

## **IV Ketamine Infusions for the Treatment of Depression: An Evidence Based Practice Analysis**

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### **Introduction**

According to the World Health Organization, major depressive disorder (MDD) is a mental health condition which affects a significant portion of the worldwide population and is projected to become the leading cause of disability by 2020.<sup>1</sup> There are several treatment options for the diagnosis of depression, with the most popular being antidepressant drugs such as the selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs); and electroconvulsive therapy (ECT). The significant drawbacks to the current treatments are the extended timeframe required for drugs to reach therapeutic efficacy and resistance to ECT over time. These disadvantages can lead to increased risk of self-harm and suicidal tendencies. A drug with fast onset and efficacy in treating depression can improve patient's quality of life.

Even though the exact MOA is still unknown there is growing evidence for the role of ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, in rapidly alleviating depressive symptoms in patients who have treatment-resistant depression.<sup>2</sup> Recent clinical trials have shown that a single dose of low-dose ketamine produces a rapid antidepressant response.<sup>3</sup> The purpose of this evidence-based-analysis is to examine the effects of intravenous (IV) ketamine infusions of 0.5 mg/kg over 40 to 100 minutes in reducing depression scale scores, and the side effects of ketamine. The independent variable includes the administration of an IV ketamine infusion of 0.5 mg/kg ranging from 40 to 100 minutes. The dependent variable includes depression scores as measured by the Montgomery-Asberg Scale.

### **Methodology**

A population, intervention, comparison and outcome (PICO) question was used to guide the clinical framework, "What are the effects of IV ketamine infusions of 0.5mg/kg over 40 to 100 minutes (I) in adult patients diagnosed with depression (P) on depression scale scores and side effects (O) compared to patients being treated with oral antidepressant medications, ECT, or placebo (C)?"

A comprehensive search of the literature was conducted using the Cochrane collection, CINAHL, Google Scholar, MedlinePlus, EBSCO, PubMed, and Academic Search Premier databases through April 2017. The query was conducted with the keywords ketamine and any of the following terms: depression, antidepressant, resistant depression, IV infusion, MOA, side effects, adverse reactions, safety, efficacy, serial infusion. The studies were included if they were: 1) published within 10 years; 2) published in English in a peer-reviewed journal; 3) randomized, double-blind and placebo-controlled trials; 4) systematic reviews; and 5) meta-analyses.

### **Literature Review**

**Mechanism of Action.** Ketamine is an IV anesthetic drug that has been safely used for both induction and maintenance of anesthesia and for its analgesic effects. The MOA of ketamine

consists of the noncompetitive binding to voltage-dependent NMDA receptors, members of the glutamate receptor subfamily. Glutamate is the major excitatory neurotransmitter in the brain and spinal cord. Ketamine inhibits the activation of NMDA receptors by glutamate, decreases the presynaptic release of glutamate, and potentiates the release of the neurotransmitter gamma-aminobutyric acid (GABA). The exact MOA of ketamine's ability to treat depressive disorders is not fully understood and beyond the scope of this paper, but several important receptors and neurotransmitters have been identified: mammalian target of rapamycin, eukaryotic elongation factor 2, and glycogen synthase kinase-3, and 2-amino-3-propanoic acid (AMPA). The effects that ketamine exerts on these receptors in addition to NMDA antagonism is believed to contribute to its antidepressant effects.<sup>4</sup>

**Depression Measurement Scales.** The Montgomery-Asberg Depression Rating Scale (MADRS) is commonly used in evaluation of depression symptoms.<sup>5</sup> The scale is not meant to be a tool to diagnose depression, but instead is utilized to assess the level, type, and severity of symptoms present, and thus is considered a reliable method to measure depression severity. The MADRS is a fixed seven-point (0-6) scale that is conducted as a clinician and patient interview. When evaluating depression using the MADRS scale, higher scores indicate a higher depressive state. The MADRS has an overall score which ranges from 0 to 60, with each item yielding a score of 0 to 6. The questionnaire includes questions on the following symptoms: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The scoring categories are: symptoms absent (0-6), mild depression (7-19), moderate depression (20-34), and severe depression (>34).<sup>5</sup>

**Dosages and Duration of Infusion.** Each study reviewed utilizes a consistent ketamine dose of 0.5 mg/kg.<sup>6-11</sup> The meta-analysis by Mcgirr et al.<sup>8</sup> is the only study to review the administration of an additional dose of ketamine. The dosing included an infusion of ketamine 0.5 mg/kg over 40 minutes with an additional IV bolus of 0.27 mg/kg and an additional 0.27 mg/kg infused over 20 minutes. Mcgirr et al. is also the only study in which an intranasal application of ketamine 50 mg was given. Patients in the intranasal study showed an improvement in symptoms at 24 hours (MADRS mean score decrease of 7.6 points) when compared to placebo ( $p < 0.001$ ). In addition to the primary 24-hour outcome, ketamine was significantly different from placebo at 40 min ( $p < 0.001$ ), 240 min ( $p = 0.026$ ) and 48 hours ( $p = 0.048$ ).<sup>8</sup>

Five of the studies reviewed used an infusion duration of 40 minutes.<sup>6-9,11</sup> The RCT by Singh et al.<sup>6</sup> demonstrated that efficacy in sustaining an initial antidepressant effect was significantly improved in the ketamine groups compared to placebos ( $p < 0.001$ ).<sup>6</sup> Overall MADRS scores between the two ketamine groups did not differ statistically.<sup>6</sup> The onset of an antidepressant response within week one and observed through day 15 was improved in both ketamine groups when compared to placebo groups.<sup>6</sup> The change in MADRS score improved from baseline to day 29 in both ketamine groups.<sup>6</sup> Rot et al.<sup>7</sup> found onset of infusions to be two hours and their efficacy remained at 24 hours ( $p = 0.0001$ ). Mcgirr et al.<sup>8</sup> found an onset of ( $p = < 0.0001$ ) after 24 hours. Murrough et al.<sup>11</sup> found that there was a large mean decrease in MADRS at two hours after the first ketamine infusion ( $p < 0.001$ ), and this decrease was largely sustained for the duration of the infusion.

Relapse time was measured in four of the six studies.<sup>7,8,10,11</sup> In the Rot et al.<sup>7</sup> study the average relapse time was three weeks. Study results suggest that patients who respond to an initial IV ketamine infusion maintain efficacy if they receive repeated infusions for at least six days after the initial infusion.<sup>7</sup> The meta-analysis by Mcgirr et al.<sup>8</sup> found remission was statistically significant ( $p < 0.001$ ) for up to seven days. In the Vande Voort et al.<sup>10</sup> study improvement in depressive symptoms was seen with four weeks of continuous therapy. The average relapse time in the Murrough et al.<sup>11</sup> study was 18 days.

The meta-analysis by Murrough et al.<sup>9</sup> is the only study that compared ketamine with another drug (midazolam). The patients were assigned randomly in a 2:1 ratio and received either an IV infusion of ketamine 0.5 mg/kg or a midazolam IV infusion of 0.045 mg/kg infused over 40 minutes. Patients who received ketamine had a greater improvement in their symptoms at 24 hours compared to midazolam (MADRS score of 14.77 vs 22.72 respectively,  $p \leq 0.001$ ). The 24-hour response to infusions was also higher in the ketamine group (64%) vs midazolam (28%) ( $p \leq 0.006$ ). However, the duration of effects demonstrated small decreases in MADRS scores for every additional day post-infusion with the mean score being ketamine 16.93 and versed 23.19 ( $p \leq 0.02$ ). After seven days, differences were not statistically significant ( $p = 0.18$ ).

The pilot study by Vande Voort et al.<sup>10</sup> is the only one in which the duration of the ketamine infusion was 100 minutes. Those who remitted during the infusion received treatments that consisted of four weekly ketamine infusions, followed by four weeks of follow-ups. Of the 12 enrollees, 5 (41.7%) remitted and 7 (58.3%) responded to ketamine treatment after the infusion. All five subjects who remitted during the initial infusion experienced further depressive symptom improvement during the continuation treatments. MADRS scores were taken at baseline, 24 hours and weekly for four weeks. Scores were the lowest in all the literature. The findings of this study suggest that a continuation of once-weekly infusions can be used to extend the efficacy in treating depression symptoms in those patients who respond well to the initial infusion treatment.

**Frequency of Infusions.** There was variability in the frequency of infusions. Mcgirr et al.<sup>8</sup> and Murrough et al.<sup>9</sup> were the only studies which administered a single IV infusion. Mcgirr et al.<sup>8</sup> was the only study which also examined a single dose via intranasally (six IV and one intranasally). An additional IV bolus of ketamine 0.27 mg/kg and an additional 0.27 mg/kg infusion over 20 minutes was administered by Mcgirr et al.<sup>8</sup> Thrice per week infusions were administered in three studies.<sup>7,10,11</sup> Rot et al.<sup>7</sup> administered the infusions on days 1,3,5,8,10 and 12. Vande Voort et al.<sup>10</sup> received up to six infusions thrice-weekly during the acute-phase of the study. If the subjects remitted during the acute-phase, they received an additional infusion once a week for four weeks. Murrough et al.<sup>11</sup> administered six infusions three times per week over a 12-day period. Singh et al.<sup>6</sup> was the only study administering two different ketamine infusions. The infusions were given either two or three times a week.

The frequency of infusion does have an impact on MADRS scores, initial onset and duration of efficacy. Each study reported a rapid initial onset in decreasing MADRS scores within the first two hours post-infusion.<sup>6-11</sup> All studies found a statistically significant duration of efficacy within the first 24 hours post-infusion.<sup>6-11</sup> There was variation regarding the duration of efficacy with varied infusion frequencies. The single infusion studies by Mcgirr et al.<sup>8</sup> and Murrough et

al.<sup>9</sup> reported a statistically significant rapid antidepressant onset at 24 hours ( $p < 0.001$  and  $p < 0.006$ ). Both studies found that the duration of antidepressant response was still present at seven days post infusion, but MADRS scores were worsening each day post infusion. At seven days the MADRS were statistically insignificant  $p < 0.01$  and  $p \leq 0.02$ .<sup>8,9</sup> These findings indicate that an initial infusion may only be beneficial for less than seven days.

The infusion frequency of three times per week for two weeks was the same in the studies by Rot et al.<sup>7</sup> and Murrough et al.<sup>11</sup> Both reported a relapse at approximately 20 days. Singh et al.<sup>6</sup> was the only study with two different infusion frequencies (two versus three times per week). MADRS scores 15 days post-infusion were significantly reduced in both groups ( $p < 0.001$ ).<sup>6</sup> This suggests that there is no difference in onset of efficacy and duration between two and three times per week infusions. The serial infusion study by Vande Voort et al.<sup>10</sup> generated the longest duration of efficacy of all the studies. Findings indicate a single weekly infusion after the initial infusion can lead to a rapid onset in decreasing depression symptoms and can have a prolonged duration of efficacy.

**Side Effects.** The side effects of ketamine are due to the anticholinergic effects and the inhibition of NMDA glutamate receptors.<sup>5</sup> All the six studies reported adverse effects, with none being categorized as severe.<sup>6-11</sup> The most common side effects encountered in the literature were dissociative symptoms, nausea, dizziness, and transient changes in blood pressure and heart rate.<sup>6-11</sup>

All studies reported dissociative symptoms that lasted only a short duration of time (2-3hrs) post-infusion.<sup>6-11</sup> Dissociative symptoms began shortly after infusion (40 minutes) in both ketamine groups for the Singh et al. study, however the frequency and intensity of symptoms were reduced with repeated dosing.<sup>6</sup> Mcgirr et al. found the dissociative symptoms to be transient with the height of the symptoms occurring for 30-60 minutes post-infusion.<sup>8</sup> No study reported distressing psychotic symptoms or suicidal ideations.<sup>6-11</sup> Mcgirr et al.<sup>8</sup> was the only study that reported one episode of mania/hypomania during the induction phase. Interestingly the manic episode was caused by the placebo and not the ketamine infusion. The intranasal application in the Mcgirr et al. study did not have significant changes in hemodynamic parameters, and had minimal dissociative effects.<sup>8</sup> All studies found transient changes in blood pressure and heart rate.<sup>6-11</sup> In the Rot et al. and Mcgirr et al. studies,<sup>7-8</sup> two patients experienced brief hypertensive and tachycardic episodes, but they were resolved  $< 5$  minutes after the infusion. One patient developed bradycardia during the first infusion that resolved within one hour.<sup>7-8</sup>

Singh et al.<sup>6</sup> was the only study that compared adverse effects between two different ketamine infusion dosing regimens. Both ketamine groups presented with a significant number of adverse events when compared to the placebo groups. This also differed by frequency of infusion (2x/week ketamine= 83.3% vs placebo=56%, and 3x/week ketamine= 76.5% vs placebo= 50.0%). Serious treatment-emergent events were reported in two patients leading to hospitalization. However, the ketamine infusion was not thought to be the cause of the events. Discontinuation from the study due to adverse effects occurred in two patients (11.1%) in the twice-weekly ketamine group due to anxiety and paranoia/palpitations. All the adverse events dissipated within two hours from the beginning of the infusion. There are differences when comparing the frequency of infusions and adverse effects. The two studies that administered only

a single infusion had fewer side effects when compared to the other studies. These two studies had the largest sample size (n=183 and n=73), yet they only had two participants that experienced transient changes in blood pressure and/or heart rate.<sup>8,9</sup>

The study by Murrough et al.<sup>9</sup> was unique because it compared the adverse effects of ketamine and another medication (not a placebo). The adverse effects were similar in both the ketamine and midazolam groups, with the most common being: dizziness, nausea, vomiting, blurred vision, dry mouth, and restlessness. Mild transient changes in vital signs were noted during the infusion. Two participants had to terminate the infusion prematurely. One developed hypertension (187/91 mmHg), was given a beta blocker and was unresponsive to the therapy. The second patient had a severe hypotensive and bradycardic episode that was transient but did result in hospital observation overnight.

**Strengths and limitations.** This literature review has strengths and limitations. A major strength is that all the studies were consistent in using the same route and dose of 0.5 mg/kg.<sup>6-11</sup> The major limitation of this review is that all the studies reviewed were of short duration. The longest study took six weeks to complete.<sup>6-11</sup> Depression is a chronic condition that cannot be treated in such a short timeframe. Studies with a more extended timeframe are needed to fully identify whether the benefits of ketamine infusions can be continued.<sup>10</sup> Studies that examine longer duration of treatment can also direct whether infusion doses and frequency can be reduced or if they need to be increased.<sup>10</sup> The literature points to ketamine being a relatively safe drug with minimal adverse effects in the short-term.<sup>6-11</sup> More extensive research is needed to identify the full spectrum of adverse effects that ketamine exerts.<sup>11</sup>

Author	Design and Sample	Independent Variable	Results	Side Effects
Singh et al., 2016 <sup>6</sup>	RCT n=67	<u>Dose:</u> Ketamine 0.5 mg/kg  <u>Duration of Infusion:</u> 40 minutes  <u>Frequency:</u> 2x/week 3x/week	<u>Depression Scores:</u> MADRS day 1-15* 2x/week (p<0.001) • Ketamine: mean= -18.4 • Placebo: mean= -5.7  3x/week (p<0.001) • Ketamine: mean= -17.7 • Placebo: mean=-3.1	<u>Ketamine:</u> • Headache n=11 • Anxiety n=6 • Dissociation n=6 • Nausea n=7 • Dizziness n=6 <u>Placebo:</u> • Headache n=6 • Nausea n=3 • Dizziness n=1
Rot et al., 2010 <sup>7</sup>	Pilot Study n=10	<u>Dose:</u> Ketamine 0.5 mg/kg	<u>Depression Scores:</u> MADRS: 0-24h post infusion: (p=0.0001) • 0= 33.8 • 2h= 16.9	• Hypertension n=2 • Tachycardia n=2

		<u>Duration of Infusion:</u> 40 minutes  <u>Frequency:</u> 6 over 2 weeks	<ul style="list-style-type: none"> <li>• 4h= 11.4</li> <li>• 24h=6.9</li> </ul> Relapse Time: <ul style="list-style-type: none"> <li>• Average 3/weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Bradycardia n=1</li> <li>• Hypotension n=1</li> <li>• Bradypnea n=1</li> <li>• Decreased SPO2 n=1</li> </ul>
Mcgirr et al., 2014 <sup>8</sup>	Systematic review  n=183	<u>Dose:</u> Ketamine 0.5 mg/kg  <u>Duration of Infusion:</u> 40 minutes  <u>Frequency:</u> Once	<u>Clinical Remission/Response:</u> 24h: (p=<0.001)  3 days: <ul style="list-style-type: none"> <li>• P=&lt;0.01</li> <li>• P=&lt;0.0001</li> </ul> 7 days: <ul style="list-style-type: none"> <li>• P=&lt;0.01</li> <li>• P=&lt;0.0001</li> </ul>	<u>Ketamine:</u> <ul style="list-style-type: none"> <li>• Hypertension n=1</li> <li>• Bradycardia n=1</li> </ul> <u>Placebo:</u> <ul style="list-style-type: none"> <li>• Mania n=1</li> </ul>
Murrough et al., 2013 <sup>9</sup>	Systematic review  n=73	<u>Dose:</u> Ketamine 0.5 mg/kg Midazolam 0.045 mg/kg  <u>Duration of Infusion:</u> 40 minutes  <u>Frequency:</u> Once	<u>MADRS Mean:</u> (P= $\leq$ 0.001) Ketamine: 14.77 Midazolam: 22.72  24h response: (p=<0.006) <ul style="list-style-type: none"> <li>• Ketamine: 64%</li> <li>• Midazolam: 28%</li> </ul> 7 days: (p= $\leq$ 0.02) <ul style="list-style-type: none"> <li>• Ketamine: 16.93</li> <li>• Versed: 23.19</li> </ul>	<u>Ketamine:</u> <ul style="list-style-type: none"> <li>• Dizziness n=21</li> <li>• Headache n=15</li> <li>• Nausea n=16</li> <li>• Dry mouth n=12</li> <li>• Blurred vision n=20</li> <li>• Restlessness n=10</li> <li>• Dissociation n=8</li> <li>• Hypertension n=1</li> <li>• Hypotension n=1</li> <li>• Palpitations n=5</li> </ul> <u>Midazolam:</u> <ul style="list-style-type: none"> <li>• Malaise n=7</li> <li>• Dizziness n=2</li> <li>• Headache n=5</li> </ul>

				<ul style="list-style-type: none"> <li>• Restlessness n=5</li> <li>• Nausea n=3</li> <li>• Vomiting n=3</li> <li>• Dry mouth n=4</li> </ul>
Vande Voort et al., 2016 <sup>10</sup>	Single-arm, open-label  n=12	<u>Dose:</u> Ketamine 0.5 mg/kg  <u>Duration of Infusion:</u> 100 minutes  <u>Frequency:</u> 3x/week  1x/week-4/weeks	<u>Depression Scores:</u> MADRS: <ul style="list-style-type: none"> <li>• Baseline=29.4</li> <li>• 24h= 7.7</li> <li>• week 1= 3.2</li> <li>• week 2= 2.9</li> <li>• week 3= 3.6</li> <li>• week 4= 0.8</li> <li>• N=5 remitted</li> <li>• N=7 not remitted</li> </ul>	<ul style="list-style-type: none"> <li>• Dissociation n=8</li> <li>• Dizziness n=7</li> <li>• Numbness n=7</li> <li>• Sleepiness n=6</li> <li>• Emotionality n=3</li> <li>• Facial numbness n=3</li> <li>• Hypertension n=5</li> </ul>
Murrough et al., 2013 <sup>11</sup>	Systematic review  n=24	<u>Dose:</u> Ketamine 0.5 mg/kg  <u>Duration of Infusion:</u> 40 minutes  <u>Frequency:</u> 3x/week	<u>Depression Scores:</u> MADRS: (p<0.001) <ul style="list-style-type: none"> <li>• 2h= 18.9</li> <li>• 4h= 10.35</li> <li>• 24h= 8.35</li> </ul> Relapse time: 18 days	<ul style="list-style-type: none"> <li>• Dissociation n=14</li> <li>• Dizziness n=11</li> <li>• Blurred Vision =12</li> <li>• Dry mouth n=9</li> <li>• Hypertension n=8</li> <li>• Tachycardia n=8</li> </ul>

**Conclusions.** IV infusion of ketamine 0.5 mg/kg over 40-100 minutes is effective in reducing depression scores in the short-term. Serial infusions have been found to be beneficial in sustaining the efficacy and prolonging the duration of treatment. Twice and thrice per week infusions have been found to have the same efficacy and can lead to better tolerability by patients and potentially fewer side effects. Adverse effects are a common finding; however, most are transient or not significant enough to warrant a discontinuation of therapy. The key limitation in this review is the relatively short timeframe of the studies. Future studies examining the effects of efficacy and side effects over longer treatment durations are needed. More research is also needed to determine the optimal dose, frequency of infusions, route of delivery, safety and tolerability of repeated doses, and long-term adverse effects.

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