# Ketamine: Quo Vadis?

Charles B. Nemeroff, M.D., Ph.D.

> "It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair."
>
> —Charles Dickens, *A Tale of Two Cities*

The choice of a title for this commentary was not willy-nilly, but quite deliberate. Our field very much wants and needs to know where the ketamine story is going. Here, I attempt to succinctly summarize the ketamine story in the context of the recent findings reported by Grunebaum and colleagues (1) in this issue.

Ketamine, administered parenterally, was approved by the U.S. Food and Drug Administration (FDA) in 1970 for general anesthesia. For the next 20 years, ketamine was exclusively used for this indication. In 1990, Berman et al. (2) reported on a saline-controlled clinical study of seven patients showing that a low, subanesthetic dose of ketamine possessed antidepressant properties. This was followed several years later by a virtual avalanche of studies that have sought to confirm and extend those initial observations on the beneficial effects of ketamine on depressive symptoms and suicidality. In my capacity as Chair of the APA Task Force on Biomarkers and Novel Treatments, I have been a contributor to the meta-analysis of the ketamine treatment database (3) and the recent expert consensus report on its use in the treatment of depression (4), as well as several commentaries (5, 6).

There is little debate over the antidepressant effects of intravenously administered low-dose (0.5 mg/kg) ketamine in major depressive disorder and bipolar depression (the interested reader can refer to recent reviews in references 4, 7). The antidepressant effects are clear but transient, with most but not all studies observing the effects abating by 7 days postinfusion. There is substantially less information on the beneficial and adverse consequences of repeated ketamine administration. This is of paramount importance, because the excitement about ketamine in our field is a reflection of the serious challenges we face in managing treatment-resistant depression. Estimates vary, but even in the Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT) team's recent study of never-treated depressed patients randomly assigned to receive escitalopram, duloxetine, or cognitive-behavioral therapy (8), remission rates were approximately 50%. The National Institute of Mental Health–funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial found a remission rate of only 28% with citalopram monotherapy (9). In addition, treatment-resistant depression is associated with reduced life expectancy because of an increased risk for suicide as well as major medical disorders, including myocardial infarction, diabetes, and others.

Suicide is the 10th most common cause of death in the United States and the only one in the top 10 increasing in rate and number. Grunebaum et al. (1), in a very well designed study of suicidal inpatients with major depression randomly assigned to receive intravenous ketamine or midazolam (an "active" control), found a significant antisuicidal effect of ketamine, an effect maintained for up to 6 weeks when combined with optimized pharmacotherapy. The enantiomer of ketamine, esketamine, administered intranasally, is currently being studied by Janssen Pharmaceuticals in patients with major depression and prominent suicidality. With all of these positive results, in spite of a database that is a mere fraction of what the FDA would normally require for approval, why all this concern? The concerns can be simply classified in five main categories:

1. Who regulates or should regulate the use of ketamine for the treatment of major depression, posttraumatic stress disorder (PTSD), and other psychiatric disorders? Related to this question is another: What oversight is currently in place for the myriad of ketamine clinics that have sprung up virtually overnight?
2. How much of a problem is ketamine as a drug of abuse? Is this a problem that is being addressed in ketamine clinics?
3. What is the mechanism of therapeutic action of ketamine? Can elucidation of this mechanism lead to development of novel antidepressant/antisuicidal compounds without abuse liability?
4. Do the ketamine data support the view that other drugs of abuse, such as psilocybin and opioids, possess antidepressant properties, and, conversely, does ketamine act primarily by the same mechanisms as these agents?
5. What are the limitations of the current ketamine treatment database?

**It is unclear exactly how many ketamine clinics are operating in the United States, but they are believed to number in the range of 60–100. Many of them do not follow the minimal recommendations of the recent APA task force consensus report.**

Below, I briefly address each of these cardinal issues.

It is unclear exactly how many ketamine clinics are operating in the United States, but they are believed to number in the range of 60–100. Many of them do not follow the minimal recommendations of the recent APA task force consensus report (4). More specifically, several of these clinics make outlandish claims, including treatment of not only depression but also PTSD, migraines, obsessive-compulsive disorder (OCD), and chronic pain. Many have no psychiatrist on staff, do not perform a thorough psychiatric evaluation, do not screen for drug and alcohol abuse, and do not follow the American Heart Association guidelines (10). In my view, the curious happenstance that has led to the off-label prescribing of ketamine for patients with psychiatric disorders should be overseen by the state medical boards. This is fundamentally a credentialing issue, and non-psychiatrists should not be managing the treatment of patients with severe treatment-resistant depression. Moreover, the data on the efficacy of ketamine in other psychiatric disorders, such as PTSD and OCD, are meager.

Ketamine remains a significant drug of abuse in the United States and elsewhere. Schak et al. (11) reported on a patient with treatment-resistant depression and a comorbid alcohol use disorder who repeatedly abused ketamine and died in a single-car crash. I recently evaluated a patient who received five ketamine treatments in 1 week in a clinic on the West Coast and who was provided with a vial of ketamine to administer intranasally on an as-needed basis.

The mechanism of action of ketamine remains obscure. In spite of its classification as an NMDA receptor antagonist, it is known to exert manifold effects; moreover, other NMDA antagonists, such as memantine, lack antidepressant properties. An ongoing study is seeking to determine whether the therapeutic effects of ketamine are mediated by μ-opioid receptors, a finding that would have major therapeutic and regulatory implications. Several investigators and pharmaceutical companies are exploring signal transduction pathways through which ketamine is believed to act, in order to identify new therapeutic candidates (12).

It is unclear whether the psychotomimetic effects of ketamine are integral to its therapeutic effects. However, there has been a major resurgence of interest in the potential utility of psilocybin, LSD, and opioids in the treatment of depression (13). It is not unreasonable to ask whether the property these agents all share, namely, the ability to create a "high" or euphoric state, is essential for their antidepressant effects.

Finally, there is the question of the strength of the current evidence base. One obvious major problem is the clear lack of blinding, even in the double-blind randomized controlled trials. Certainly, patients and investigators can distinguish between the effects of ketamine and midazolam or saline.

The vast majority of patients with treatment-resistant depression whom I have evaluated over the past 5 years have not received treatment with all of the FDA-approved augmentation strategies, not to mention the non-FDA-approved treatments for which there is a considerable database. When treated with monoamine oxidase inhibitors, tricyclic antidepressants, ECT, repetitive transcranial magnetic stimulation, or augmentation with lithium, $T_3$, atypical antipsychotics, or pramipexole, many patients with treatment-resistant depression show remarkable improvement. As the ketamine database on efficacy and safety grows, and particularly as data are generated on the safety of repeated administration, ketamine will find its appropriate place in our armamentarium.

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Accepted January 2018.

*Am J Psychiatry 2018; 175:297–299; doi: 10.1176/appi.ajp.2018.18010014*

## REFERENCES

1. Grunebaum MF, Galfalvy HC, Choo TH, et al: Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. Am J Psychiatry 2018; 175: 327–335
2. Berman RM, Cappiello A, Anand A, et al: Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000; 47: 351–354
3. Newport DJ, Carpenter LL, McDonald WM, et al: Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry 2015; 172:950–966
4. Sanacora G, Frye MA, McDonald W, et al: A consensus statement on the use of ketamine in the treatment of mood disorders. JAMA Psychiatry 2017; 74:399–405
5. Newport DJ, Schatzberg AF, Nemeroff CB: Whither ketamine as an antidepressant: panacea or toxin? Depress Anxiety 2016; 33: 685–688
6. Sanacora G, Heimer H, Hartman D, et al: Balancing the promise and risks of ketamine treatment for mood disorders. Neuropsychopharmacology 2017; 42:1179–1181
7. Naughton M, Clarke G, O'Leary OF, et al: A review of ketamine in affective disorders: current evidence of clinical efficacy, limitations of use, and pre-clinical evidence on proposed mechanisms of action. J Affect Disord 2014; 156:24–35

8. Dunlop BW, Kelley ME, Aponte-Rivera V, et al: Effects of patient preferences on outcomes in the Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT) study. Am J Psychiatry 2017; 174:546–556
9. Rush AJ, Trivedi MH, Wisniewski SR, et al: Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 2006; 354:1231–1242
10. Fletcher GF, Ades PA, Kligfield P, et al: Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013; 128:873–934
11. Schak KM, Vande Voort JL, Johnson EK, et al: Potential risks of poorly monitored ketamine use in depression treatment. Am J Psychiatry 2016; 173:215–218
12. Cavalleri L, Merlo Pich E, Millan MJ, et al: Ketamine enhances structural plasticity in mouse mesencephalic and human iPSC-derived dopaminergic neurons via AMPAR-driven BDNF and mTOR signaling. Mol Psychiatry (Epub ahead of print, Nov 21, 2017)
13. Carhart-Harris RL, Goodwin GM: The therapeutic potential of psychedelic drugs: past, present, and future. Neuropsychopharmacology 2017; 42:2105–2113

# Contraceptive Conundrum: Use of Hormonal Contraceptives Is Associated With an Increased Risk of Suicide Attempt and Suicide

David Brent, M.D.

Over 100 million women use hormonal contraception worldwide, and many health benefits have been documented (1). Although a relationship between hormonal contraception and depression is known in clinical lore and is supported by some research, relatively little work has focused on suicidal outcomes. In this issue, Skovlund and colleagues (2) provide an elegant and lucid report of their study finding that hormonal contraceptive use doubles the risk of suicide attempt and triples the risk of suicide.

The study used a nationwide registry to identify 475,802 women who were observed for an average of 8.3 years. Of this cohort, 54% were using hormonal contraceptives at some point during follow-up. Those with a previous history of antidepressant use or of a psychiatric disorder were excluded. The outcome measures were suicide attempt as recorded in the medical record and death by suicide. The authors found that the impact of hormonal contraceptive use on suicidal behavior was higher in adolescents compared with older women, that the incidence of suicidal behavior peaked 2 months after initiation of hormonal contraception, and that nonoral forms of hormonal contraception conferred the highest risks.

The strengths of this study are those typical of Scandinavian epidemiological samples: a large and representative sample, a long prospective follow-up, and careful methodology, censoring data during pregnancy, parsing the effects of current and past exposures to hormonal contraceptives, and reporting effects by type of hormonal contraceptive.

Among the study's limitations is that we know very little about risk factors that may confound the relationship between hormonal contraceptive use and suicide attempt, such as past maltreatment, relationship discord, exposure to domestic violence, and family history of psychiatric disorders, all of which may predispose hormonal contraceptive users to suicidal behavior. This information may help identify who is likely to be vulnerable to these negative sequelae of hormonal contraceptive use. While the authors showed that the findings would be robust even in the face of one large confounding factor, there could be multiple confounders of smaller magnitude that may explain at least part of the reported relationship between hormonal contraceptive exposure and suicidal behavior. The method of selection of comparison groups may also have led to bias. A comparison of women using hormonal and nonhormonal forms of birth control may be a more valid one, particularly for adolescents, when earlier sexual debut and risky sexual behavior could be related to an increased risk for suicidal behavior. Finally, as in all registry studies, diagnostic data are based only on those who present for treatment.

The ways to evaluate the extent to which an observational study supports a causal relationship between exposure and outcome are that it successfully addresses confounders, demonstrates a temporal sequence between exposure and outcome, shows a dose-response effect, and produces findings that are biologically plausible.

While unmeasured confounders are a concern, at least two studies have shown that adolescent and adult women who use hormonal contraceptives are at *lower* risk for depression compared with those using less effective forms of contraception. In one study of adolescents, those with *lower* depressive symptoms were more likely to elect hormonal contraception rather than an intrauterine device (3). In another study of sexually active women, those who used hormonal contraception were of higher socioeconomic status and had a more physically active lifestyle compared with women who used less effective or no contraception (4). The Skovlund et al. study clearly demonstrated that hormonal contraceptive use preceded suicidal behavior, although past users continued to be at increased risk long after they stopped using hormonal contraceptives. Perhaps these individuals had a preexisting vulnerability to mood disorders unmasked by exposure to hormonal contraceptives.

**Psychiatrists should routinely inquire about the use of hormonal contraceptives in their female patients and chart the temporal relationship of hormonal contraceptive use against depressive symptoms.**

With respect to dose-response effects, the risk of suicidal behavior tended to be higher in women who received 50 μg compared with those who received 20–40 μg of ethinyl estradiol, and higher in those who used progestins with androgenic properties.

The relationship between hormonal contraceptive exposure and suicidal behavior is plausible for several reasons.

# Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial

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**Objective:** Pharmacotherapy to rapidly relieve suicidal ideation in depression may reduce suicide risk. Rapid reduction in suicidal thoughts after ketamine treatment has mostly been studied in patients with low levels of suicidal ideation. The authors tested the acute effect of adjunctive subanesthetic intravenous ketamine on clinically significant suicidal ideation in patients with major depressive disorder.

**Method:** In a randomized clinical trial, adults (N=80) with current major depressive disorder and a score ≥4 on the Scale for Suicidal Ideation (SSI), of whom 54% (N=43) were taking antidepressant medication, were randomly assigned to receive ketamine or midazolam infusion. The primary outcome measure was SSI score 24 hours after infusion (at day 1).

**Results:** The reduction in SSI score at day 1 was 4.96 points greater for the ketamine group compared with the midazolam group (95% CI=2.33, 7.59; Cohen's d=0.75). The proportion of responders (defined as having a reduction ≥50% in SSI score) at day 1 was 55% for the ketamine group and 30% for the midazolam group (odds ratio=2.85, 95% CI=1.14, 7.15; number needed to treat=4.0). Improvement in the Profile of Mood States depression subscale was greater at day 1 for the ketamine group compared with the midazolam group (estimate=7.65, 95% CI=1.36, 13.94), and this effect mediated 33.6% of ketamine's effect on SSI score. Side effects were short-lived, and clinical improvement was maintained for up to 6 weeks with additional optimized standard pharmacotherapy in an uncontrolled follow-up.

**Conclusions:** Adjunctive ketamine demonstrated a greater reduction in clinically significant suicidal ideation in depressed patients within 24 hours compared with midazolam, partially independently of antidepressant effect.

*Am J Psychiatry 2018; 175:327–335; doi: 10.1176/appi.ajp.2017.17060647*

There is a lack of evidence-based pharmacotherapy for suicidal patients with major depressive disorder. The 26.5% increase in U.S. suicide rates from 1999 to 2015 (1) underscores this treatment need. The American Psychiatric Association's practice guideline on management of patients with suicidal behavior states that "evidence for a lowering of suicide rates with antidepressant treatment is inconclusive" (2, p. 14). Standard antidepressants may reduce suicidal ideation and behavior in depressed adults, mediated by improvement in depressive symptoms, but this effect takes weeks (3). Other somatic treatments with some evidence for antisuicidal effects include clozapine in schizophrenia (4) and ECT (5) and lithium (6) in mood disorders.

Suicidal depressed patients need rapid relief of suicidal ideation. Depression remits in one-third or fewer patients, and fewer than half achieve even 50% relief with typical first-line medications (7). Although suicidal behavior is usually associated with depression (8), most antidepressant trials have excluded suicidal patients and did not assess suicidal ideation and behavior systematically, which has resulted in limited data on this topic (9). Depression predicts suicide attempts via its effect on suicidal ideation (10).

Ketamine, a drug with dissociative and glutamate receptor–blocking properties that was approved by the U.S. Food and Drug Administration in 1970 for anesthetic use, has recently become a target of research for its antidepressant effects, which occur within hours at subanesthetic doses (11). Reports of reduction in suicidal ideation after ketamine infusion are promising, but the conclusiveness of results for major depression has been limited by measurement of suicidal ideation with a single item from a depression inventory (12–16), lack of a control group (15–17), use of a saline control (12, 13), and use of samples with low levels of suicidal ideation (16, 18) or mixed diagnoses (19).

*See related features:* **Editorial** *by Dr. Nemeroff (p. 297) and* **AJP Audio** *(online)*

We conducted a randomized clinical trial of an adjunctive infusion of ketamine compared with the short-acting benzodiazepine anesthetic midazolam in patients with major depressive disorder who had clinically significant suicidal ideation, as assessed by score on the Scale for Suicidal Ideation (SSI) (20). The primary outcome measure was SSI score 24 hours after infusion. Other outcome measures included global depression ratings, clinical ratings during 6-week open follow-up treatment, and safety measures. Given ketamine's dissociative effects, there is no ideal comparator, so, as in the trial by Murrough et al. (21), we used midazolam because it is a psychoactive anesthetic agent with a similar half-life and no established antidepressant or antisuicidal effects. We hypothesized that ketamine would produce a greater reduction in suicidal ideation at 24 hours compared with midazolam.

## METHOD

### Participants

Eligible patients were 18–65 years old and had a DSM-IV diagnosis of major depressive disorder, a score ≥16 on the 17-item Hamilton Depression Rating Scale (HAM-D) (22), and a score ≥4 on the SSI, which is considered a clinically significant cutoff for suicidal ideation (18, 23, 24). A prospective study of 6,891 psychiatric outpatients (23) found that a baseline SSI score >2 predicted suicide during up to 20 years of follow-up, adjusting for other risk factors.

Eligible patients had a voluntary admission to an inpatient research unit at New York State Psychiatric Institute, and patients were discharged when assessed as stable and not an imminent safety risk. Exclusion criteria included unstable medical or neurological illness, significant electrocardiographic abnormality, pregnancy or lactation, current psychosis, history of ketamine abuse or dependence, other drug or alcohol dependence within the past 6 months, suicidal ideation due to binge substance use or withdrawal, prior ineffective trial of or adverse reaction to ketamine or midazolam, daily opioid use greater than 20 mg of oxycodone or equivalent during the 3 days before infusion, a score <25 on the Mini-Mental State Examination (25) for persons >60 years old, lack of capacity to consent, and inadequate understanding of English. There was no exclusion for body mass index or weight. Participants were allowed to continue on stable dosages of current psychiatric medications, except that benzodiazepines could not be taken within 24 hours before the infusion. Recruitment was conducted via Internet and local media advertisements and clinician referral. The protocol was approved by the Institutional Review Board of the New York State Psychiatric Institute, and written informed consent was obtained from all participants.

### Intervention

Participants were randomly assigned to receive intravenous racemic ketamine hydrochloride at 0.5 mg/kg or midazolam at 0.02 mg/kg, in 100 mL normal saline infused over 40 minutes. To minimize additive sedation, we used a lower midazolam dose than the 0.045 mg/kg dose used in studies where participants underwent a washout of concomitant psychotropic medications (21). In addition to safety concerns, excessive sedation could compromise blinding, since subanesthetic ketamine does not tend to induce sleep and can be stimulating. Blood pressure, blood oxygen saturation, heart rate, and respiratory rate were monitored every 5 minutes during the infusion. A psychiatrist certified in advanced cardiac life support administered the infusion, and an anesthesiologist was available for consultation by telephone. After assessments at 24 hours, participants received optimized standard clinical pharmacological treatment for 6 months, with weekly research ratings for the first 6 weeks in an uncontrolled follow-up observation.

### Outcome and Measures

Raters were doctoral- or master's-level psychologists. Diagnoses, including substance abuse or dependence, were made using the Structured Clinical Interviews for DSM-IV axis I and II disorders (SCID I and II) (26, 27) in a weekly consensus conference of research psychologists and psychiatrists. Suicidal ideation due to binge substance abuse was assessed by clinical history, and past antidepressant trials and current medications were inventoried with our baseline clinical-demographic form, which surveys a range of variables not captured by other instruments. Videotaped assessments were used for weekly reliability monitoring. Intraclass correlation coefficients for key clinical ratings were 0.94 for the SCID I, 0.96 for the HAM-D, and 0.98 for the SSI.

The clinician-rated SSI assessed current severity of suicidal ideation with 19 items scaled from 0 (least severe) to 2 (most severe) (20). Items probe wish to die, passive and active suicide attempt thoughts, duration and frequency of ideation, sense of control, deterrents, and preparatory behavior for an attempt (23). The SSI has moderately high internal consistency and good concurrent and discriminant validity (28). It was administered at screening, at baseline within 24 hours before infusion, at 230 minutes after infusion, at 24 hours after infusion, and at weeks 1–6 of follow-up. For brevity we use "day 1" to refer to the 24-hour postinfusion assessment. Depressive symptoms were assessed with the 17- and 24-item HAM-D (22), the Beck Depression Inventory (BDI) (29), and the Profile of Mood States (POMS) (30). Anxiety was measured with a 5-point Likert scale asking patients to self-rate from 0 (not at all) to 4 (extremely anxious).

Adverse effects were measured with the Systematic Assessment for Treatment Emergent Events–General Inquiry (31), the Clinician-Administered Dissociative States Scale (CADSS; score range, 0–92) (32), and the positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS), which includes conceptual disorganization, grandiosity, hallucination, and delusions (subscale score range, 0–24) (33). Efficacy ratings and the CADSS and BPRS positive symptom subscale (at baseline, at 230 minutes, and at day 1) were collected by psychologist raters who were not present during the infusion. Administration of the immediate postinfusion CADSS and BPRS positive symptom subscale and all adverse effect ratings were done by the physician who supervised the infusion.

Participants were asked at 3 and 6 months about poststudy ketamine use.

### Randomization and Blinding

A permuted, blocked design was used, with 1:1 assignment between treatments and block size randomized between 4 and 6 with equal probability. Randomization was stratified on two baseline factors: whether the patient was taking psychiatric medication (yes/no), and whether the patient's baseline SSI score was <8 or ≥8. The latter stratification factor, based on median baseline SSI score in our previous clinical trial in suicidal depressed patients (34), was to increase the likelihood that the treatment groups would be similar in baseline SSI severity.

Patients and study personnel were blind to treatment. To assess the adequacy of the blind, patients and raters were asked in the day 1 ratings whether they thought the infusion was midazolam or ketamine or if they had "no idea." Treatment response was defined as a day 1 SSI score ≥50% below baseline. We defined remission more stringently as a day 1 SSI score ≥50% below baseline and less than the eligibility threshold of 4. A remission level of improvement was defined to ensure that the midazolam group would have every opportunity to receive ketamine. Nonremitters were unblinded, and those who had received midazolam were offered an open ketamine infusion, usually the following day. Preexisting medications were held constant from preinfusion baseline until completion of day 1 ratings after the final infusion. Remitters remained blind and received a letter from the pharmacy after completing follow-up treatment informing them of their randomized drug.

### Statistical Analysis

The study was powered assuming a two-sided test of the group effect at an alpha level of 0.05. Effect size estimates, standard deviations, and correlations were based on previous reports (15, 34). A planned sample size of 70, assigned 1:1 to each treatment, provided ≥80% power to detect a 25% reduction in SSI score over 24 hours in the ketamine group and none in the midazolam group. The actual sample size is 80.

Histograms and residual plots of outcomes were inspected for normality. Group comparisons on baseline characteristics were made using the chi-square test or Fisher's exact test as appropriate for categorical variables and the two-sample t test for continuous variables. The modified intent-to-treat analysis included all randomized participants who were assessed for the primary outcome measure, SSI score at day 1 (N=80). The primary hypothesis was tested using an analysis of covariance (ANCOVA) model of the change in SSI score from baseline to day 1, with treatment group and baseline SSI score as the predictors. Randomization stratum (taking or not taking psychiatric medication), by definition not associated with treatment group, was not associated with the primary outcome measure (p=0.84) and so was not included in the model. Effect size calculations used Cohen's d and number needed to treat. Cohen's d was calculated as the difference in mean group change divided by the standard deviation of baseline values for the whole sample.

Secondary analyses used ANCOVA models to test for differential change between groups in SSI score and depressive symptom ratings (the 17- and 24-item HAM-D, the BDI, and the POMS) from baseline to 230 minutes and in depressive symptom ratings from baseline to day 1. Response was compared by drug using logistic regression. Linear regression was used in an exploratory analysis of treatment effects on the suicidal desire/ideation and planning subscales of the SSI (35). Mediation analyses were performed using a structural equation modeling framework in Mplus, version 7 (36). Paired t tests were used to determine whether the participants assigned to midazolam who received an open ketamine treatment after day 1 (N=35) experienced significant subsequent change in SSI or HAM-D scores. For the longitudinal data analysis, mixed-effects linear regression of SSI and 17-item HAM-D scores over the 6-week follow-up period was used to test for significant change from baseline across the entire sample, regardless of treatment group, since 35 of 40 patients in the midazolam group were nonremitters and received a subsequent open ketamine infusion. Safety analyses included univariate tests comparing infusion-related cardiorespiratory effects, adverse events, and postinfusion severity of positive, dissociative, and anxiety symptom ratings between groups. SAS, version 9.4 (SAS Institute, Cary, N.C.), and SPSS, version 23 (IBM, Armonk, N.Y.), were used for the analyses.

## RESULTS

### Participants

Enrollment was conducted from November 2012 to December 2016, and data collection was completed in February 2017. (A CONSORT chart is available in the data supplement that accompanies the online edition of this article; see Figure S1.) Of the 82 participants who underwent randomized assignment to treatment, two (one in each group) withdrew before the day 1 assessment and were excluded from the analysis. The groups did not differ significantly in baseline characteristics except for frequency of borderline personality disorder (Table 1). No participant met SCID criteria for current substance abuse; two participants had substance abuse in partial remission (alcohol abuse in one case, cannabis abuse in the other). At baseline, participants reported a lifetime medication history of, on average, four (SD=2.4) antidepressants and two (SD=1.2) antidepressant classes; 45 participants (56%) had previously taken a mood stabilizer, 49 (61%) a second-generation antipsychotic, 32 (40%) a stimulant, 51 (64%) a benzodiazepine, 25 (31%) other anxiolytics, and 27 (34%) sleep medications. These frequencies did not differ significantly between groups. Three participants had never taken any psychiatric medications, including any antidepressants, and 22 participants had received ECT. Frequencies of current medication classes at baseline were as follows: antidepressants, N=43; anticonvulsants, N=21;

**TABLE 1. Baseline Characteristics of Patients With Major Depressive Disorder and Clinically Significant Suicidal Ideation Treated With a Subanesthetic Infusion of Ketamine or Midazolam[a]**

| Variable[b] | Midazolam Group (N=40) | | Ketamine Group (N=40) | |
|---|---|---|---|---|
| | N | % | N | % |
| Female | 26 | 65.0 | 22 | 55.0 |
| White race | 39 | 97.5 | 35 | 87.5 |
| Hispanic ethnicity | 1 | 2.5 | 0 | 0.0 |
| Married | 7 | 18.0 | 7 | 18.0 |
| Currently employed | 15 | 37.5 | 10 | 25.0 |
| Prior psychiatric hospitalization | 29 | 73.0 | 27 | 68.0 |
| Prior suicide attempt[c] | 22 | 55.0 | 17 | 42.5 |
| Personality disorder[d] | 13 | 36.0 | 16 | 41.0 |
| Borderline personality disorder[d,e] | 3 | 8.0 | 11 | 28.0 |
| History of substance use disorder | 9 | 22.5 | 11 | 27.5 |
| Mood disorder in first-degree relative | 23 | 57.5 | 24 | 60.0 |
| Suicide or attempt in first-degree relative | 3 | 7.5 | 2 | 5.0 |
| | Mean | SD | Mean | SD |
| Age (years) | 40.7 | 13.1 | 38.4 | 13.2 |
| Scale for Suicidal Ideation score | 15.7 | 6.9 | 14.3 | 6.3 |
| Hamilton Depression Rating Scale (17-item) score | 22.6 | 3.9 | 22.2 | 4.6 |
| Beck Depression Inventory score | 33.9 | 8.1 | 31.8 | 8.1 |
| Years of education | 15.9 | 2.4 | 15.9 | 2.8 |
| | Median | Range | Median | Range |
| Duration of current episode (weeks) | 50 | 2–2,860 | 60 | 8–572 |
| Age at onset of first major depressive episode (years) | 14 | 5–45 | 16 | 6–51 |
| Lifetime number of major depressive episodes | 3 | 1 to "too many to count" | 4.5 | 1 to "too many to count" |
| Body mass index | 27.8 | 17.2–51.5 | 25.3 | 19.9–46.7 |

[a] The data are based on the modified intent-to-treat sample. Ns for the measures reported as means or medians range from 35 to 40 for each group. There were no significant differences between groups except as otherwise noted.
[b] Assessed with the study's research Baseline Clinical-Demographic form unless otherwise noted.
[c] Assessed with the Columbia Suicide History Interview (48).
[d] Assessed with the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (27).
[e] Significant difference between groups (p=0.03).

antipsychotics, N=14; benzodiazepines, N=27; and lithium, N=2 (see Table S1 in the data supplement). These frequencies did not differ significantly between groups.

### Primary Outcome Measure: Day 1 Suicidal Ideation

The average SSI score at day 1 was 4.96 points lower in the ketamine group compared with the midazolam group (estimate=4.96, 95% CI=2.33, 7.59; t=3.75, df=77, p<0.001) (Figure 1). Cohen's d for the difference in mean group change was 0.75, a medium effect size. Including baseline borderline personality disorder diagnosis as a covariate had little effect on the results (estimate=4.76, 95% CI=1.89, 7.63; t=3.30, df=71, p=0.002).

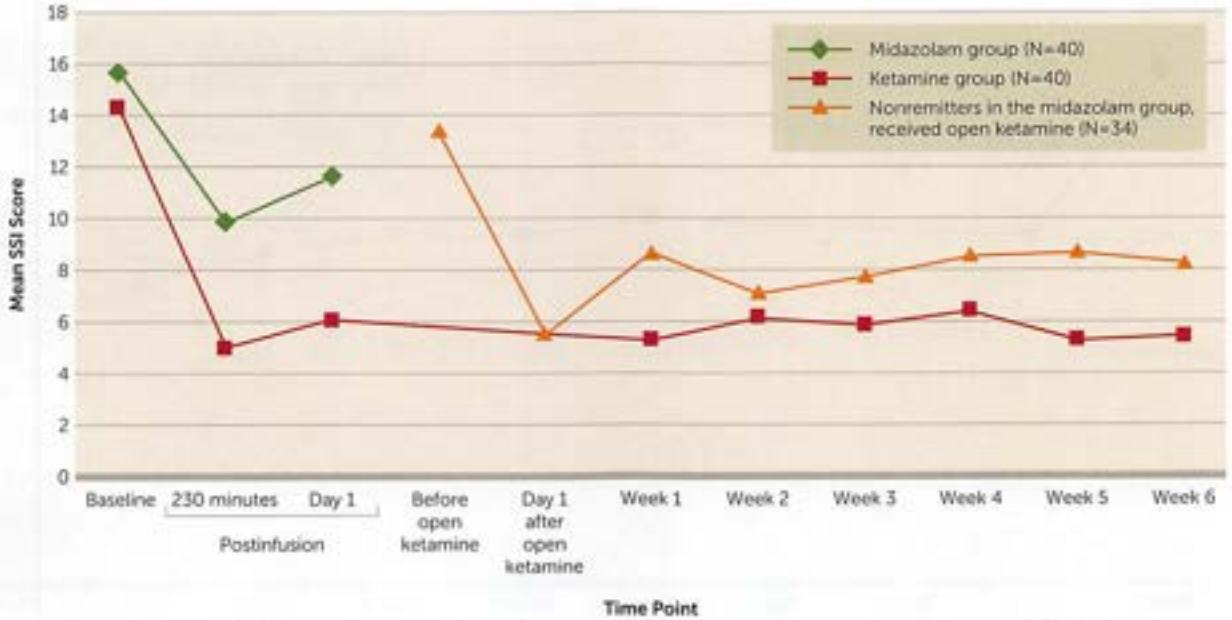
### Secondary Outcome Measures

*Suicidal ideation.* The proportion of responders on the SSI at day 1 was 55% in the ketamine group and 30% in the midazolam group (odds ratio=2.85, 95% CI=1.14, 7.15; p=0.024; number needed to treat=4.00). The decrease in suicidal ideation at 230 minutes after the infusion was greater in the ketamine group compared with the midazolam group (mean reduction, 9.69 points and 5.41 points, respectively; differential drug effect estimate=4.29 points, 95% CI=1.73, 6.84; t=3.34, df=77, p=0.001). Exploratory analysis showed that the odds of an SSI score of 0 at day 1 were 2.8-fold greater for the ketamine group, although the difference fell short of statistical significance (p=0.088). Among those who continued to have suicidal ideation on day 1, we found no differential drug effect on the SSI planning subscale but greater improvement in the ketamine group in the suicidal desire and ideation subscale (35) (estimate=1.37, df=58, t=2.02, p=0.049).

Postinfusion worsening of SSI ratings at 230 minutes was observed in four patients in the midazolam group, and at day 1 in nine patients in the midazolam group and two in the ketamine group.

*Depressive symptoms.* The day 1 POMS total mood disturbance score showed greater improvement in the ketamine group compared with the midazolam group (estimate=21.19, 95% CI=2.95, 39.43; df=75, t=2.31, p=0.023), as did scores on the depression subscale (estimate=7.65, 95% CI=1.36, 13.94; df=75, t=2.42, p=0.018) and the fatigue subscale (estimate=4.12, 95% CI=0.73, 7.50; df=75, t=2.42, p=0.018). There was partial mediation (33.6%) of ketamine's effect on day 1 SSI score through its effect on POMS depression rating

**FIGURE 1. Change in Suicidal Ideation Over Time in Suicidal Patients With Major Depression Treated With a Subanesthetic Infusion of Ketamine or Midazolam[a]**




[a] The data are based on the modified intent-to-treat sample (N=40 per group). The primary outcome measure was score on the Scale for Suicidal Ideation (SSI) 24 hours after infusion (day 1); the reduction was greater for the ketamine group than for the midazolam group ($p<0.001$). SSI scores range from 0 to 38, with higher scores indicating greater severity. Remission was defined as an SSI score ≥50% below baseline at day 1 and less than the study eligibility threshold of 4. For nonremitters, the blind was broken and patients who were allocated to midazolam were offered an open ketamine infusion, usually the following day. Thirty-five midazolam nonremitters received an open ketamine infusion, and one withdrew from the study before the day 1 assessment.

(indirect path estimate=−1.62, SE=0.81, $p<0.050$; direct path estimate=−3.20, SE=1.12, p=0.005).

Ketamine showed advantages that fell short of statistical significance on the day 1 clinician-rated 17-item HAM-D (estimate=2.83 points, 95% CI=−0.12, 5.77; t=1.91, df=77, p=0.06), the 24-item HAM-D (estimate=3.54 points, 95% CI=−0.29, 7.36; t=1.84, df=77, p=0.07), and the self-rated BDI (estimate=4.66 points, 95% CI=−0.04, 9.36; t=1.98, df=69, p=0.05). The proportions of responders in the ketamine and midazolam groups, respectively, were as follows: on the 17-item HAM-D, 30% and 15% (odds ratio=2.43, 95% CI=0.81, 7.30; number needed to treat=6.67; p=0.11); on the 24-item HAM-D, 25% and 15% (odds ratio=1.89, 95% CI=0.61, 5.82; number needed to treat=10.00; p=0.26); on the BDI, 36% and 17% (odds ratio=2.83, 95% CI=0.93, 8.57; number needed to treat=5.14; p=0.06).

*Open ketamine infusion.* In the midazolam group, 35 participants did not meet the SSI remission criteria and received an open ketamine infusion (Figure 1). Day 1 ratings showed improvement from postmidazolam scores as follows: on the SSI, estimate=−7.85 (SD=6.58; df=33, t=−6.96, $p<0.001$); on the 17-item HAM-D, estimate=−7.26 (SD=6.93; df=33, t=−6.11, $p<0.001$); and on the 24-item HAM-D, estimate=−9.85 (SD=9.43; df=33, t=−6.09, $p<0.001$).

*Follow-up ratings for weeks 1–6.* Longitudinal analysis of the uncontrolled 6-week follow-up showed that clinical improvement after randomized and open ketamine treatment was generally maintained through 6 weeks of open, optimized clinical follow-up treatment with respect to SSI score and depression ratings (Figures 1 and 2; see also Tables S2 and S3 in the online data supplement).

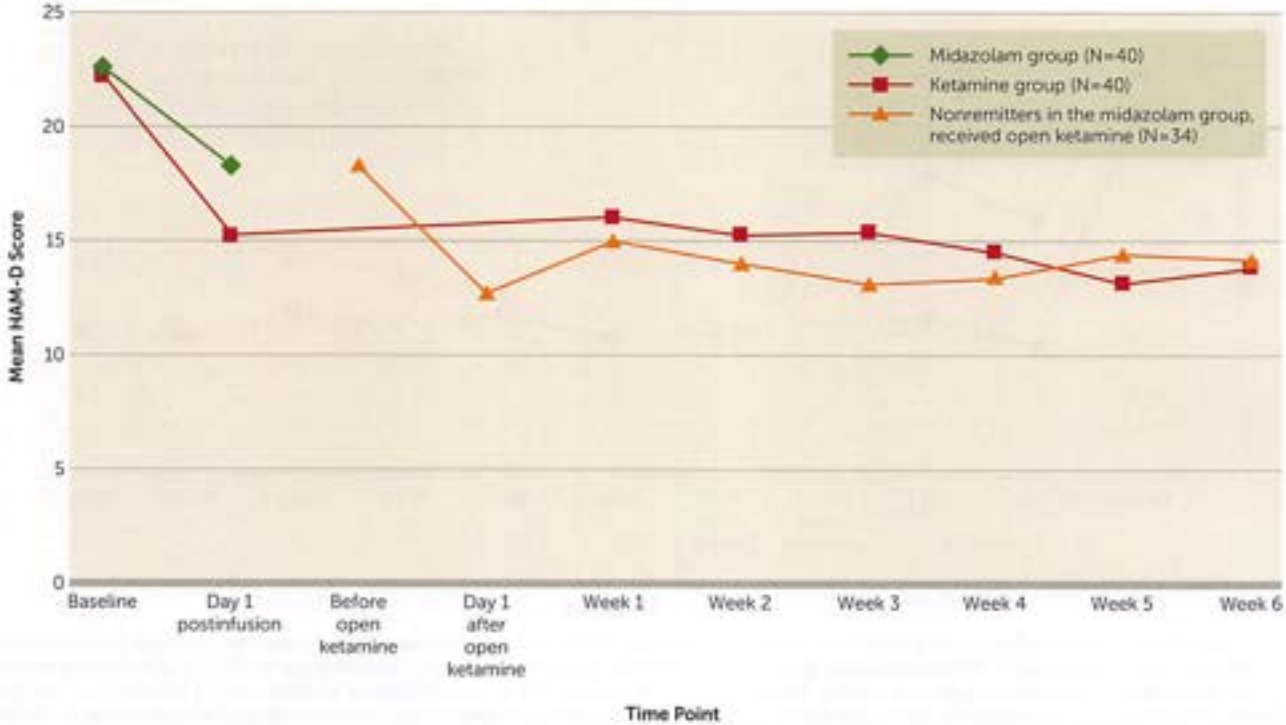
*Blinding.* On day 1, raters correctly guessed the blinded drug in 42% of midazolam and 44% of ketamine cases ($\chi^2$=0.02, df=1, p=0.895). Patients guessed correctly 55% of the time with both drugs ($\chi^2$=0.00, df=1, p=1.000).

## Safety Outcomes

*Cardiorespiratory effects.* Ketamine was associated with a mean transient increase in systolic blood pressure of 15.28 mmHg (SD=9.79), compared with 3.75 mmHg (SD=6.46) for midazolam (t=−6.22, df=78, $p<0.001$). A mean increase in diastolic blood pressure of 13.38 mmHg (SD=8.48) was observed with ketamine, compared with 4.03 mmHg (SD=5.50) with midazolam (t=−5.85, df=78, $p<0.001$). It took a mean of 5.28 minutes for blood pressure to return to baseline after ketamine, and 0 minutes after midazolam. Cardiorespiratory effects are summarized in Table S4 in the data supplement.

*Psychiatric and other adverse effects.* Baseline dissociative symptom scores and BPRS positive symptom subscale scores did not differ significantly between groups ($p>0.7$). CADSS scores were higher immediately after ketamine (mean=17.63, SD=13.55) than after midazolam (mean=0.88, SD=1.42)

**FIGURE 2. Change in Depressive Symptoms Over Time in Suicidal Patients With Major Depression Treated With a Subanesthetic Infusion of Ketamine or Midazolam[a]**




[a] The data are based on the modified intent-to-treat sample (N=40 per group). Score on the 17-item Hamilton Depression Rating Scale (HAM-D) 24 hours after infusion (day 1) was a secondary outcome measure. Remission was defined as a Scale for Suicidal Ideation score ≥50% below baseline at day 1 and less than the study eligibility threshold of 4. For nonremitters, the blind was broken and patients who were allocated to midazolam were offered an open ketamine infusion, usually the following day. The reduction in HAM-D score was greater in the ketamine group compared with the midazolam group, but the difference fell short of statistical significance (p=0.06).

(U=1475.50, p<0.001), but the groups did not differ significantly in CADSS score at 230 minutes (p=0.82) or at day 1 (p=0.83) (see Figure S2 in the data supplement). BPRS positive symptom subscale scores were higher immediately after ketamine treatment (mean=0.68, SD=1.80), whereas no patient had a score >0 after midazolam treatment (U=980.00, p=0.002); there were no significant group differences at 230 minutes (p=0.32) or at day 1 (p=0.63).

Participants in the midazolam group reported higher anxiety 230 minutes after infusion (mean=2.10, SD=1.34) than did those in the ketamine group (mean=1.40, SD=1.13) (estimate=2.68, 95% CI=1.15, 6.23; p=0.023), but there was no significant difference between groups at day 1 (p=0.497). Adverse effects, mostly physical, assessed with the Systematic Assessment for Treatment Emergent Events, are summarized in Table S5 in the online data supplement.

At the follow-up assessments for ketamine abuse, 68 (85%) participants were reached at 3 months and 62 (78%) at 6 months. None showed evidence of abuse, five (6%) reported receiving ketamine off-label in private clinics, and one had contemplated using some provided by a friend.

*Serious adverse events.* There were 10 serious adverse events requiring institutional review board report: two were for unrelated medical illness, one for sedative misuse without suicidal intent, four for suicide attempts (three after and one before study procedures), and three for inpatient admissions for increased suicidal ideation. No serious adverse event resulted in serious medical sequelae or institutional review board–required protocol modification. (Details are provided in Table S6 in the online data supplement.) No suicides occurred during the protocol. Two suicides occurred after the study, at 6 and 26 months, during treatment in the community, both by patients in the ketamine group, one of whom had been a remitter and the other a nonresponder.

## DISCUSSION

In major depression with clinically significant suicidal ideation, a single subanesthetic ketamine infusion, adjunctive to ongoing pharmacotherapy, was associated with a greater reduction in suicidal thoughts at day 1, the primary outcome measure, compared with midazolam control infusion. The adjusted mean difference of 4.96 points on the clinician-rated SSI, a Cohen's d of 0.75, and a number needed to treat of 4 for response represent a medium-sized effect. Adverse effects—mainly blood pressure increase and dissociative symptoms—were similar to those reported in other ketamine studies (37) and were mostly mild to moderate, and transient, typically resolving within minutes to hours after infusion. Improvement in suicidal ideation largely persisted during the

6-week period of uncontrolled observation, during which standard pharmacological treatments were also optimized.

To our knowledge, there is no established definition of a clinically meaningful reduction in score on a standard suicidal ideation scale. A prospective study (N=6,891) of patients with depressive disorders (23) found that a baseline SSI score >2 predicted suicide during up to 20 years of follow-up. In a prospective study of 562 inpatients (64% with a mood disorder) who endorsed suicidal thoughts (38), those who experienced a 50% reduction within 24 hours from a severe level (suicidal ideation "most of the time") had one-third the risk of subsequent self-harm events during a mean length of stay of 24 days, compared with those whose suicidal thoughts remained elevated. Trials during recent decades show that the average advantage for antidepressant drug compared with placebo was 2 to 4 points on measures such as the 17-item HAM-D (39). The United Kingdom's National Institute for Health and Care Excellence considers a standardized mean difference such as a Cohen's d value ≥0.5, or a between-group difference of ≥3 points on the HAM-D or the BDI, to be clinically significant (40). Together these data suggest that the advantage found in this study for reduction of suicidal ideation 24 hours after ketamine, compared with midazolam, is clinically meaningful.

Given concerns about ketamine's 1- to 2-week antidepressant effect in previous studies (11), it is notable that the improvement in suicidal ideation in this trial was largely maintained through the 6-week follow-up ratings. This may be partly explained by the fact that patients continued prior psychotropic medication, which was optimized after completion of day 1 postinfusion ratings. Our result is consistent with the Hu et al. trial (41), in which patients with major depression who were randomly assigned to receive a single ketamine infusion on day 1 of escitalopram therapy experienced a faster response compared with patients who received a saline control infusion, and the benefits were maintained for 4 weeks.

We found greater reductions in overall mood disturbance, depression, and fatigue, assessed with the POMS, on day 1 after ketamine compared with midazolam. The response rates we found for depression using the HAM-D and the BDI were surprisingly low compared with other randomized controlled ketamine trials (42). Contributing factors may include concurrent antidepressant and other psychiatric medications, the effect of hopelessness as a feature of suicidal states, and the possibility that our sample was not treatment resistant and may have been more prone to midazolam placebo response.

The fact that the differential drug effect on global mood and depression was strongest for the POMS and the BDI may be related partly to their emphasis on subjective experience of core depressive symptoms, which correlate more strongly with suicidal ideation than do other symptom types (43). A secondary analysis of adjunctive ketamine (N=14) found a reduction in suicidal ideation even when depression did not remit (17). Ketamine is mechanistically distinct from currently approved antidepressants, its therapeutic effects possibly involving rapid synapse formation (44). Our mediation model results suggest that its effects on depression and suicidal thoughts are at least partially independent.

The only other midazolam-controlled trial of adjunctive ketamine infusion using SSI score at day 1 as the primary outcome measure was a study of patients with mood and anxiety disorders (N=24) and a score ≥4 on the suicide item of the Montgomery-Åsberg Depression Rating Scale (MADRS) (19). Differences from our trial included mixed diagnoses, inpatient and outpatient settings, a higher midazolam dose (0.045 mg/kg), and use of the self-report SSI, which correlates >0.90 with the clinician-rated version that we used, although patients report higher scores than clinicians (45). The results did not show a differential treatment effect on the primary outcome measure, but a difference favoring ketamine was found at 24 hours on the MADRS suicide item and at 48 hours on the SSI, which was no longer significant at 72 hours. The study did not find a differential effect on global depression ratings or correlations between changes in SSI and total MADRS scores.

A midazolam-controlled ketamine trial (21) in treatment-resistant depression (N=73) found an 8-point advantage for ketamine on the primary outcome measure, MADRS score at day 1 (Cohen's d=0.81; odds ratio for response=2.2). A subsequent analysis reported an advantage at day 1 for ketamine in reduction of a suicidal ideation index comprising the self-report SSI (mean baseline score=6) and suicide items from two depression scales, which was fully mediated by reduction in MADRS score minus the suicide item (18).

We found stronger effects on suicidal ideation than on global depression compared with the latter trial (21), although both studies involved patients with moderate to severe baseline depression severity according to MADRS and HAM-D guidelines (46). Reasons for the difference may include our study design, in which we allowed patients to stay on their current, stable dosage of antidepressant medication instead of employing a medication washout during the week before the trial began. Fifty-four percent of our sample was taking antidepressant medication at baseline. Residual antidepressant effects from the concomitant medication in both treatment groups in our study may have diminished the antidepressant effect of ketamine. Another study difference was in the samples; the earlier study included patients with treatment-resistant depression, and our study included patients with clinically significant suicidal ideation.

Limitations of our study include the primary outcome measure of suicidal ideation as opposed to behavior. Suicide or attempts are more significant, but their low base rates, even in at-risk populations, mean that very large samples and long follow-up periods are required. Suicidal ideation is feasible and significant as an outcome measure, as clinicians assess it when evaluating need for hospitalization because it predicts suicide attempts (47) and suicide (23). Among patients in our study who had suicidal ideation at day 1, there was no differential drug effect on the SSI planning subscale, but greater improvement in the ketamine group on the suicidal desire and ideation subscale, which correlated with depression,

hopelessness, and past suicide attempt in a study by Witte et al. (35).

In our sample, there were more patients with borderline personality disorder in the ketamine group than in the midazolam group (28% compared with 8%). While there is no reason to think this would affect study infusion response in a particular direction, when it was included as a covariate it had little effect on the primary outcome measure. The higher rate of dissociative side effects with ketamine, found in other studies, makes midazolam an imperfect control (21), but differences in rates of correct guesses on the blinded infusion drug were not statistically significant, among raters or participants. Other limitations include open-label treatment during the week 1–6 follow-up ratings, during which standard pharmacological treatments were optimized, and the small percentages of Hispanic and nonwhite participants.

In summary, in this randomized trial in suicidal depressed patients, a single adjunctive subanesthetic ketamine infusion was associated with a clinically significant reduction in suicidal ideation at day 1 that was greater than with the midazolam control infusion. In the context of standard, optimized treatment after the ketamine infusion, this improvement appeared to persist for at least 6 weeks. The clinical applicability of our findings was improved with infusion administration by a psychiatrist and without a medication washout, as has been done in some studies (12, 13, 21). Research is needed to understand ketamine's mechanism of action and to investigate strategies and safety of longer-term treatment.

## AUTHOR AND ARTICLE INFORMATION

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Supported by NIMH grant R01 MH-096784 to Dr. Grunebaum.

The authors thank S. Ellis, B. Stanley, G. Blinn, A. Frawley, the New York State Psychiatric Institute 5-South unit staff, the Institutional Review Board, the Data and Safety Monitoring Board, the Biological Studies Unit, and Manny de la Nuez for their contributions, and all of the participants who volunteered their time and trust.

ClinicalTrials.gov identifier: NCT01700829.

Dr. Galfalvy's family owns stock in Illumina, Inc. Dr. Oquendo's family owns stock in Bristol-Myers Squibb. Drs. Burke, Oquendo, and Mann receive royalties for commercial use of the Columbia Suicide Severity Rating Scale. The other authors report no financial relationships with commercial interests.

Received June 12, 2017; revision received Aug. 23, 2017; accepted Sept. 18, 2017; published online Dec. 5, 2017.

## REFERENCES

1. Centers for Disease Control and Prevention (CDC): Fatal Injury Reports, National, Regional, and State, 1981–2015. Atlanta, CDC, Web-based Injury Statistics Query and Reporting System (WISQARS) https://webappa.cdc.gov/sasweb/ncipc/mortrate.html
2. American Psychiatric Association: Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors. Washington, DC, American Psychiatric Association, 2003. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/suicide.pdf
3. Gibbons RD, Brown CH, Hur K, et al: Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. Arch Gen Psychiatry 2012; 69:580–587
4. Meltzer HY, Alphs L, Green AI, et al: Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry 2003; 60:82–91
5. Prudic J, Sackeim HA: Electroconvulsive therapy and suicide risk. J Clin Psychiatry 1999; 60(suppl 2):104–110
6. Cipriani A, Hawton K, Stockton S, et al: Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ 2013; 346:f3646
7. Trivedi MH, Rush AJ, Wisniewski SR, et al: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163:28–40
8. Mann JJ, Apter A, Bertolote J, et al: Suicide prevention strategies: a systematic review. JAMA 2005; 294:2064–2074
9. Zimmerman M, Mattia JI, Posternak MA: Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? Am J Psychiatry 2002; 159:469–473
10. Nock MK, Hwang I, Sampson NA, et al: Mental disorders, comorbidity, and suicidal behavior: results from the National Comorbidity Survey Replication. Mol Psychiatry 2010; 15:868–876
11. Newport DJ, Carpenter LL, McDonald WM, et al: Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry 2015; 172:950–966
12. Berman RM, Cappiello A, Anand A, et al: Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000; 47:351–354
13. Zarate CA Jr, Singh JB, Carlson PJ, et al: A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006; 63:856–864
14. Kudoh A, Takahira Y, Katagai H, et al: Small-dose ketamine improves the postoperative state of depressed patients. Anesth Analg 2002; 95:114–118
15. Price RB, Nock MK, Charney DS, et al: Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry 2009; 66:522–526
16. DiazGranados N, Ibrahim LA, Brutsche NE, et al: Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry 2010; 71:1605–1611
17. Ionescu DF, Swee MB, Pavone KJ, et al: Rapid and sustained reductions in current suicidal ideation following repeated doses of intravenous ketamine: secondary analysis of an open-label study. J Clin Psychiatry 2016; 77:e719–e725
18. Price RB, Iosifescu DV, Murrough JW, et al: Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety 2014; 31:335–343
19. Murrough JW, Soleimani L, DeWilde KE, et al: Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol Med 2015; 45:3571–3580
20. Beck AT, Kovacs M, Weissman A: Assessment of suicidal intention: the Scale for Suicide Ideation. J Consult Clin Psychol 1979; 47:343–352
21. Murrough JW, Iosifescu DV, Chang LC, et al: Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 2013; 170:1134–1142
22. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
23. Brown GK, Beck AT, Steer RA, et al: Risk factors for suicide in psychiatric outpatients: a 20-year prospective study. J Consult Clin Psychol 2000; 68:371–377

24. Holi MM, Pelkonen M, Karlsson L, et al: Psychometric properties and clinical utility of the Scale for Suicidal Ideation (SSI) in adolescents. BMC Psychiatry 2005; 5:8
25. Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–198
26. First MB, Spitzer RL, Gibbon M, et al: Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). New York, New York State Psychiatric Institute, Biometrics Research Department, 1994
27. First MB, Spitzer RL, Gibbon M, et al: Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (Version 2.0). New York, New York State Psychiatric Institute, Biometrics Research Department, 1996
28. Beck AT, Brown GK, Steer RA: Psychometric characteristics of the Scale for Suicide Ideation with psychiatric outpatients. Behav Res Ther 1997; 35:1039–1046
29. Beck AT, Ward CH, Mendelson M, et al: An inventory for measuring depression. Arch Gen Psychiatry 1961; 4:561–571
30. McNair DM, Lorr M, Droppleman LF: Manual for the Profile of Mood States. San Diego, Educational and Industrial Testing Service, 1981
31. Levine J, Schooler NR: SAFTEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacol Bull 1986; 22:343–381
32. Bremner JD, Krystal JH, Putnam FW, et al: Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress 1998; 11:125–136
33. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10:799–812
34. Grunebaum MF, Ellis SP, Duan N, et al: Pilot randomized clinical trial of an SSRI vs bupropion: effects on suicidal behavior, ideation, and mood in major depression. Neuropsychopharmacology 2012; 37: 697–706
35. Witte TK, Joiner TE Jr, Brown GK, et al: Factors of suicide ideation and their relation to clinical and other indicators in older adults. J Affect Disord 2006; 94:165–172
36. Muthén LK, Muthén BO: Mplus User's Guide, 7th ed. Los Angeles, Muthén & Muthén, 2012
37. Sanacora G, Frye MA, McDonald W, et al: A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. JAMA Psychiatry 2017; 74:399–405
38. Restifo E, Kashyap S, Hooke GR, et al: Daily monitoring of temporal trajectories of suicidal ideation predict self-injury: a novel application of patient progress monitoring. Psychother Res 2015; 25:705–713
39. Thase ME: The small specific effects of antidepressants in clinical trials: what do they mean to psychiatrists? Curr Psychiatry Rep 2011; 13:476–482
40. National Institute for Health and Care Excellence: Depression in Adults: Recognition and Management (Clinical Guideline 90). London, National Institute for Health and Care Excellence, 2009
41. Hu YD, Xiang YT, Fang JX, et al: Single iv ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study. Psychol Med 2016; 46:623–635
42. Murrough JW, Abdallah CG, Mathew SJ: Targeting glutamate signalling in depression: progress and prospects. Nat Rev Drug Discov 2017; 16:472–486
43. Keilp JG, Grunebaum MF, Gorlyn M, et al: Suicidal ideation and the subjective aspects of depression. J Affect Disord 2012; 140:75–81
44. Duman RS, Aghajanian GK, Sanacora G, et al: Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat Med 2016; 22:238–249
45. Beck AT, Steer RA, Ranieri WF: Scale for Suicide Ideation: psychometric properties of a self-report version. J Clin Psychol 1988; 44: 499–505
46. Carmody TJ, Rush AJ, Bernstein I, et al: The Montgomery Asberg and the Hamilton ratings of depression: a comparison of measures. Eur Neuropsychopharmacol 2006; 16:601–611
47. Oquendo MA, Galfalvy HC, Russo S, et al: Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. Am J Psychiatry 2004; 161:1433–1441
48. Oquendo MA, Halberstam B, Mann JJ: Risk Factors for Suicidal Behavior: utility and limitations of research instruments, in Standardized Evaluation in Clinical Practice. Edited by First MB. Washington, DC, American Psychiatric Publishing, 2003, pp 103–130

# Association of Hormonal Contraception With Suicide Attempts and Suicides

Charlotte Wessel Skovlund, Ph.D., Lina Steinrud Mørch, Ph.D., Lars Vedel Kessing, D.M.Sc., Theis Lange, Ph.D., Øjvind Lidegaard, D.M.Sc.

**Objective:** The purpose of this study was to assess the relative risk of suicide attempt and suicide in users of hormonal contraception.

**Method:** The authors assessed associations between hormonal contraceptive use and suicide attempt and suicide in a nationwide prospective cohort study of all women in Denmark who had no psychiatric diagnoses, antidepressant use, or hormonal contraceptive use before age 15 and who turned 15 during the study period, which extended from 1996 through 2013. Nationwide registers provided individually updated information about use of hormonal contraception, suicide attempt, suicide, and potential confounding variables. Psychiatric diagnoses or antidepressant use during the study period were considered potential mediators between hormonal contraceptive use and risk of suicide attempt. Adjusted hazard ratios for suicide attempt and suicide were estimated for users of hormonal contraception as compared with those who never used hormonal contraception.

**Results:** Among nearly half a million women followed on average for 8.3 years (3.9 million person-years) with a mean age of 21 years, 6,999 first suicide attempts and 71 suicides were identified. Compared with women who never used hormonal contraceptives, the relative risk among current and recent users was 1.97 (95% CI=1.85–2.10) for suicide attempt and 3.08 (95% CI=1.34–7.08) for suicide. Risk estimates for suicide attempt were 1.91 (95% CI=1.79–2.03) for oral combined products, 2.29 (95% CI=1.77–2.95) for oral progestin-only products, 2.58 (95% CI=2.06–3.22) for vaginal ring, and 3.28 (95% CI=2.08–5.16) for patch. The association between hormonal contraceptive use and a first suicide attempt peaked after 2 months of use.

**Conclusions:** Use of hormonal contraception was positively associated with subsequent suicide attempt and suicide. Adolescent women experienced the highest relative risk.

*Am J Psychiatry 2018; 175:336–342; doi: 10.1176/appi.ajp.2017.17060616*

Hormonal contraception is used worldwide by more than 100 million women to avoid unintended pregnancies and to alleviate menstrual pain, heavy bleeding, premenstrual syndrome, and acne. Use of hormonal contraception has been associated with depression and adverse mood effects (1, 2). Apart from the daily burden depression imposes, it also increases the risk of suicide and suicide attempt (3). We found no study assessing the association between hormonal contraceptive use and risk of suicide attempt. Five studies have assessed the association between use of hormonal contraception and risk of death, including death by suicide (4–8), and most of these studies found no statistically significant association. The study with the largest number of suicides, however, showed a statistically significant relative risk of suicide of 1.4 (95% CI=1.05–1.87) among users of oral contraceptives compared with never-users (see Table S1 in the data supplement that accompanies the online edition of this article). A limitation of the published studies is the inclusion of women over the age of 25, which on average is several years after they began using hormonal contraception. Because mood symptoms are a known reason for cessation of hormonal contraceptive use (9–11), the inclusion of women several years after they started using hormonal contraceptives is likely to cause a selection of those women who can tolerate hormonal contraception, resulting in an underestimation of any potential association between hormonal contraceptive use and risk of suicide.

In a nationwide prospective cohort study (1), we recently found an association between hormonal contraception and depression, and the association was most pronounced among adolescent women. Adolescence is a period characterized by endogenous sex hormone changes and changing external cultural and social demands, which are likely to enhance the influence of any additional factor that might cause mood disturbances, such as use of hormonal contraception.

In this study, we followed a complete national cohort of women from age 15, before their first use of hormonal contraceptives, to assess their daily use of hormonal

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