg, though lower doses may achieve sedation.

Ketamine is most commonly used in anesthesia and sedation, but in recent years its psychiatric uses are being explored in refractory depression. This paper will explore the role of ketamine in the improvement of symptoms in refractory depression including suicidal ideation along with the potential benefits and limitations of use.

Methods:

Initial search of UpToDate, then PubMed with the following search terms: 'ketamine and depressive disorders', 'ketamine and depression,' and 'ketamine and refractory depression'. Uptodate search was used to supplement background information and provide framework and structure for searching in Pubmed.

A literature search was performed using Pubmed with the follow terms: *ketamine; depression; depressive disorder*. Included articles that were clinical trials, written in English, published within the last 5 years. Of the original 539 articles the filtered search yielded 57 articles.

The Cochrane Bias Tool was utilized in order evaluate articles by analyzing selection, performance, detection, attrition, and reporting bias. The criteria that were analyzed included: Drug administration, dosage and treatment duration, blinding versus non-blinded studies, sample sizes, placebo versus active drugs, remission rates, side effects, follow-up, and outcomes of the study. See table below for further details.

Results:

Murrough et al. (2015) demonstrated that after a single dose of ketamine suicidal ideation was decreased in the sample group at 48 hours[12]. This trial used a single dose of ketamine and then the patient's symptoms were assessed at 24, 48, and 72 hours and 7 days. Patients' symptoms were significantly decreased in the Ketamine group at 48 hours (8.8+/-8.3 and 15.3+/-10.9 $F_{1,21}$=4.45, p=0.047). The most common observed side effects of ketamine were headache, dizziness, anxiety, poor concentration and coordination, most of which resolved by the end of infusion. This trial was limited in the fact that there was no long-term follow up and it only looked at reduction of suicidal ideation as the outcome. The same size was small at 24 participants.

Singh et al. (2016) was a clinical trial consisting of 67 participants (45 women) who were administered ketamine 2 or 3 times weekly or IV placebo[15]. The outcomes were measured using Montgomery Asberg Depression Rating scale (MADRS). Both ketamine groups had improvement in their MADRS score from day 1 to 15 (twice weekly = -18.4 (SD 12) and thrice weekly = -17.7 (SD 7.3) compared to placebo: -5.7 (SD 10.2) and -3.1 (SD 5.7). The study also looked at the secondary outcome of baseline MADRS score to day 29 and found that the ketamine groups showed improvement over a longer period of time compared to the placebo (twice weekly -21.2 (SD 12.9) and thrice weekly -21.2 (SD 11.2) versus placebo (-4.0 (SD .1) and -3.6 (SD 6.6)). The study was limited because there was no long-term follow up beyond 6 weeks. Also, because patients did have side effects while taking ketamine infusions (headache, anxiety, dissociation, nausea, and dizziness) there is the possibility of unblinding. Overall, this study did demonstrate that improvement in patients' subjective symptoms of depression is possible with ketamine even at less frequent dosing, such as twice weekly vs thrice weekly.

Losifescu et al. (2013) was a clinical trial of 72 participants who had failed 3 or more trials of antidepressants and had a diagnosis of major depressive disorder[4]. The participants were randomized into control (midazolam) or active (ketamine) groups. Participants received 1 dose over 40 minutes. Severity of depression was assessed continuously for the first 24 hours and then again at 48 and 72 hours and 7 days utilizing the MADRS scoring system. The mean score was lower in the ketamine group by 7.95 points (CI 3.20 to 12.71). Both groups showed worsening of MADRS score each day after infusion. (B=0.0004; 95% CI 0.00009 to 0.00062). The time to relapse was measured between 4 midazolam responders and 21 ketamine responders, which showed a greater portion of patients without relapse in the ketamine responder group. The single infusion administration of ketamine was a limitation for the study, as the effects of more frequent dosing and remission rates at greater time intervals from the infusion are unknown. This study does support that even with a single infusion or dose of ketamine there is reduction in the severity of depression measured subjectively by the participants.

Lapidus et al. (2014) demonstrated a novel use of intranasal ketamine. The sample size was 18 and randomized into control (saline solution) and intranasal ketamine[8]. Participants were assessed at 40, 120, 240 minutes and 48, 72 hours and 7 days. Symptoms improved after 24 hours in the treatment group compared to the placebo (T= 4.39, p <0.001) with a mean difference in MADRS score of 7.6+/- 3.7 (95% CI, 3.9-11.3). The greatest effect was seen at 24 hours with no significant difference seen between both groups at 7 days. Limitations for this study include the small sample size, possibility of unblinding with side effects from ketamine (dissociation, poor memory, weakness and fatigue), short time frame of study, and ketamine use in conjunction with the patient's current therapy rather than as a monotherapy. The study did show that there was a favorable response when using MADRS scoring and there were minimal side effects. This introduced intranasal ketamine versus IV infusion, which may be significant because intranasal may be more easily administered to patients than IV.

Burger et al. (2016) looked at acute depression and suicidality in a military emergency department setting. A sample size of 10 participants with depression measured using the Beck Suicidality Scale (BSS) was randomized into a ketamine group and a placebo (normal saline) group[2]. Patients were assessed before drug administration and 40,

80, 120, and 240 minutes after administration. BSS showed significant linear effects of time ($p < 0.05$), but not group ($p > 0.05$). There was significant linear time x group interaction ($p < 0.05$) over the 4 hour ED observation period. BSS at follow-up or discharge was not significant between groups. BHS, Beck Hopelessness score, showed neither significant effect of time or group, but the time x group intervention was significant. BHS scores were significantly different at discharge, but not at follow-up. Limitations include a small sample size and lack of data on long-term effects on remission and side effects of ketamine use. The study was considered a failed trial due to record-keeping trouble and was terminated early. There was sparse data on the results and statistical analysis. It did indicate that there was potential for ketamine in an acute setting with a reported 67% of patients showing a decrease in SI and depression symptoms.

Loo et al. (2016) compared dose titration with IV, IM, and SQ routes for ketamine in depression[10]. The sample size was 15 participants who received either ketamine or midazolam. Ketamine was administered by IV, IM, or SQ routes and dose titrated up at 0.1 mg/kg to 0.4 mg/kg. MADRS was measured on day 1 of ketamine treatment and at 4 hours and 2, 4, and 7 days after each treatment. 12 out of 15 patients met the criteria for both response and remission at some point during the trial, with an overall acute response/remission rate of 75% (IV), 60% (IM) and 100% (SQ). Mean time to relapse was 23.2 days. There was no difference in MADRS scores between routes of administration. Overall, there was short-term improvement in both 0.2mg/kg and 0.1mg/kg dosing versus placebo, although there was no linear trend. Placebo and ketamine groups showed no statistical difference at day 7 post-treatment. Side effects for ketamine were observed at higher doses. The limitations in this trial include the small sample size, placebo vs treatment group was by sequential cohorts rather than randomized, dosing was titrated rather than randomized, and ketamine was not studied as a monotherapy. This study did reveal that dosing response was based on the individual. Different individuals responded differently to different doses, indicating that ketamine may need to be dosed on an individual basis. This was the first trial reviewed which included SQ, IM, and IV administration of ketamine.

Study	Dosing and administration	Side Effects:	Results	Remission Rates	Limitations	Conclusions
Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial ***Murrough et al. 2015***[12]	Sample size: 24. Active versus Placebo: 0.5 mg/kg racemic ketamine HCL or 0.045 mg/kg IV midazolam over 40 minutes	Most common side effects of ketamine were headache, dizziness on standing, anxiety, poor concentration, poor coordination and restlessness	Assessed at 24, 48, 72 hours and 7 days post-treatment. 24 hours after treatment there was no significant difference in baseline SI between groups (10.8+/- 8.5 and 14 +/- 10.2 for ketamine and midazolam) At 48 hours decrease in baseline suicidal ideation compared to the control group (8.8+/-8.3 and 15.3+/-10.9 $F_{1,21}$=4.45, p=0.047) No statistical difference between groups at 72 hours and 7 days	Not available	Single dose of ketamine with no long term follow up. Only looked at reduction of SI for outcomes Small sample size No data on effects of Ketamine as monotherapy	Demonstrated tolerability to ketamine and supports the data that ketamine has potential for rapid decrease in SI. More studies needed to study the long-term effects of ketamine.
A double-blind, randomized, placebo-controlled, dose-frequency study of Intravenous ketamine in patients with Treatment-resistant depression ***Singh et al., 2016***[15]	Sample size: 67 (45 women) ages 18 -64 years old. Patients randomized in 1 of 4 treatment groups: IV ketamine (0.5mg/kg); administrated 2 or 3 times weekly or IV placebo (0.9% sodium chloride); administered 2 or 3 times weekly. Depression measured using MADRS = Montgomery-Asberg	Most common treatment adverse events were headache, anxiety, dissociation, nausea, and dizziness (most commonly on day of dosing and resolved within 2 hours) No deaths were reported, but two serious emergent adverse events occurred (unrelated to ketamine); anxiety (life related) and suicide	Primary Outcomes: mean baseline in MADRS score from day 1 to 15 improved in both ketamine frequency groups (twice weekly = -18.4 (SD 12) and thrice weekly = -17.7 (SD 7.3) compared to placebo: -5.7 (SD 10.2) and -3.1 (SD 5.7) Secondary outcomes: MADRS mean score improved from baseline to day 29 in ketamine groups (twice weekly -21.2 (SD 12.9) and thrice weekly -21.2 (SD 11.2))	MADRS remission at day 15: Ketamine group (twice weekly N = 6; 37.5%. thrice weekly N = 3; 23.1%) Placebo group (twice weekly N= !; 7.7% and thrice weekly N= 0)	Short time period assessed of 4-6 weeks No long-term follow-up Possibility for un-blinding due to adverse events occurring in treatment group.	Short-term improvement in depression is possible with ketamine, even at less frequent dosing such as twice weekly. Further studies are needed to assess long-term effects of ketamine and rates of remission of treatment resistant depression.

	Depression Rating Scale	attempt on day 40 – more than 40 weeks after last dose	versus placebo (-4.0 (SD .1) and -3.6 (SD 6.6))			
Antidepressant Efficacy of Ketamine in treatment-resistant Major depression: A two site Randomized *controlled trial Losifescu et al., 2013*[4]	Sample size: 72. Ages 21 to 80 years old with primary diagnosis of MDD with treatment failure of ≥ 3 therapeutic trials. Randomized and received either single dose IV ketamine HCL (0.5 mg/kg) or midazolam (0.045 mg/kg) infused over 40 minutes.	Ketamine: most common AE for up to 4 hours post-infusion were dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, poor concentration and restlessness. Midazolam: most common AE for same time frame were general malaise, dizziness, headache, restlessness, nausea or vomiting, dry mouth, decreased energy and poor coordination. 8/47 ketamine patients reported dissociative symptoms; which resolved within 2 hours post-infusion	Assessed continuously for 24 hours, then at 48 hours, 72 hours and 7 days post-infusion. Primary outcome: reduction in depression severity assessed by MADRS 24 hours post-infusion. Mean score was lower in ketamine group by 7.95 points (CI 3.20 to 12.71).	Both groups showed worsening of MADRS score each day after infusion. (B=0.0004; 95% CI 0.00009 to 0.00062). The time to relapse was measured between 4 midazolam responders and 21 ketamine responders which showed a greater portion of patients without relapse in the ketamine responder group	Single dose of ketamine trial; unknown what the effect would be of multiple dosing over the same period studied. Unknown long-term effects of ketamine	Study supports data that ketamine causes a rapid response with only one infusion as monotherapy
A Randomized Controlled Trial of Intranasal ketamine in Major Depressive disorder *Lapidus et al., 2014*[8]	Sample size 18. Ages 21-65 years old. Have failed at least 1 trial of antidepressant medication. Maintained standard treatment during trial. Randomized into intranasal ketamine HCL 50mg and placebo (0.9% saline solution) and there were two treatment days.	Associated with small increases in psychosis and dissociation, systolic blood pressure increases. Most common emergent AE were feeling strange or unreal, poor memory and weakness or fatigue – most of these symptoms resolved after 4 hours.	Assessment occurred at 40, 120, 240 minutes, and 48, 72 hours and 7 days. Symptoms improved after 24 hours in the treatment group compared to the placebo (T= 4.39, p <0.001) with a mean difference in MADRS score of 7.6+/- 3.7 (95% CI, 3.9-11.3)	Greatest effect was seen at 24 hours. MADRS scores were similar in ketamine and control group at 7 days.	Did not assess Ketamine as monotherapy Use of non-active placebo with no side effects could result in un-blinding. Small sample size and short study time frame with no long-term effects measured.	There were limited AE and patients who received ketamine had a favorable response when evaluated using MADRS. Introducing intranasal ketamine as form. Need to evaluate long term effects and with larger sample size
A Double-Blinded, Randomized, placebo-controlled sub-dissociative dose Ketamine pilot study in the treatment of Acute Depression and Suicidality in a Military Emergency Department setting *Burger et al., 2016*[2]	Sample size 10. Ages 18 to 65 years old. Depression measured using Beck Suicidality Scale (BSS), BHS, and Beck Depression Inventory. Randomized into ketamine active group 0.2 mg/kg infused over 2 minutes and placebo group with normal saline.	No depersonalization, confusion, hallucinations or other adverse symptoms associated with ketamine and no other adverse effects were noted by participants.	Assessed before drug administration and 40, 80, 120, and 240 minutes after administration. BSS showed significant linear effects of time ($p < 0.05$), but not group ($p > 0.05$). There was significant linear time x group interaction ($p < 0.05$) over the 4 hour ED observation period. BSS at follow-up or discharge was not significant between groups. BHS showed neither significant effect of time or group, but the time x group intervention was significant. BHS scores were significantly different at discharge, but not at follow-up.	Not available	Small sample size. No long-term effects on remission available or long-term effects of ketamine use. Sparse data on results and statistical analysis. Study was terminated early because of record-keeping trouble.	Considered failed trial but showed potential for ketamine for acute depression in the ED setting with 67% of patients showing a decrease in SI and depression symptoms.

Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression ***Loo et al., 2016***[10]	Sample size: 15 patients diagnosed as treatment refractory who received ketamine or midazolam. Ketamine was administered by IV, IM, or SQ routes and dose titrated up at 0.1 mg/kg to 0.4 mg/kg.	SE were observed at higher doses. Symptoms included: depersonalization, derealization, altered body perception and altered time perception. All resolved after 40 minutes post-infusion. Transient elevation occurred in heart rate, systolic and diastolic blood pressure. Most common side effects were fatigue, light-headedness, dizziness, blurred vision and emotional lability.	MADRS was measured on day 1 of ketamine treatment and at 4 hours, 2, 4, and 7 days after each treatment. 12 out of 15 patients met the criteria for both response and remission at some point during the trial. With an overall acute response/remission rate of 75% (IV), 60% (IM) and 100% (SQ). Mean time to relapse was 23.2 days. There was no difference in MADRS scores between routes of administration. Overall, there was short-term improvement in both 0.2mg/kg and 0.1mg/kg dosing versus placebo, although there was no linear trend.	Placebo and ketamine groups showed no statistical difference at day 7 post-treatment.	Small sample size Treatment group was by sequential cohorts rather than randomized. Dosing was titrated versus randomized. Ketamine was not studied as monotherapy	Revealed that dosing response differed among individuals, therefore ketamine treatment may need to be dosed on an individual basis. Analyzed different routes of administration including SQ, IM, and IV.

Discussion:

Ketamine use for depression is most often limited to clinical trials because it is not currently indicated by the Federal Drug Administration for depression. It is not a standard of therapy even with its rapid reduction in suicidal ideation due to its limitations. Ketamine is given in IV form the majority of the time. In order to give a ketamine infusion, the safety of the patient must be monitored which includes vital sign checks, staffing an infusion center, and having a provider oversee the process. It is unknown whether a psychiatrist or another provider, such as an anesthesiologist, should be monitoring the patient during an infusion. Having an anesthesiologist present for the infusion would be beneficial, in that they are familiar with ketamine due to its common use in sedation; however, they may not be well equipped to handle the depressive symptoms and any acute emerging symptoms from the patient's mental disorder with which a patient may present.

Current clinical studies focus on short-term ketamine use and the potential to rapidly reduce symptoms including suicidal ideation. This is important for providers because ketamine may have a future potential to treat a patient in an emergent setting and then discharge them home with a safety plan and follow up for further therapy and perhaps continuing infusions in an outpatient setting. There is also a possibility that with short-term ketamine use a patient may be able to re-titrate their antidepressants, as research does not clearly demonstrate how ketamine works to help with the rapid improvement of symptoms.

Ketamine may also have other novel roles in the treatment of mental disorders that are unexplored. It may have a role as an adjunct in ECT therapy. Currently, ketamine is not regularly used as the sedative in ECT. Most often midazolam, or versed, is the sedative of choice in ECT. There may be potential for ketamine use if the rapid decline in SI will allow the patient to return to normal function more quickly than the time of standard ECT therapy.

Another future path in which ketamine can be evaluated in clinical trials is analyzing its effects over a greater period of time. Currently, the majority of randomized control trials are ones that test ketamine over a short period of time with short term follow up. By analyzing the long-term use and effects of ketamine, researchers can further test if the efficacy is extended for a greater amount of time and if the side effects that are experienced after infusion persist. Ketamine has a history of abuse, so incorporating close short and long-term follow-up with patients is crucial in order to analyze who is benefiting from ketamine use and whether it should be more widely available as a treatment for refractory depression.

Limitations to ketamine use include availability and cost. As mentioned above, Ketamine is often given in IV form, which has the benefit of 100% bioavailability and is the most widely available. Patients with severe depression may

not have the funds or insurance to cover extensive ketamine infusions. Mental illness treatment can be a costly lifetime expense with hospitalizations, medication changes, and more extensive somatic therapies. Making a treatment that is sustainable to the healthcare system and to patients is crucial for it to be successful.

Conclusion:

Severe refractory depression has limited treatment options. Ketamine has demonstrated a reduction in symptoms of depression and suicidality in the acute setting in patients with treatment resistant depression through IV, IM, SQ, and intranasal administration. Future studies should focus on the long-term effects of ketamine, continuing to evaluate the efficacy of ketamine on symptoms of depression and suicidality, especially in the long term, and the different methods of drug administration. Future ketamine use will depend on accessibility and affordability to patients and providers.

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