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Ketamine infusion therapy for treatment-resistant major depressive disorder and suicidal ideation: Nursing care and considerations

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Abstract
Major depressive disorder (MDD) affects approximately 332 million people worldwide. Among those diagnosed with MDD, approximately 53% receive pharmacologic treatment, such as ketamine. Nurses must be knowledgeable about ketamine and other emerging, effective behavioral health therapies used to treat chronically depressed mood and acute suicidal ideation. This article outlines the best nursing practices for using ketamine in the behavioral health setting, focusing on off-label ketamine infusion continuation therapy for treatment-resistant MDD and acute suicidal ideation and behaviors. Special attention is paid to using ketamine as an adjuvant versus primary treatment.

Keywords: behavioral health, esketamine, ketamine, ketamine infusion, major depressive disorder, suicidal ideation, veterans

Introduction

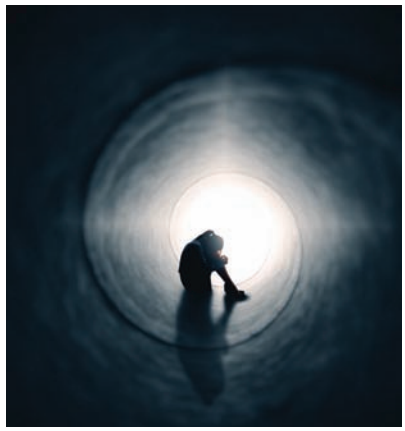
Nurses are on the front line of behavioral health with every patient encounter, regardless of setting. Because primary nursing responsibilities include patient education, safety, and advocacy, nurses must stay up-to-date on the latest advances in care and know the benefits and potential adverse effects of treatments. In addition,

nurses must be knowledgeable about emerging, effective behavioral health therapies, such as ketamine, which can be used to treat chronically depressed mood and acute suicidal ideation.[1]

In 2020, 18.4% of American adults self-reported having ever been diagnosed with depression,[2] and approximately 7% of adults nationwide had a major depressive episode in the same year.[3] Reported rates approached 30% in some states and exceeded 30% in some counties.[2] The World Health Organization (WHO) has identified that approximately 332 million people are diagnosed with major depressive disorder (MDD) worldwide,[4] and, based on increases in new-onset mental health conditions postpandemic, current rates may be even higher.

Among those diagnosed with MDD, approximately 53% receive pharmacologic treatment,[5] and one-third of those receiving pharmacologic treatment report symptom remission.[4,5] Nearly one-third of patients diagnosed with MDD are unresponsive to the first two antidepressant trials and thus have treatment-resistant depression (TRD).[6,7] For nearly 50 years, the standard of care for treating MDD has been pharmacologic intervention in the form of antidepressants.[8] However, new treatments targeting pathways beyond the monoamine system in the brain are emerging and gaining traction.

One such treatment is ketamine. Unlike conventional antidepressants, ketamine can attenuate even treatment-resistant and refractory depressive mood symptoms within minutes to hours.[9] In recent years, one-time infusions of ketamine have been used off-label in patients with suicidal ideation, and maintenance infusion therapy has been used in patients with TRD. Although the emergence of ketamine in the behavioral health setting is new,[10] it has been used as an anesthetic since the 1960s.[10,11] Used to treat a variety of conditions, including acute suicidal ideation and MDD, ketamine has proven itself to be one of the most versatile medications in health care.[12]



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This article outlines the best nursing practices for using ketamine in the behavioral health setting, focusing on off-label ketamine infusion continuation therapy for treatment-resistant MDD and acute suicidal ideation and behaviors. Special attention is paid to using ketamine as an adjuvant versus primary treatment.

Background

To meet diagnostic criteria for MDD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (DSM-5-TR), the patient must experience at least one major depressive episode that lasts 2 or more weeks, during which the patient experiences depressed mood, loss of interest or pleasure in all or nearly all activities, or both.[2] This period of depressed mood must occur in the absence of periods of elevated mood (mania or hypomania).[2] Additional criteria must also be met for a diagnosis of MDD, including but not limited to changes in appetite, sleep, and concentration.[2]

MDD often creates a heavy burden of morbidity and mortality, including an increased risk of acute suicidal ideation.[5] Among individuals with mental health disorders, the incidence of death by suicide is particularly high.[2] Those with TRD are at an even higher risk for suicide: 30% of patients with TRD attempt suicide at least once in their lifetime.[7] There is a tremendous need for new treatments for MDD, TRD, and suicidal ideation, especially in the most acute phases.

Global statistics from 2021 indicate that 727 000 people die by suicide every year and suicide is the third leading cause of death in 15 to 29 year olds.[4] Compared with the general population, people with depressed mood have a 17-fold increased risk for dying by suicide.[3] Common depressive symptoms, such as loss of interest and pleasure in daily activities, are closely associated with suicidal actions.[3] To prevent suicidal ideation and behaviors, any underlying contributing mood disorders must also be treated.

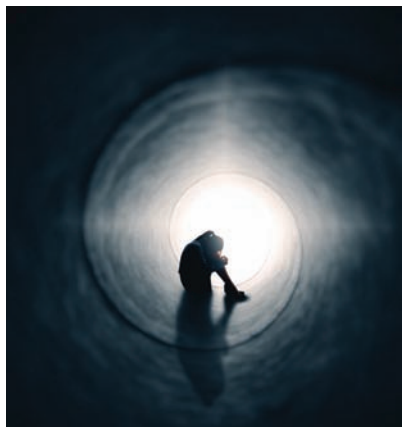
MDD has typically been treated with traditional antidepressants, such as selective serotonin reuptake inhibitors, but recent advances in MDD treatment, such as ketamine, have been shown to be beneficial. There are several routes for ketamine administration in behavioral health, including sublingual, intravenous (IV), and intranasal. Although esketamine (Spravato), the intranasal formulation of ketamine, is the only Food and Drug Administration (FDA)-approved formulation of ketamine for TRD and acute

suicidal ideation,[11,13] this article focuses on IV ketamine infusion. Off-label IV administration has been the basis of most ketamine research in recent years,[10] and the recent proliferation of freestanding infusion clinics in the US[14] yields a present need for nursing education on this topic.

Current theories of depression and conventional antidepressants

Traditional hypotheses of depression center on the role of neurotransmitters called monoamines, such as serotonin and dopamine.[15] Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and similar conventional antidepressants impact the availability (amount) of monoamines in the brain.[11] SSRIs, SNRIs, and similar conventional antidepressants take effect slowly (over the course of weeks to months) and have a low efficacy rate, with only one-third of patients achieving symptom remission during their first treatment trial.[5] Despite these drawbacks, clinicians continue to rely on the monoamine hypothesis for the basis of pharmacologic interventions for depression as the standard of care. However, research has shown that some patients respond to nonserotonergic interventions such as ketamine.[16]

MDD is associated with significant differences in brain structure and function compared with healthy controls.[17] Structurally, there are marked decreases in gray matter volume throughout the brain in patients with chronic depression, including in the thalamus, hippocampus, amygdala, and multiple areas in the cerebral cortex,[18] which can impact a person's memory, emotions, behavior, speech, and perception of the world.[19] Functionally, chronic depression is associated with changes in activity within and between neural networks in both MDD[20] and its TRD variation.[21]



Ketamine appears to restore functioning in brain regions typically over- or underactive in depressed patients.

Ketamine mechanism of action

Ketamine acts differently from traditional antidepressants. It is lipophilic and crosses the blood-brain barrier, which contributes to its efficacy and rapid onset.[12] When administered at subanesthetic doses, it can rapidly attenuate depressive symptoms within 40 minutes.[11] The medication's antidepressant effects are likely a result of its widespread action on receptors not traditionally implicated in depression, although ketamine does also impact the serotonin system.[22] Specifically, ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist, but it also acts as an opioid receptor and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor agonist, both of which are strongly implicated in ketamine's antidepressant effects.[18,23,24] NMDA and AMPA receptors are ionotropic glutamate receptors. As glutamate is the most abundant excitatory neurotransmitter in the brain, its receptors are more prevalent than those for the monoamines targeted by conventional antidepressants.[5] These and other glutamatergic receptors are involved in critical processes such as neuroplasticity, learning, and memory,[5] all of which are adversely affected by chronic depression.[18] Finally, ketamine also has an anti-inflammatory effect on the brain, which may further contribute to its antidepressant effects.[18]

Ketamine appears to restore functioning in brain regions typically over- or underactive in depressed patients. Specifically, postadministration neuroimaging studies indicate that ketamine enhances activity in brain regions associated with reward processing while diminishing activity in regions associated with self-monitoring.[24] These areas are thought to play a critical role in the pathophysiology of depression, and reestablishing healthy neural network communication, especially in these notable areas, may help improve multiple dimensions of MDD symptomatology.

Ketamine is an anesthetic that produces sedation, immobility, and dissociation, sometimes with hallucinogenic features.[11,17] When under the influence of ketamine, the patient may experience transient changes in perception of reality, time, and place, and they may observe, hear, or otherwise experience things that are not there.[17] Although ketamine is not a classic serotonergic psychedelic, some patients report psychedelic-like altered states of consciousness when under the influence of ketamine at therapeutic doses.[18,19] The resulting altered state of consciousness appears to be a catalyst for therapeutic change when used in conjunction with psychotherapy.[25]

Ketamine is not limited to an oral or parenteral formulation like many conventional antidepressants. It is used in behavioral health in

three formulations: sublingual, IV infusion, and nasal spray. Only the nasal spray is approved by the FDA to treat TRD and MDD with acute suicidal ideation,[13] but ketamine infusions are used off-label to treat the same concerns. This article focuses on ketamine infusion in support of behavioral health because it is rapidly gaining popularity for its off-label utility in private ketamine infusion clinics across the US.[14] The off-label use of ketamine infusions has been found to have faster onset and stronger effect, increased control and precision, and greater bioavailability, therefore offering increased efficacy over nasal spray ketamine.[26-29]

Ketamine has several significant advantages over most conventional antidepressants. Beyond its rapidity of action, it has few contraindications and medication interactions; most routine medications may be continued at their usual dose during ketamine infusion treatment, including SSRIs.[10,11] Thus, ketamine may be used as a monotherapy or as an adjuvant treatment for patients whose current antidepressant has lost efficacy.[30]

Interindividual variability in neural, cognitive, and behavioral responses is more common with ketamine use than with other emerging, nontraditional antidepressant therapies that may be attractive to patients who are willing to try off-label, novel therapies (eg, psilocybin, a classic hallucinogen).[31] Variability in response may be related to ketamine's diverse neural targets, unlike new SSRIs and even psilocybin, which target a limited number of receptors.[31] Response variability should be considered when treating patients, as not all patients will respond the same to a standard treatment regimen. Unlike most traditional antidepressants and other medications used to treat suicidal ideation and behaviors, there is little data on the long-term effects of ketamine infusion therapy beyond 120-day studies.[30,31]

Ketamine for TRD

Ketamine is routinely used off-label to treat TRD in infusion clinics across the US.[11] Patients with TRD meet the DSM-5-TR criteria for MDD and additionally have not achieved at least 50% symptom remission through adequate trials of two or more antidepressants, despite using the maximum effective dose for an appropriate duration.[30,32]

Unfortunately, TRD is relatively common among people experiencing a chronically depressed mood. Despite adequate trials of two or more antidepressants, approximately one-third of people diagnosed with depression do not experience a clinically significant remission of depressive symptoms.[21] Because the use of ketamine in these cases is off-label, there are no established guidelines for administration. The most common regimen entails two or three IV infusions per week over 2 to 4 weeks[11] with variability in

Best practices using ketamine for TRD

Topic	Details
Common TRD infusion schedule	0.5 mg/kg diluted in saline infused over 40 minutes, twice per week for 3 weeks[11]
Lower dose effects	Some patients respond to doses as low as 0.1 mg/kg.[10]
Higher dose for refractory symptoms	Patients may benefit from higher doses (up to 0.75 mg/kg) for refractory symptoms.[10]
Slow infusion rate to reduce adverse effects	Infusion over 100 minutes may reduce adverse effects.[10]
Medication safety	Ketamine is available in three concentrations (10 mg/mL, 50 mg/mL, and 100 mg/mL); monitor for any potential medication errors.[11]
Dose calculation for patients with obesity	For patients with a body mass index of 40 or greater, ideal body weight should be used to avoid adverse reactions such as hypertension.[45]
Off-label TRD infusion	Doses and infusion rates are not well established due to off-label use.[10]
Routine medications during ketamine infusion	Patients should continue their routine medications unless interactions exist, which are few.[39]
Ketamine and lithium interaction	No interaction problems reported between ketamine and lithium[39]
Interindividual variability	Greater variability in neural and behavioral responses to ketamine than other therapies such as psilocybin[29]
Treatment considerations	Not all patients will respond similarly to a standard ketamine regimen.[29]
Remission outcomes in infusion schedules	Twice-weekly and thrice-weekly infusion schedules produce similar remission outcomes after 15 days.[36]

infusion schedule and dosage (see *Best practices using ketamine for TRD*).

IV ketamine has demonstrated an ultra-rapid antidepressant effect in patients with TRD.[32] Symptom remission onset may occur as fast as 5 to 30 minutes,[26,28] and the effects peak approximately 2 hours postinfusion.[9] Symptom remission may continue to improve over the following 7 days.[28] Ketamine infusion used as an augmentation to escitalopram, an SSRI and conventional antidepressant therapy, was found to accelerate response to the conventional treatment.[11]

A single infusion of ketamine may produce symptom remission for up to 50% of patients, but effects begin to dissipate by day 14, indicating the need for repeated administration.[33] Maintenance therapy (infusions occurring up to three times per week for more than 1 week) shows efficacy compared with placebo after 15 days.[11] Research has been conducted on various dose ranges, which have shown different levels of effects and efficacy.[25]

Research indicates that maintenance therapy produces sustained, relatively significant remission of depressive symptoms, but these studies have been limited in duration or sample size.[4] In head-to-head trials, maintenance therapy was found to be more effective than more traditional and established therapies such as electroconvulsive therapy.[3-35]

Ketamine for acute suicidal ideation

Over 700 000 people die by suicide annually worldwide, a rate of approximately one person every 44 seconds.[4,36] In the US, approximately 500 000 people per year present to a hospital emergency department (ED) for acute suicidal ideation or behaviors.[36] Another 3% to 11.6% of all people who present to EDs report suicidal ideation or behaviors in addition to their chief complaint.[36]

Patients with TRD have an increased risk of all-cause mortality, including an increased risk of self-harm and suicide.[21,37,38] Patients who do not respond to antidepressant treatment are more likely to die by suicide than those who do respond.[10] With or without TRD or other mood disorders, suicide continues to be a leading cause of death in the US.[39] Despite its prevalence, the experience and human costs of suicidal ideation are poorly addressed, especially in terms of acute pharmacologic treatment.[39]

Routine lithium pharmacotherapy, a mood-stabilizing agent, is associated with fewer suicide attempts, a lower rate of deliberate self-harm, and mood stabilization.[40] These effects make lithium a preferred treatment for chronic suicidal ideation, especially in the presence of mood disorders,[40] but it is not recommended to treat acute phases of the disorder due to delayed effects during initiation of treatment.[35] Worth noting, ketamine and lithium have shown no adverse interactions, and ketamine has demonstrated robust efficacy in achieving symptom remission as an adjunctive treatment to lithium.[40]

With or without the presence of TRD, single-dose ketamine infusions have been used in EDs to address acute suicidal intent for at least a decade, although research on its use in emergency settings is limited and heterogeneous.[35] Like with TRD, use of ketamine for acute suicidal ideation is off-label.[11] A single infusion of ketamine, whether as a primary or adjunctive treatment for acute suicidal ideation, has been reported to be effective in attenuating suicidal ideation within 4 hours.[35]

Other recent studies have found that a single ketamine infusion as an adjunctive therapy demonstrated greater reduction in clinically significant suicidal ideation in patients with depression within 24 hours compared with an adjunctive infusion of midazolam, a benzodiazepine.[40] In that study, clinical improvement was maintained for up to 6 weeks following an infusion of 0.5 mg/kg in 100 mL 0.9% sodium chloride over 40 minutes,[40] which is identical to the typical, off-label infusion of ketamine for TRD. Hopelessness, a common symptom of depression and contributor to acute suicidal ideation, is decreased in the hours

Formulations of ketamine most often used in behavioral health

Formulation	Indications	Information
Oral: Sublingual formulations	FDA: none[48] Off-label: TRD, posttraumatic stress disorder (PTSD)[39,48]	Poor bioavailability and may need to be used more frequently for similar effects as IV and nasal routes;[39] only available through compounding pharmacies by prescription[48]
IV infusion	FDA: Anesthesia[11] Off-label: TRD, acute suicidal ideation,[11] chronic pain, severe agitation[11]	Rapid onset and peak plasma concentrations[48]
Intranasal spray	FDA: TRD, major depression with acute suicidal ideation or behavior[11] Off-label: Pain, migraine[11]	Available commercially as Spravato; effective as monotherapy and adjunctive; administered in medical facilities[11]

Best practices before, during, and after ketamine infusion[45]

Pretreatment best practices	Administration best practices	Recovery and follow-up best practices

• History and physical
  ○ Medical clearance
  ○ Preprocedure labs (eg, liver function tests, creatinine)
  ○ Assess for contraindications
• Administer premedication
• Trial infusions to assess for responsiveness, efficacy, and tolerability
	• Location
	  ○ Comfortable infusion rooms
	  ○ Recovery area
	  ○ Emergency equipment
	• Dosage
	  ○ Dosage (dosage is weight-based with range of 0.5-1.0 mg/kg)
	  ○ Volume
	  ○ Infusion time (typically infused over 40 min)
	  ○ Frequency (typically twice per wk for 4-5 wk with taper)
	• Monitor during infusion
	  ○ Vital signs
	  ○ Level of consciousness
	  ○ Signs/symptoms of ketamine toxicity
	  ○ Dissociative effects
	• Establish an emergency response system
		• Monitor recovery to baseline vital signs and sensorium
		• Psychiatric evaluation
		• Assess cognitive function
		• Assess potential for ketamine use disorder
		• Limit number and frequency of treatments to the minimum necessary

following IV ketamine administration, but the long-term effect of ketamine on feelings of hopelessness has not yet been studied.[41-43]

Formulations of ketamine commonly used for behavioral health

All formulations of ketamine are Schedule III nonopioid controlled substances (see *Formulations of ketamine most often used in behavioral health*). Despite regulations that require IV and nasal spray formulations to be administered in a medical facility under close monitoring by licensed health care professionals, some compounding pharmacies can skirt these laws by producing oral formulations, such as lozenges.[13] For important nursing considerations related to ketamine therapy, see *Best practices before, during, and after ketamine infusion*.[44,45]

Outpatient ketamine therapy

Esketamine (Spravato), a noncompetitive NMDA receptor antagonist, is FDA indicated for use for TRD and acute suicidal ideation and behavior, so its dispensing and use is standardized. Esketamine is sold directly to certified outpatient medical facilities through a Risk Evaluation and Mitigation Strategy program, which reinforces provider and patient safety-associated decision-making

Patient care considerations and rule-out criteria of ketamine infusion

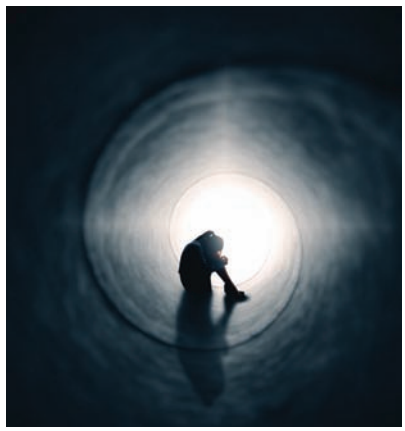
General considerations	Common rule-out criteria
• Higher doses may elicit more severe hypertensive events and increase cardiac output;[28] consider an electrocardiogram if questionable.[11] • Limited data on use among patients who are pregnant or breastfeeding[11] • Most trials exclude patients with psychotic features • Ketamine has fewer drug interactions than many conventional antidepressants.[11] • Close monitoring of vital signs (blood pressure, heart rate, respiratory rate, pulse oximetry) should be conducted throughout infusion.[11,44] • No reversal agent[49] • Continuation infusion therapy typically costs in the thousands and is rarely covered by insurance[14] • Metabolized through alternative pathways; fewer drug-to-drug interactions than most conventional antidepressants[11]	• Unstable cardiac abnormalities • Substance abuse history, especially those who used ketamine • Unstable medical or neurologic illnesses • Pregnancy or lactation • Current psychotic features • Daily use of benzodiazepines, or inability to skip doses for at least 24 h

and use behaviors.[13] The medication is self-administered by the patient, and they must remain at the facility under observation for 2 hours postadministration.[13] Like most medications, the cost of esketamine is standardized, as are the clinic practice standards.[13] In contrast, the cost of ketamine infusion is not standardized, and can be prohibitively expensive to patients.

Unlike esketamine, ketamine infusion practices are nonstandardized and most commonly occur in private, freestanding outpatient clinics.[10] As new purposes for off-label ketamine infusion are found, such as eating disorders and peripartum depression, for-profit ketamine infusion clinics are becoming more prevalent across the US (see *Patient care considerations and rule-out criteria of ketamine infusion*).[14] Because the use of ketamine infusion therapy is unregulated and clinic regulations vary from state to state, results and experiences may vary (see *Potential side effects and adverse reactions of ketamine infusion*).[14] Some clinics may require patients to undergo mental health screening and care at their clinic prior to providing an infusion, whereas others may accept referrals from nonclinic providers.

Ketamine in combination

Ketamine may act as a powerful tool as a primary or adjunctive agent for conventional therapies, especially for conditions such as TRD and suicidal ideation.[11,40] Combining ketamine infusion with conventional antidepressants for MDD treatment on Day 1 of treatment initiation can accelerate the patient's treatment response.[33] Ketamine was also reported to be clinically significant when used as an adjunctive treatment for acute suicidal ideation reduction in patients with depression within 24 hours compared with control.[38]



Because the use of ketamine infusion therapy is unregulated and clinic regulations vary from state to state, results and experiences may vary.

In the past decade, ketamine infusion has been studied in combination with other emerging and novel therapies among unique and underserved populations, such as veterans, that commonly experience treatment-resistant symptoms.[46,47] Some populations' mental health concerns, such as TRD, may be enhanced by their unique lived experiences. For example, a history of traumatic brain injury (TBI) or occupational exposures may affect mental health, especially among certain veteran populations.[46,47] Meeting the mental health needs of these populations may require the use of atypical or more potent interventions that are beyond the typical first- and second-line treatments.[46,47] For these patients, first-line SSRIs and second-line SNRIs may not work, but a more potent intervention, such as ketamine, may address their symptom constellation more effectively.

Ketamine infusion has been used successfully with other novel, repurposed treatments, such as bilateral cervical sympathetic blocks.[48] First introduced in the 1950s for pain management, cervical sympathetic blocks have been repurposed in behavioral health settings and are effective for treating the symptoms of PTSD.[49] In a year-long case study, a military veteran with a special operations background was provided five ketamine infusions and bilateral cervical sympathetic blocks to address symptoms of PTSD and TBI.[49] The patient experienced a significant reduction or remission of his symptoms of PTSD, anxiety, suicidal ideation, depression, and cognitive deterioration (per patient report).[49] The authors concluded that ketamine infusion maintenance therapy combined with cervical sympathetic blocks can dramatically

Potential side effects and adverse reactions of ketamine infusion

Side effects	Adverse reactions
• Psychedelic experience: dissociation; confusion; blurred vision; feeling spaced-out; disconnect with time, setting, and situation[11]	• Respiratory depression[11]
• Poor coordination, fall risk[11]	• Delirium[11]
• Transient hypertension (180/100 or greater) and tachycardia (110 or greater)[11]	• Emergence phenomenon[49]
• Headache[47]	• Bladder toxicity[50]
• Nausea[44,47]	
• Anxiety[47]	

decrease symptoms of PTSD, TBI, psychiatric comorbidities such as depression, and general cognitive dysfunction.[49]

Conclusion

Given the global prevalence of depressive disorders and acute suicidal ideation, and the frequency with which nurses encounter these conditions in their practice, nurses should be aware of ketamine as a primary or augmentive treatment modality for TRD and acute suicidal ideation. Ketamine's efficacy and delivery options for treating acute suicidal ideation and TRD make it an appealing and realistic choice for use in a variety of clinical settings. The established use of ketamine as an anesthetic offers further practical advantages over other nontraditional depression therapies, such as psilocybin. Additional research will be needed to establish clinical practice guidelines about dosing and administration, but preliminary findings indicate that ketamine may soon play an increasing role in the field of behavioral health. ■

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Ketamine infusion therapy for treatment-resistant major depressive disorder and suicidal ideation: Nursing care and considerations

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