AANA Journal Course

Ketamine and Treatment-Resistant Depression

Jennifer K. Lent, DNAP, CRNA
Albert Arredondo, DNAP, CRNA
Marilyn A. Pugh, PhD
Paul N. Austin, PhD, CRNA

Major depressive disorder affects tens of millions of people each year. One-third of those affected have depression that is resistant to conventional pharmacologic, psychologic, or somatic treatments. Patients with treatment-resistant depression have few remedies other than electroconvulsive therapy or transcranial magnetic stimulation. Recent research has highlighted the promising antidepressant effects of subanesthetic ketamine infusions. This journal course examines the efficacy of ketamine for treatment-resistant depression. Evidence from 10 systematic reviews and randomized controlled trials suggest that most of the researchers concluded ketamine significantly decreased depression severity ratings at short-term assessment intervals, whereas evidence examining the long-term effects is lacking. Ketamine infusion therapy was generally well tolerated, with minimal untoward effects. Large, randomized controlled trials are needed to discern the longer-term efficacy, tolerance, and dependence profiles of ketamine infusions. Optimal dosing schedules to best prolong the antidepressant effects of ketamine have yet to be determined.

Keywords: Ketamine, MADRS, major depressive disorder, refractory depression, treatment-resistant depression.

Objective

Upon completion of this course, the reader will be able to:

1. Discuss the role of ketamine in alleviating treatment-resistant depression.

Introduction

Major depressive disorder (MDD) affects approximately 13 to 16 million people in the United States annually.[1,2] Individuals with MDD experience persistent feelings of sadness, loss, anger, and disinterest.[3] These feelings affect physical health as well as affecting thinking and behavior.[3] Depressive disorders have a wide range of classifications, categories, and attributes.[3] The primary problem is that 5 to 6 million patients with MDD are resistant to conventional pharmacologic, psychologic, or somatic treatments.[4] This clinical condition is called treatment-resistant depression (TRD).[1]

Individuals with TRD are at increased risk of alcoholism, drug abuse, hospitalizations, and suicide.[2,3] Two alternative treatments reserved for patients with TRD are electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS).[4] Although either remedy may prove effective, relief from depression or suicidal ideation may not occur for 2 to 6 weeks.[1,2,4] Few treatment options remain for patients with TRD who have failed to respond to ECT or TMS.[1,2,4] New therapies for MDD/TRD must bridge the therapeutic gap that exists between current pharmacotherapy regimens. Subanesthetic ketamine infusions may be a safe and effective therapy for TRD.[2,5]

Epidemiology and Treatment of Treatment-Resistant Depression

The risk of MDD occurring during a lifetime is approximately 15%.[6] The prevalence rates for males are half the rates for females.[6] Major depressive disorder is most often diagnosed in women between the ages of 25 and 44 years.[3] Those with severe MDD suffer restlessness, agitation, flattened affect, and body weight fluctuations.[3] Up to two-thirds of individuals with depression do not recognize the symptoms of depressive disorder in themselves and seldom seek professional consultation.[3] Conventional therapies for MDD include pharmacotherapy, psychotherapy, and other somatic remedies.[1-3]

Current antidepressant pharmacotherapy regimens include monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors,

The *AANA Journal* Course is published in each issue of the *AANA Journal*. Each article includes objectives for the reader and sources for additional reading. A 5-question open-book exam for each course is published on www.AANALearn.com and will remain live on the site for a period of 3 years. One continuing education (CE) credit can be earned by successfully completing the examination and evaluation. Each exam is priced at $35 for members and $21 for students **but can be taken at no cost by using one of the six free CEs available annually to AANA members as a benefit of membership.** For details, go to www.AANALearn.com. This educational activity is being presented with the understanding that any conflict of interest has been reported by the author(s).

Class of antidepressant	Drug generic (trade) name	Common side effects
Tricyclic antidepressants, also known as selective norepinephrine reuptake inhibitors	Amitriptyline (Elavil), amoxapine (Asendin), clomipramine (Anafranil), desipramine (Norpramin), doxepin (Adapin), imipramine (Tofranil), maprotiline (Ludiomil), nortriptyline (Pamelor)	Negligible to moderate-severe agitation, mild to moderate-severe seizures, minimal to moderate-severe sedation, mild to moderate-severe hypotension, minimal to moderate-severe anticholinergic effects, minimal to mild GI effects, mild to moderate weight gain, moderate to moderate-severe sexual effects, moderate to moderate-severe cardiac effects
Monoamine oxidase inhibitors	Tranylcypromine (Parnate), phenelzine (Nardil), isocarboxazid (Marplan), selegiline (Eldepryl, Emsam)	Negligible to moderate agitation, negligible seizures, negligible to mild sedation, negligible to mild hypotension, negligible anticholinergic effects, negligible to minimal GI effects, negligible to mild weight gain, mild to moderate-severe sexual effects, negligible cardiac effects
Selective serotonin reuptake inhibitors	Citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft)	Negligible to mild agitation, negligible to minimal seizures, minimal sedation, negligible hypotension, negligible to minimal anticholinergic effects, moderate severe GI effects, negligible to minimal weight gain, moderate-severe sexual effects, negligible to minimal cardiac effects
Serotonin-norepinephrine reuptake inhibitors	Duloxetine (Cymbalta), venlafaxine (Effexor)	Minimal to mild agitation, negligible seizures, negligible to minimal sedation, negligible to minimal hypotension, negligible anticholinergic effects, minimal to moderate-severe GI effects, negligible to minimal weight gain, minimal to moderate-severe sexual effects, minimal cardiac effects
Atypical antidepressants	Bupropion (Wellbutrin), mirtazapine (Remeron), atomoxetine (Strattera)	Negligible to moderate-severe agitation, negligible to severe seizures, negligible to severe sedation, negligible to minimal hypotension, negligible anticholinergic effects, minimal to moderate GI effects, negligible to minimal weight gain, negligible sexual effects, negligible cardiac effects

Table 1. Antidepressant Side Effects[6]
Abbreviation: GI, gastrointestinal.

serotonin-norepinephrine reuptake inhibitors, and selective norepinephrine reuptake inhibitors.[6] Medication regimens are often prescribed concurrently with counseling or psychotherapy.[3] Multimodal therapy relieves the symptoms of depression for many patients.[3] Researchers estimate that 70% to 80% of individuals can attain a substantial decline in symptoms when they are compliant with appropriate treatment.[3] Unfortunately, patients may be noncompliant with pharmacotherapy regimens because of side effects such as dry mouth, insomnia, dizziness, weight gain, cardiac dysrhythmias, hypertension, decreased libido, and suicidal ideation (Table 1).[1,2] Additionally, achievement of therapeutic blood levels for conventional antidepressants may take 3 to 8 weeks.[1,2,6]

The causative and clinical correlational factors of TRD include neurotransmitter dysfunction, history of trauma, neurotransmitter polymorphisms, and social interaction disorders.[3] Current pharmacologic treatments of MDD enhance transmission in the serotonergic or noradrenergic neurotransmitter systems.[6] Patients may be noncompliant with their pharmacologic regimens because of the aforementioned adverse side effects.[1,2] Up to 30% of patients with MDD do not respond adequately to standard therapy regimens.[6] Consequently, researchers seek a greater understanding of the etiology of MDD and novel treatment strategies.[6] Neuromodulative therapeutic techniques, such as ECT and TMS, are an option for patients with TRD.[1]

Electroconvulsive therapy is considered by some to be very effective in treating TRD.[1,4,5] Induced seizures and generalized cortical postictal electroencephalographic suppression are thought to be responsible for the beneficial antidepressant effects, which appear within 7 days of treatment.[1,5] Electroconvulsive therapy relieves symptoms of depression for 60% of patients with TRD.[1,5] However, this remedy is associated with persistent, negative cognitive side effects such as memory loss as well as with severe social stigma.[1,5] Another consideration is that patients receiving ECT must undergo general anesthesia.[1]

Those patients unwilling or unable to undergo a general anesthetic may benefit from noninvasive TMS, which does not require anesthesia.[1] Electrical currents generated by a magnetic coil placed on the scalp modulate neural activity by producing changes in cortical excitability.[1,4] Transient headaches, discomfort, insomnia, and unpleasant phantosmia are the most commonly reported side effects of TMS therapy.[1] Because of the limited study of TMS therapy in TRD, information about its long-term efficacy is lacking.[1] Further limiting the use of TMS is the small number of facilities equipped to provide this therapy.[1,4] Therefore, additional treatment options for TRD, such as ketamine infusion therapy, should be investigated for the benefit of patients who are unwilling or unable to undergo or are unresponsive to the neuromodulatory techniques of ECT and TMS.[2]

Figure 1. Potential Mechanism of Action of Ketamine in Treating Treatment-Resistant Depression[2,3]
Abbreviations: BDNF, brain-derived neutrotrophic factor; GABA, γ-aminobutyric acid; NMDA, *N*-methyl-D-aspartate.

Possible Mechanism of Action of Ketamine in Treating Treatment-Resistant Depression

In 2017, Ionescu and Papakostas[2] hypothesized that ketamine manipulates the glutamatergic system and the release of brain-derived neurotrophic factor. Improved mood as a result of elevated levels of brain-derived neurotrophic factor may provide some relief from depressive symptoms (Figure 1).[7] In contrast to TMS therapy, ketamine is widely available, and its use does not require providers trained and equipped to use specialized devices such as with ECT and TMS.[5]

Evidence Examining Ketamine in Treating Treatment-Resistant Depression

Providers should be familiar with the evidence examining the use of ketamine in the treatment of TRD. A systematic search and appraisal of the quality of evidence pertaining to a problem helps decrease bias.[8,9] The following is based on a systematic search of randomized controlled trials and systematic reviews (2007-2017) examining the use of ketamine in humans as a therapy for TRD. The search initially revealed 11 evidence sources meeting the inclusion criteria.[10-20] Closer examination revealed that one of those sources[16] included all of the studies reviewed by Wan et al,[14] and it is therefore excluded from Table 2. See Figure 2 and Table 2 for a description of the search and a summary of the evidence, respectively. All but 2[14,17] of the sources were systematic reviews.

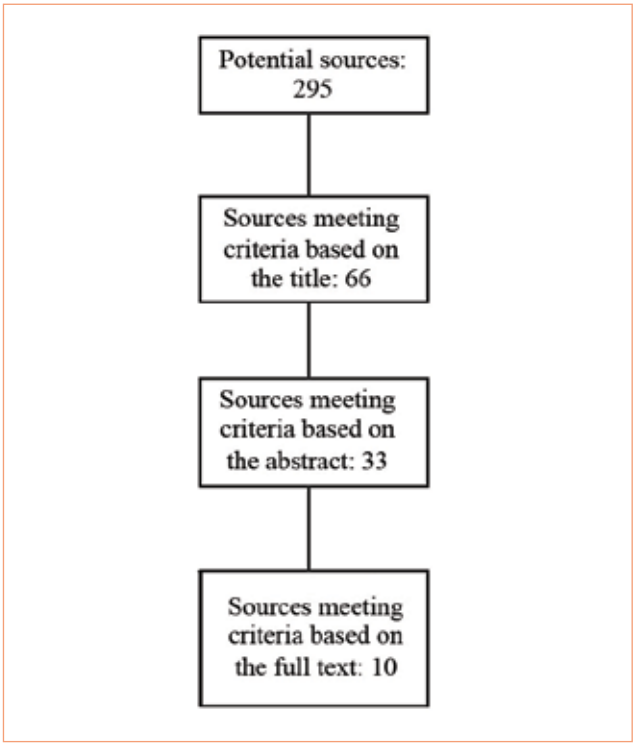

Figure 2. Flow Diagram of Literature Search Examining Studies to Appraise Efficacy of Ketamine on Major Depressive Disorder/Treatment-Resistant Depression

All sources compared the efficacy of ketamine therapy for the treatment of depressive symptoms in MDD/TRD.[10-20] The studies included adults with current diagnoses of TRD and MDD (including bipolar and unipolar). Exclusion criteria included serious comorbidities, postpartum depression, substance abuse/dependence, psychosis/psychotic disorders, recreational use of ketamine or phencyclidine, or serious suicidal/homicidal ideation.[10-20] Trials involving ketamine administration in the context of surgery or ECT were specifically excluded by Lee et al[12] and Xu et al.[18] Caddy et al[10] specifically included ECT data. There were no significant age or gender differences between the control and intervention groups within studies. For all sources, adequate blinding was difficult because of the temporary dissociative and psychotomimetic effects of ketamine, which appear shortly after administration.[10-20]

Investigators used a variety of administration protocols. The most common was a single infusion of ketamine, 0.5 mg/kg, administered over 40 minutes. Nine groups of investigators[10-16,19,20] used this protocol. Six sources[10,12,13,15,18,19] included results from ketamine infusions at lower dosages and different infusion rates (0.1-0.4 mg/kg over 40 minutes or a 0.27 mg/kg infusion over 10 minutes followed by 0.27 mg/kg over 20 minutes). Multiple-infusion protocols were used by 9

Source	Type/ level of evidence[a]	No. of participants and characteristics	Ketamine dose and series	Control comparison or placebo	Findings 24 hours after intervention	Comments
Caddy et al,[10] 2015	Level I: SR with meta-analysis of 9 RCTs	277 Major depressive disorder and bipolar disorder	Single infusion, 0.5 mg/kg over 40 min Single infusion, 0.4 mg/kg over 40 min Series[b] of infusions, 0.5 mg/kg over 40 min	Saline	Ketamine more efficacious than placebo at 24 h: OR, 10.77 (95% CI, 2.00-58.00[c]); NNTB = 3; ketamine MADRS[d] and HAM-D[e] scores greater than placebo at 24 h: SMD −1.42; 95% CI, −2.26 to −0.57[f]	• Cochrane review: search strategy and appraisal methods described • Quality of evidence was limited by risk of bias and small sample size • Intention-to-treat analysis • Adequate blinding difficult because of dissociative-psychotomimetic side effects of ketamine • Confusion and emotional blunting most common troubling side effects • Further studies with adequate blinding and longer follow-up needed; longest follow-up at 2 wk
Coyle & Laws,[11] 2015	Level I: SR with meta-analysis of RCTs (21 studies)	437 Major depressive disorder and bipolar disorder	Single infusion, 0.5 mg/kg over 40 min Series[g] of infusions, 0.5 mg/kg over 40 min	Saline	Effect size at 24 h for single and repeated ketamine infusions Single: Hedges g = −1.11; 95% CI, −1.38 to −0.83[h] Repeated: Hedges g = −4.16; 95% CI, −5.67 to −2.64[h]	• Search strategy, appraisal methods described • Risk of bias examined and described as low to high • Intention-to-treat analysis • Suggested future studies: sensitization-escalated response, addictive potential, ketamine for emergency treatment and longer-term treatment for depression
Lee et al,[12] 2015	Level I: SR with meta-analysis of 5 RCTs	125 Major depressive disorder, unipolar and bipolar disorder	Single infusion, 0.5 mg/kg over 40 min Loading dose of 0.27 mg/kg infused over 10 min, then 0.27 mg/kg infused over 20 min	Midazolam or saline	Significant reduction of depressive symptoms in ketamine groups at day 1 Overall SMD of effect size 1.01; 95% CI, 0.69 to 1.34[h]	• Search strategy, appraisal methods described • Bias assessed using Cochrane methods • Minimal adverse events were reported • Psychotomimetic or dissociative symptoms and transient increases in blood pressure and/or heart rate reported were resolved completely by 60 min after infusion
McGirr et al,[13] 2015	Level I: SR with meta-analysis of 7 RCTs	183 Major depressive disorder, unipolar and bipolar disorder	Single infusion, 0.5 mg/kg over 40 min 0.54 mg/kg-0.27 mg/kg bolus and 0.27 mg/kg 20 min infusion Intranasal, 50 mg	Midazolam or saline	Overall, SMD of depression scores = 0.90; 95% CI, 0.66 to 1.13[h] observed, favoring ketamine	• Search strategy, appraisal methods and risk of bias assessment described • Intention-to-treat analysis • Recommended additional research and clarification include specificity of effect to NMDA antagonism, minimal effective dose, potential benefit of repeated ketamine infusions, optimizing nonparenteral administration, long-term safety, identification of other NMDA agents with fewer adverse effects, and reduced potential for abuse

Wan et al,[14] 2015	Level I: SR with meta-analysis of 3 RCTs	84 Major depressive disorder	Single infusion, 0.5 mg/kg over 40 min	Midazolam and riluzole[i]	At day 1, mean MADRS[d] decrease (SD) of 19 (11.7) points compared with baseline in 67% of study subjects. Mean age of ketamine responders significantly higher,[j] other demographic and clinical predictors not significant[k]	• Search strategy is described • Appraisal methods not described • Potential bias in shared items of the 2 different adverse events reporting instruments • Several different trial designs included in this study limit the confidence of summary statistics • Long-term follow-up was absent of dissociative or psychotomimetic effects
Kishimoto et al,[15] 2016	Level I: SR with meta-analysis of 9 RCTs	234 TRD and major depressive disorder	Single infusion, 0.5 mg/kg over 40 min 0.27 mg/kg infused over 10 min, followed by same dose over 20 min	Midazolam or saline	Superior antidepressant efficacy for ketamine compared with placebo/pseudoplacebo. Day 1: Hedges g = −1.00; 95% CI, −1.28 to −0.73[h]; heterogeneity I^2 = 0, Q = 2.14[k]	• Search strategy, appraisal methods, and risk of bias assessment described • No significant difference in reporting of adverse side effects between ketamine and placebo/pseudoplacebo groups: tiredness/fatigue, woozy/loopy, dizziness/faintness • Nausea and vivid dreams were reported
Singh et al,[17] 2016	Level II: evidence from single RCT	68 TRD and major depressive disorder	Series[l] of infusions, 0.5 mg/kg over 40 min	Saline	Primary endpoint was change from baseline to day 15. Mean change in MADRS[d] score from baseline to day 15 was significantly improved in both ketamine frequency groups compared with respective placebo groups: twice weekly ketamine: −18.4,[h] SD = 12.0; placebo: −5.7, SD = 10.2; thrice-weekly ketamine: −17.7,[h] SD = 7.3; placebo: −3.1, SD = 5.7	• Methods and study design described • Intention-to-treat analysis • An improvement in suicidal ideation (measured by Columbia–Suicide Severity Rating Scale) was observed in all 4 treatment groups • TRD improvement was similar in both groups • Because less frequent treatment administration usually is preferred to reduce patient's and clinic's burden and costs, this suggests that twice per week treatment regimen administered for 4 to 6 wk can induce and maintain (through day 15) a robust antidepressant effect in TRD population
Xu et al,[18] 2016	Level I: SR with meta-analysis of 9 RCTs	201 Major depressive disorder, unipolar and bipolar disorder	Single infusion, 0.5 mg/kg over 40 min Single very low dose, 0.1-0.5 mg/kg IV/IM/SC over 40 min Intranasal, 50 mg	Midazolam or saline	Change in depression severity rating on MADRS[d] of ketamine over placebo at day 1: SMD −1.4; 95% CI, −2.0 to −0.9 Large treatment effect compared with placebo at day 1: response rate = 2.6; 95% CI, 1.6 to 4.4,[c] NNTB = 2.9	• Search strategy and appraisal methods described • Bias assessed using Cochrane methods • Doses at 0.5 mg/kg infused over 40 min were generally well tolerated, with transient, mild to moderate dissociative symptoms and transient increases in blood pressure and/or heart rate with most resolving within 2 h or less after completion of infusion • One reported episode of transient manic symptoms potentially attributable to ketamine

continues on page 416

continued from page 415

Kraus et al,[19] 2017	Level II: evidence from 12 RCTs	226 Major depressive disorder, unipolar and bipolar disorder	Single/series[m] infusion, 0.5 mg/kg over 40 min 0.27 mg/kg infused over 10 min, followed by same dose over 20 min 0.2 mg/kg over 40 min vs 0.4 mg/kg over 40 min Intranasal, 50 mg	Midazolam or saline	Ketamine consistently superior to placebo with average response rates of 59% (37%-88%) after 24 h. This equaled an average reduction of 10.91 points on HAM-D[e] and 20.8 points on MADRS[d]	• Search strategy discussed • No description of appraisal methods or bias assessment • Ketamine is a highly effective and rapid-acting antidepressant • Large, transient effect sizes seen at 24 h after treatment, lasting 7-14 d • Future research needed to determine how to prolong antidepressant effects
Papadimitropoulou et al,[20] 2017	Level I: SR with meta-analysis of 31 RCTs	5,515 TRD and major depressive disorder unipolar and bipolar disorder	Single/series[n] infusion, 0.5 mg/kg over 40 min	Placebo and sham,[o] active comparator	Ketamine resulted in a 9-fold higher response rate vs placebo: OR, 9.10; 95% CI, 4.28 to 19.34	• Search strategy and appraisal methods described • Bias assessed using Cochrane methods • Ketamine treatment demonstrated rapid antidepressant effects and was ranked first among all 12 pharmacologic and 2 somatic interventions

Table 2. Systematic Reviews and Randomized Controlled Trials Examining Efficacy of Ketamine Infusions on Major Depressive Disorder/Treatment-Resistant Depression

Abbreviations: HAM-D, Hamilton Depression Rating Scale; IM, intramuscular; IV, intravenous; MADRS, Montgomery-Åsberg Depression Rating Scale; NMDA, *N*-Methyl-D-aspartate; NNT, number needed to treat; NNTB, number needed to treat to benefit; OR, odds ratio; PTSD, posttraumatic stress disorder; RCT, randomized controlled trial; SC, subcutaneous; SMD, standardized mean difference; SR, systematic review; TRD, treatment-resistant depression.

[a]Levels of evidence appraised using the method described by Melnyk and Fineout-Overholt.[13] Level I evidence is from systematic reviews with or without a meta-analysis of all relevant RCTs, and level II evidence is from well-designed RCTs.

[b]Infusions 3 times a week.

[c]$P < .0001$.

[d]An MADRS score equal to or greater than 35 indicates severe depression.[8,9] Each item is scored on a scale of 0 to 6, with higher scores significant for the presence of symptoms.

[e]The variables of the HAM-D are scored on 3-point and 5-point scales by 2 trained raters during the same interview. Combined scores greater than 19 indicate severe depression.[10]

[f]$P = .001$.

[g]Infusions twice weekly for up to 2 wk.

[h]$P < .001$.

[i]Riluzole is a glutamate inhibitor.

[j]$P < .05$.

[k]$P > .05$.

[l]Infusions 2-3 times a week.

Ketamine dose, mg/kg	Duration of infusion, min
0.5[10-16,19,20]	40
0.1-0.4[18,19]	40
0.27, followed by 0.27[12,13,15,19]	10 (for initial infusion); 20 for subsequent infusion

Table 3. Common Administration Protocols Described in Evidence Sources Examining Use of Ketamine for Treatment-Resistant Depression

sources.[10-13,16-20] Additionally, 4 sources[13,16,18,19] administered 50 mg of ketamine via intranasal atomization. Xu et al[18] placed no restrictions on the method of ketamine administration included in the study. Coyle and Laws[11] and Papadimitropoulou et al[20] did not explain the ketamine infusion regimens included in the studies. The most common comparator was saline placebo.[10-13,15-19] Active placebo or pseudoplacebo was used in 5 sources.[12-15,20]

Four sources discussed a washout period of 1 to 4 weeks for all psychotropic medications before beginning experimental treatment.[13-15,18] Four sources[12,13,17,18] did not place restrictions on the continuation of current psychotropic medications during the trials. Kishimoto et al[15] stated that patients' current antidepressant and antipsychotic medications continued for the duration of the trial.

It was unclear whether the participants were treated as hospital outpatients or in outpatient centers in the majority of sources.[10-14,16,18-20] Singh et al[17] specified that participants were treated as outpatients for the duration of the trial. Kishimoto et al[15] cited trials treating participants as both outpatients and inpatients.

Sources measured the primary outcome as a 50% or greater decrease in the severity of depressive symptoms as measured by scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) or the Hamilton Depression Scale (HAM-D).[10-20] These instruments measure clinically significant affective, cognitive, somatic, and behavioral symptoms of depression and response to treatment over time.[21-23] The 10-item MADRS assesses perceived sadness, sleep abnormalities, appetite fluctuations, concentration difficulties, pessimistic thoughts, and suicidal ideation.[21-23] Items on the HAM-D scale include depressed mood, suicidal ideation, somatic complaints, gastrointestinal symptoms, and loss of interest.[23] The investigators obtained baseline depression severity ratings from all participants before the intervention and again at specific timepoints after the intervention.[10-23] Assessment scores at 24 hours after the intervention were the main outcome parameter.[10-16,18,19] Papadimitropoulou et al[20] and Singh et al[17] recorded postintervention depression severity rating scores at 14 days and 15 days, respectively, rather than 24 hours.

Dose, Improvement, Untoward Effects

Overall, the authors of the sources reviewed concluded that ketamine was efficacious in treating TRD.[10-20]

- ***Dose.*** Most of the researchers observed that a single dose of intravenous ketamine, 0.5 mg/kg infused over 40 minutes, significantly decreased depression severity rating scores at 24 hours compared with baseline assessments.[10-20] Most sources reported rapid and robust antidepressant effects first apparent within 40 minutes[15] to 4 hours[18] of a single ketamine infusion. Table 3 summarizes common dosing regimens.
- ***Short-term Improvement.*** Authors[10-16,18,19] reported significant decreases in depression severity scores at 24 hours after infusion. Compared with saline placebo and active placebo effects, Kraus et al[19] reported an average reduction of 10.9 points on the HAM-D and 20.8 points on the MADRS when measured 24 hours after ketamine infusion and compared with baseline scores. Wan et al[14] discussed similar results, finding the mean reduction (SD) in MADRS scores at 24 hours after ketamine infusion to be 19 (11.7) points. McGirr et al[13] concurred, reporting a standardized mean difference (SMD) of 0.90 (95% CI, 0.66 to 1.13; $P \leq .001$) in favor of ketamine for a reduction in depression severity scores at 24 hours. Caddy et al[10] reported a statistically significant reduction in scores at 24 hours favoring ketamine over placebo (SMD, –1.42, 95% CI –2.26 to 0.57; $P = .001$) and over the active placebo midazolam (SMD, 7.95, 95% CI, –12.67 to –3.23; $P = .001$). Lee et al[12] and Xu et al[18] reported similar findings. Compared with placebo, ketamine significantly decreased depression severity scores at 24 hours (SMD, 1.01, 95% CI, 0.69 to 1.34; $P < .001$[12] and SMD, –1.4, 95% CI, –2.0 to –0.9).[18] Kishimoto et al[15] also found in favor of ketamine over placebo or pseudoplacebo in reducing depressive symptoms and severity at 24 hours (Hedges g = –1.00, 95% CI, –1.28 to –0.73; $P < .001$).
- ***Long-term Improvement.*** Only 2 sources[17,20] examined the long-term efficacy of ketamine to reduce depression severity scores from baseline to days 14 and 15 after treatment. Papadimitropoulou et al[20] found that ketamine significantly reduced depression severity scores at day 14 (SMD, –14.0, 95% CI, –19.9 to –8.0; no *P* value reported) compared with placebo.

Singh et al[17] compared a twice-weekly and thrice-weekly 0.5 mg/kg ketamine infusion schedule vs placebo for reduction in depression scores from baseline to day 15. At day 15, depression scale scores for the twice-weekly dosing group declined by a mean (SD) of –18.4

points (12.0; $P < .001$) compared with placebo's mean reduction of –5.7 points (10.2; $P < .001$). At day 15, depression scale scores for the thrice-weekly dosing group declined by a mean (SD) of –17.7 points (7.3; $P < .001$) compared with placebo's mean reduction of –3.1 points (5.7; $P < .001$).[17]

• ***Untoward Effects.*** Mild side effects such as headache, dizziness, nausea, transient increases in heart rate and/or blood pressure, transient dissociative effects, and transient psychotomimetic effects were reported by 10 groups of researchers.[10-19] Wan et al[14] described a discretional study protocol using the short-acting ß-blocker labetalol to treat transient increases in blood pressure (up to 180/100 mm Hg) or heart rate (up to 110/min). If the hemodynamic variations were treated, yet still outside of the study parameters after 3 consecutive measurements, the ketamine infusion was discontinued.[14] Ten sources[10-19] reported the occurrence of mild psychotomimetic and dissociative effects, which resolved between 60 and 240 minutes after administration. In some instances, serial infusions were reported to attenuate this response.[12,14,16,18] No participant displayed severe psychotic symptoms, and few serious adverse events occurred.[10-20] The sources concluded that the adverse events were unrelated to ketamine administration.[11,17-18] One participant experienced extreme anxiety related to stressful life events and withdrew from the study.[17] One participant experienced affective switch.[11] Two participants attempted suicide.[17-18] One suicide attempt occurred during the washout period before the study.[18] The second suicide attempt occurred on day 40 of the study, 28 days after the participant's last ketamine infusion.[17] One group did not report the occurrence of any side effects.[20] No deaths related to ketamine infusions were reported.[10-20]

The reported range of time to resolution of side effects and acute behavioral changes was between 1 and 4 hours after completion of the ketamine infusion.[12,14,18,19] Attrition rates throughout the sources shared similar causes, such as marked positive responses to ketamine,[13,15] lack of efficacy (from the placebo group),[17] anxiety/palpitations,[14,17] and extreme vasovagal response to venipuncture requiring inpatient observation.[14,19] Some sources did not report all-cause attrition data.[11,12,18,20]

Limitations of the Evidence Examining Ketamine in Treating Treatment-Resistant Depression

The major limitations described by most sources were short study durations and small numbers of participants.[10-14,17-18] Adequate descriptions of blinding, sequence generation, and allocation concealment were lacking in the work of Lee at al[12] and McGirr et al.[13] There was a risk of functional unblinding in any study that did not incorporate an active control because psychotomimetic and dissociative side effects caused by ketamine administration would be noticed by study participants and observers.[10,11,13,15,17] However, this was deemed inevitable and labeled as low risk.[10,15] As discussed by Xu et al,[18] any study using a crossover design is at risk of carryover effects mistakenly attributed to the incorrect intervention.

Examination of funnel plots revealed marginal evidence of publication bias in the studies by McGirr et al[13] and Kishimoto et al.[15] A high risk of reporting bias due to incomplete data recording and protocol omission was reported by Caddy et al.[10] A risk of reporting bias also was noted by Wan et al.[14] They collected data on adverse events using 2 instruments. The possibility of reporting bias exists because of the potential for shared reported results.[14] Papadimitropoulou et al[20] lacked any mention of potential bias from any source. Pooled outcomes data from different study designs may decrease the confidence of pooled statistical analyses, as discussed by Wan et al.[14]

Conclusion

An estimated 5 to 6 million patients have depression that is resistant to conventional pharmacologic, psychologic, or somatic treatments.[1] Most current therapies for TRD have a therapeutic action lag time of 2 to 6 weeks.[1,2,4] Subanesthetic ketamine infusions provide rapid onset of antidepressant effect and may be a safe, well-tolerated, and effective treatment of TRD.[2,5,10-20] Discontinuation of current antidepressant therapy is not necessary when one is considering ketamine infusions.[16,19]

A single intravenous infusion of ketamine, 0.5 mg/kg in 100 mL of sodium chloride, administered over 40 minutes has a rapid and robust antidepressant effect,[11-13,15,18,19] often apparent within 40 minutes[15] to 4 hours.[18] Unfortunately, the antidepressant effect of a single infusion of ketamine seems to rarely persist longer than 2 weeks.[20] Ketamine's short-term safety profile is well established, and ketamine is well tolerated.[10-20] Providers must make it clear to patients that this therapy does not provide long-term alleviation of symptoms and that repeated infusions are likely necessary.[24] It is particularly important to make this clear because, anecdotally, insurers rarely if ever cover the use of ketamine in treating TRD.

Further research is needed to identify optimal dosing schedules that would best prolong the antidepressant effects of ketamine when it is administered in outpatient settings.[10,13,15-19] Research studies examining longer-term use and repeated dosing are lacking.[10,11,13,14,16,18,20] Long-term cost, safety, tolerance, and dependence profiles must be determined through large, parallel-group randomized controlled trials.[10,11,13-19] Additionally, further research is needed to establish safety and use profiles in pediatric or geriatric populations within appropriate clinical constructs.[12,15] Providers are also urged to carefully read the consensus statement from the American

Psychiatric Association on the use of ketamine for treating mood disorders.[24]

REFERENCES

1. Bewernick B, Schlaepfer TE. Update on neuromodulation for treatment-resistant depression. *F1000Res*. 2015;4:Rev1389. doi:10.12688/f1000research.6633.1
2. Ionescu DF, Papakostas GI. Experimental medication treatment approaches for depression. *Transl Psychiatry*. 2017;7(3):e1068. doi:10.1038/tp.2017.33
3. Halverson J, Ravinder NB, Moraille-Bhalla P, Andrew LB, Leonard RC. Depression. Medscape website. http://emedicine.medscape.com/article/286759-overview?src=soc_tw_share#a2. Updated March 28, 2019. Accessed October 1, 2017.
4. Magnezi R, Aminov E, Shmuel D, Dreifuss M, Dannon P. Comparison between neurostimulation techniques repetitive transcranial magnetic stimulation vs electroconvulsive therapy for the treatment of resistant depression: patient preference and cost-effectiveness. *Patient Prefer Adherence*. 2016;8(10):1481-1487. doi:10.2147/PPA.S105654
5. Ionescu DF, Papakostas GI. Current trends in identifying rapidly acting treatments for depression. *Curr Behav Neurosci Rep*. 2016;3(2):185-191. doi: 10.1007/s40473-016-0075-4
6. O'Donnell JM, Shelton RC. Drug therapy of depression and anxiety disorders. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. 12th ed. New York, NY: McGraw-Hill; 2011:397-415.
7. Duncan WC, Zarate CA Jr. Ketamine, sleep, and depression: current status and new questions. *Curr Psychiatry Rep*. 2013;15(9):1-12. doi:10.1007/s11920-013-0394-z
8. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. *ACP J Club*. 1995;123(3):A12-A13.
9. Melnyk BM, Fineout-Overholt E. *Evidence-Based Practice in Nursing and Healthcare: A Guide to Best Practice*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health; 2015.
10. Caddy C, Amit BH, McCloud TL, et al. Ketamine and other glutamate receptor modulators for depression in adults. *Cochrane Database Syst Rev*. 2015(9):CD011612. doi:10.1002/14651858.CD011612.pub2
11. Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. *Hum Psychopharmacol*. 2015;30(3):152-163. doi:10.1002/hup.2475
12. Lee EE, Della Selva MP, Lui A, Himelhoch S. Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative analysis. *Gen Hosp Psychiatry*. 2015;37(2):178-184. doi:10.1016/j.genhosppsych.2015.01.003
13. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive disorder. *Psychol Med*. 2015;45(4):693-704. doi:10.1017/S0033291714001603
14. Wan L-B, Levitch CF, Perez AM, et al. Ketamine safety and tolerability in clinical trials for treatment-resistant depression. *J Clin Psychiatry*. 2015;76(3):247-252. doi:10.4088/JCP.13m08852
15. Kishimoto T, Chawla JM, Hagi K, et al. Single-dose infusion ketamine and non-ketamine *N*-methyl-D-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety, and time trajectories. *Psychol Med*. 2016;46(7):1459-1472. doi:10.1017/S0033291716000064
16. Schwartz J, Murrough JW, Iosifescu DV. Ketamine for treatment-resistant depression: recent developments and clinical applications. *Evid Based Ment Health*. 2016;19(2):35-38. doi:10.1136/eb-2016-102355
17. Singh JB, Fedgchin M, Daly EJ, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *Am J Psychiatry*. 2016;173(8):816-826. doi:10.1176/appi.ajp.2016.16010037
18. Xu Y, Hackett M, Carter G, Loo C, Gálvez V, Glozier N, et al. Effects of low-dose and very low-dose ketamine among patients with major depression: a systematic review and meta-analysis. *Int J Neuropsychopharmacol*. 2016;19(4):pyv12. doi:10.1093/ijnp/pyv124
19. Kraus C, Rabl U, Vanicek T, et al. Administration of ketamine for unipolar and bipolar depression. *Int J Psychiatry Clin Pract*. 2017;21(1):2-12. doi:10.1080/13651501.2016.1254802
20. Papadimitropoulou K, Vossen C, Karabis A, Donatti C, Kubitz N. Comparative efficacy and tolerability of pharmacological and somatic interventions in adult patients with treatment-resistant depression: a systematic review and network meta-analysis. *Curr Med Res Opin*. 2017;33(4):701-711. doi:10.1080/03007995.2016.1277201
21. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382-389. doi:10.1192/bjp.134.4.382
22. Wikberg C, Petersson A, Westman J, Björklund C, Petersson EL. Patients' perspectives on the use of the Montgomery-Asberg depression rating scale self-assessment version in primary care. *Scand J Prim Health Care*. 2016;34(4):434-442.
23. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62. doi:10.1136/jnnp.23.1.56
24. Sanacora G, Frye MA, McDonald W, et al; American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. 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

AUTHORS

Jennifer K. Lent, DNAP, CRNA, is the chief nurse anesthetist at Yukon Kuskokwim Delta Regional Hospital in Bethel, Alaska. The author was a student in the Doctor of Nurse Anesthesia Practice program at Texas Wesleyan University in Fort Worth, Texas, at the time this article was written.

Albert Arredondo, DNAP, CRNA, is the chief nurse anesthetist at Southwestern Medical Center in Lawton, Oklahoma. He is also a co-owner of the Red River Ketamine Wellness Center in Lawton, Oklahoma. The author was a student in the Doctor of Nurse Anesthesia Practice program at Texas Wesleyan University at the time this article was written.

Marilyn A. Pugh, PhD, is an associate professor of psychology at Texas Wesleyan University.

Paul N. Austin, PhD, CRNA, is a professor and the coordinator of the Research and Anesthesia Curriculum for the Doctor of Nurse Anesthesia Practice program at Texas Wesleyan University.

DISCLOSURES

Albert Arredondo, DNAP, CRNA, is the co-owner of a healthcare facility offering the administration of ketamine for treatment-resistant depression. The other authors have declared no financial relationships with any commercial entity related to the content of this article. The authors did discuss off-label use within the article.