

Is Ketamine the New Wonder Drug for Treating Suicide?

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Although the initial findings involving the use of ketamine in suicidal patients are promising, further research is needed on the short - and long-term effects of this medication.

In 2014 the suicide rate in the U.S. was 13/100,000, the highest recorded in 28 years.¹ Suicide is now considered the 10th leading cause of death for all ages, and the rate has increased every year from 2000 to 2014 among both women and men and in every age group except those aged ≥ 75 years.¹⁻³ For those aged 15 to 44 years, suicide is among the top 3 causes of death worldwide.^{4,6}

BACKGROUND

In 2013, more than 490,000 hospital visits related to suicide attempts were reported in the U.S.⁴ Health care expenditures related to suicide are estimated at \$56.9 billion in combined medical and work loss costs annually and an unmeasurable cost to the affected families.⁷ The mental health care community is desperate for ways to address this epidemic, and the National Academies of Medicine (NAM) has declared that research that directly addresses comparative effectiveness of treatment strategies following a suicide attempt should be a national priority.⁸

The most recent reports from 2014 indicate that the suicide rates

are higher for male veterans than for male nonveterans (32.1 vs 20.9 per 100,000, respectively) and are much higher for female veterans than for female nonveterans (28.7 vs 5.2 per 100,000, respectively).³ Suicide rates also may be associated with veteran-specific comorbidities, such as higher rates of depression, anxiety, posttraumatic stress disorder (PTSD), and war-related trauma.³ According to the VHA, the suicide rate for veterans aged > 30 years also is rapidly increasing, and VHA has echoed the calls from NAM to make suicide prevention research a national priority.³

The VA has tried to stem the tide of suicides in veterans by implementing many advances in suicide prevention, including hiring suicide prevention coordinators at every VA hospital, enhanced monitoring, and the availability of 24-hour crisis hotline services. Yet the suicide rates for veterans continue to rise and remain higher than the rates in the general population.³

About 90% of deaths by suicide are by persons who have a treatable psychiatric disorder, most commonly a mood disorder, such as depression.⁴ However, most studies show that antidepressant therapy does not provide rapid or significant relief of suicidal ideation (SI).⁴ Therefore, the current stan-

dard of care for the treatment of acutely suicidal patients includes a combination of hospitalization, cognitive behavioral therapy or psychotherapy, case management, antidepressant medications, and electroconvulsive therapy (ECT).⁴ Even though these therapies have become more widely available over the past decade, rates of suicide continue to increase.^{1,4} These interventions have limited effectiveness in acute settings. Although both intensive outpatient follow-up and routine outpatient care have been studied in relation to the decrease of suicidal behavior, neither intervention has been shown to immediately reduce suicidal behavior significantly in patients.

Suicidality Interventions

Therapy and case management require patients to be well enough to make office visits and follow through with care for periods as long as 1 year, which is often not possible for individuals with severe depression.⁵ One-third of patients who attended 6 months of outpatient therapy consistently still met the criteria for major depressive disorder (MDD), a major risk for suicide attempt.⁹ Antidepressant medications take a minimum of 4 weeks to reach full efficacy, and many patients stop taking the

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medications before that point because of concern that the medication is not helping or because of adverse effects (AEs), such as sleep disturbance, sexual dysfunction, or weight gain.⁹

Electroconvulsive therapy has been shown to be an effective treatment for patients with depression and suicidal behavior, but adherence with 12 weeks of recommended therapy has been a barrier for this intervention. Additionally, ECT may not provide reduction in SI for 1 to 2 weeks.^{4,10} A review of research studies showed that nearly 50% of patients with high-expressed SI did not complete the prescribed amount of ECT due to the length of time to complete the recommended 12 sessions.¹⁰ Therefore, current treatment barriers for suicidal patients include: (1) long periods in treatment for therapy, medication, and ECT before any relief of symptoms is noted; (2) high recidivism rates for MDD symptoms and risk of suicide following treatment; and (3) high treatment dropout rates.

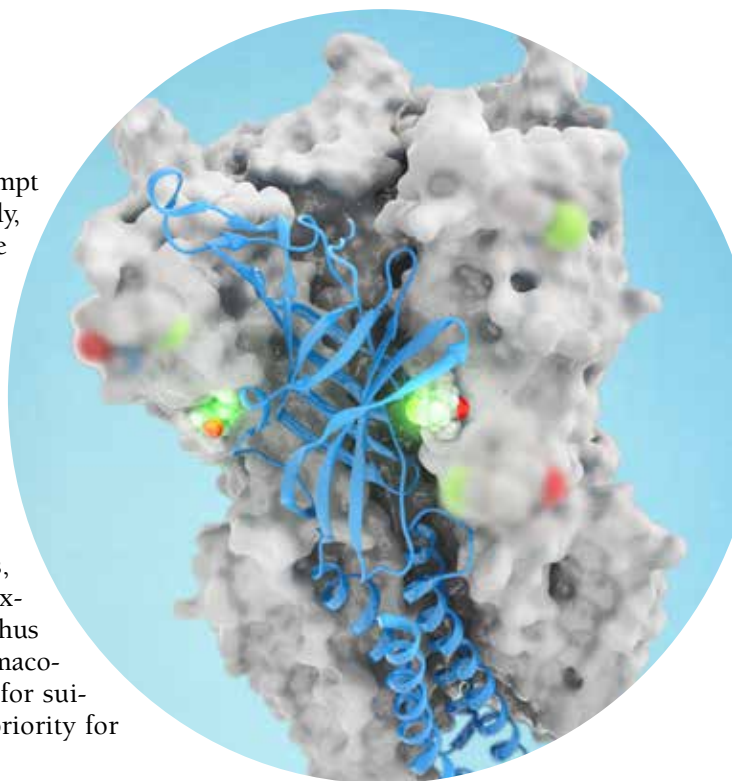
Pharmacologic treatments currently used in suicidal patients have not fared much better. Many have received FDA approval for treatment of associated mental health diagnoses such as bipolar disorder, schizophrenia, or MDD, but there are no approved treatments that specifically target suicidal behavior. Lithium is approved for reducing the long-term risk of SI primarily because it reduces the risk of mood disorders associated with SI, but lithium has not been shown to be effective in acute settings.¹¹ Clozapine is approved for reducing the long-term risk of recurrent suicide in patients with schizophrenia or schizoaffective disorder.⁴ Clozapine has not been shown to be effective in patients with mood disorders, which make up the majority

of patients who attempt suicide.⁴ Additionally, both medications are plagued by the same barriers listed earlier, such as long time to effect (it takes an average 4 weeks to reach efficacy), lack of efficacy in acute settings, and AEs (eg, sleep problems, weight gain, and sexual dysfunction).⁹ Thus finding better pharmacologic interventions for suicidal patients is a priority for current research.

KETAMINE

Recently, researchers have identified ketamine as a potential therapeutic option for depression and SI. A single ketamine infusion treatment has a rapid response, minimal AEs, and potentially long-lasting efficacy with SI, which would make it ideal for the treatment of acutely suicidal patients.⁴ Ketamine is an N-methyl-D-aspartate receptor (NMDAR) inhibitor that also has been found to be a weak μ - and κ -opioid receptor agonist and an inhibitor of the reuptake of serotonin, dopamine, and norepinephrine. Inhibition of the NMDAR results in analgesia, and ketamine is approved for the induction of anesthesia, pain relief, and sedation.¹²

Although AEs such as hallucinations and sedation create the potential for dangerous recreational use, ketamine is safely used in health care settings for a variety of indications. Effects are noted within 5 minutes of administration if given by infusion, and the main effects can last between 20 and 40 minutes.



Ketamine has a complex pharmacology and plays a role in other cell signaling mechanisms, but the significance of these additional mechanisms in the therapeutic effects of ketamine have only recently been elucidated. Preclinical studies indicate a probable NMDAR inhibition-independent mechanism responsible for the antidepressant response to ketamine.^{13,14} The complex associations with rapamycin signaling, eukaryotic elongation factor 2 dephosphorylation, increased synthesis of brain-derived neurotrophic factor, and activation of glutamatergic AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors have been linked to its rapid antidepressant effect and ketamine's induction of synaptogenesis within the limbic system.^{13,14}

Clinical Research

Ketamine was studied as an adjunctive treatment to psychotherapy for addictions as far back as the 1970s.¹⁵ The available reports indicate a

universally positive result, with increased rates of remission and decreased rates of relapse attributed to ketamine's ability to alter one's thought processes by reinforcing limbic-cortex interactions that facilitate the growth of more positive cognitive schemas and improved emotional attitudes about the self in support of the recovery process.¹⁵

Neurobiologic studies have shown that treatment with ketamine has a direct and immediate effect on neuronal pathways of the limbic system. It is known to regulate the mind's reaction to positive stimuli by reversing the depressed subject's blunted reaction to positive faces.¹⁶ This rapid normalization of the positive faces test is unique to ketamine infusion and is not seen in tests with traditional antidepressants.

Researchers need to further establish the safe and effective route, point of care, and patient type that would best respond to this novel treatment.

In 2000, the first placebo-controlled trial using ketamine for treatment resistant depression (TRD) demonstrated the rapid antidepressant effects of a single dose of ketamine, but this study only looked at these effects for 1 week.¹⁷ In multiple double blind, placebo-controlled trials since then, IV infusion of ketamine was shown to be an effective intervention for TRD.^{13,18,19} More recently, a published investigation involving the treatment of MDD showed that ketamine in conjunction with a selective serotonin reuptake inhibitor (SSRI) accelerated and enhanced the effectiveness of the SSRI in reducing depressive symptoms.²⁰

Based on the rapid resolution of depressive symptoms using ket-

amine, researchers have looked at its effect on suicidality as a secondary measure. A case study of a patient with severe depressive episodes and multiple previous suicidal attempts reported that the patient responded to a single dose of ketamine, described the experience as "being reborn," and maintained complete remission of SI for the 6-month study period.²¹ In a larger study, 133 TRD patients received a single IV dose of ketamine with significant reductions in SI independent of depressive and anxiety symptoms.²²

Depression Treatment

These results have led to an excitement for ketamine therapy as a novel treatment of depression, and off-label use by treatment centers

now exists in several countries to aid those with TRD.²³ This off-label use continues to be controversial, as research has yet to determine the safest most effective route and duration of treatment and whether the ketamine treatment AEs will exceed any accrued therapeutic benefit.¹³

The American Psychological Association Council of Research Task Force on Novel Biomarkers and Treatment critically examined the clinical evidence of ketamine use and has raised important concerns about the use of ketamine in the outpatient setting, administered in the absence of consensus therapeutic monitoring guidelines, and ambitiously marketed as a panacea for TRD.^{13,24} A study showed permanent impair-

ment of brain function for both groups compared with monkeys treated with saline infusions.²⁵ In 2016, the FDA gave fast-track approval for an intranasal ketamine that would make the treatment more easily available in the outpatient setting, but this could lead to certain patients developing a dependency on ketamine or engaging in its diversion for recreational use. There are case reports and anecdotes in the literature of patients and research subjects developing drug-seeking behaviors and overuse of ketamine.²⁴ Additionally, the comorbidities associated with TRD and SI have not been fully evaluated. For instance, there is evidence that depressed patients with obsessive compulsive disorder may have worse outcomes that include delayed onset SI.²⁶

There also is concern for the use of ketamine for chronic opioid users. The combination of ketamine with opioids may increase the response to the opioid in an otherwise drug tolerant patient, leading to risk of death by overdose in patients who have not increased their usual dose.²⁷ However, this effect was noted only when ketamine and opioids were administered together, and the effect does not seem to last postinfusion.²⁷

The challenges in treatment of TRD include finding an effective formulation—IV infusion of ketamine requires cardiovascular monitoring and is administered by anesthesiologists. The short duration of action for depression requires repeated infusions, and the frequency and quantity of infusions have not been determined. Efforts to find other NMDAR inhibitors (eg, memantine, nitrous oxide, D-cycloserine, and others) that match ketamine's antidepress-

sant efficacy but with easier delivery methods and fewer risks have thus far been unsuccessful.¹³ It is now believed that ketamine's unique ability to activate intracellular signaling pathways linked to synaptic plasticity gives it the antidepressant function. Recent studies have further narrowed ketamine's antidepressant function to the R-enantiomer of the ketamine metabolite, hydroxynorketamine.¹⁴ The nasal spray for ketamine is the S-enantiomer, which has better bioavailability but may have less antidepressant efficacy compared with the racemic mixture used in ketamine infusions.

Suicide Ideation Treatment

The many challenges faced by researchers and clinicians trying to develop ketamine treatment for TRD may not apply to the treatment of SI. Whereas repeated doses of ketamine cannot reliably produce sustained remission of depression, the few studies that have looked at the long-term effects of ketamine treatment on SI indicate the potential for long-term efficacy after a single IV infusion.^{21,22} Although treatment with IV infusions have additional costs and logistics, if it is found beneficial, it could be given in the emergency department (ED) prior to hospitalization and potentially lead to better outcomes.

In 2011, a small preliminary observational study of patients with depression and SI presenting to the ED indicated that SI was rapidly reduced following an infusion of ketamine.²⁸ This study showed that both depressive symptoms and suicidality rapidly and significantly diminished within 40 minutes with no evidence of the recurrence of symptoms 10 days postadministration.

A more recent study used ket-

amine in a military field hospital to treat SI and also concluded that it could be effective and safe when administered in an ED setting. This preliminary study suggests that ketamine could be a safe and potentially effective medication for rapid reduction of depression and suicidality in a busy ED setting.²⁹ These limited studies involving the use of ketamine in patients with SI show promise with long-term effectiveness. However, more research is needed to clarify whether the efficacy with SI will be similar to the clinical experience seen in TRD; a duration of effect limited to 2 weeks with recurrence after treatment discontinued.²⁴

CONCLUSION

There has been a compelling accumulation of scientific data since 2000 to support the use of ketamine for the treatment of depression and SI. Ketamine use in patients with these diagnoses showed a rapid decrease of symptoms and minimal AEs among a significant number of patients.^{22,30}

Although the initial findings involving the use of ketamine in suicidal patients are promising, the clinical use of ketamine needs further research, using larger sample sizes and exploring both the short-term and long-term effects of this medication. Researchers need to further establish the safe and effective route, point of care, and patient type that would best respond to this novel treatment. The initial evidence would suggest that health care providers have every right to be hopeful that ketamine will become the first pharmacologic treatment of acute SI in a majority of patients presenting to EDs, mental health clinics, community hospitals, and VA medical centers. ●

Author disclosures

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