Effects of Ketamine Versus Midazolam on Neurocognition at 24 Hours in Depressed Patients With Suicidal Ideation

John G. Keilp, PhD[a,b,*]; Sean P. Madden, MS[a,b]; Julia E. Marver, BA[a,b]; Abigail Frawley, PhD[a,b]; Ainsley K. Burke, PhD[a,b]; Mohammad M. Herzallah, PhD[c,d]; Mark Gluck, PhD[c]; J. John Mann, MD[a,b]; and Michael F. Grunebaum, MD[a,b]

ABSTRACT

Objective: Subanesthetic ketamine rapidly reduces depressive symptoms and suicidal ideation in some depressed patients. Its effects on neurocognitive functioning in such individuals with significant suicidal ideation is not well understood, even though certain neurocognitive deficits are associated with suicide behavior beyond clinical symptoms.

Methods: In this study, depressed patients with clinically significant suicidal ideation (n = 78) underwent neuropsychological testing before and 1 day after double-blind treatment with intravenous ketamine (n = 39) or midazolam (n = 39). A subgroup randomized to midazolam whose ideation did not remit after initial infusion received open ketamine and additional neurocognitive testing a day after this treatment. The primary outcome was change in performance on this neurocognitive battery. The study was conducted between November 2012 and January 2017.

Results: Blinded ketamine produced rapid improvement in suicidal ideation and mood in comparison to midazolam, as we had reported previously. Ketamine, relative to midazolam, was also associated with specific improvement in reaction time (Choice RT) and interference processing/cognitive control (computerized Stroop task)—the latter a measure that has been associated with past suicide attempt in depression. In midazolam nonremitters later treated with open ketamine and retested, reaction time and interference processing/cognitive control also improved relative to both of their prior assessments. Neurocognitive improvement, however, was not correlated with changes in depression, suicidal thinking, or general mood.

Conclusions: Overall, ketamine was found to have a positive therapeutic effect on neurocognition 1 day after treatment on at least 1 measure associated with suicidal behavior in the context of depression. Results suggest additional independent therapeutic effects for ketamine in the treatment of depressed patients at risk for suicidal behavior.

Trial Registration: ClinicalTrials.gov identifier: NCT01700829

J Clin Psychiatry 2021;82(6):21m13921

To cite: Keilp JG, Madden SP, Marver JE, et al. Effects of ketamine versus midazolam on neurocognition at 24 hours in depressed patients with suicidal ideation. *J Clin Psychiatry.* 2021;82(6):21m13921.

To share: https://doi.org/10.4088/JCP.21m13921

[a]Department of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, New York, New York

[b]Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, New York

[c]Center for Molecular and Behavioral Neuroscience, Rutgers University—Newark, Newark, New Jersey

[d]Palestinian Neuroscience Initiative, Al-Quds University, Abu Dis, Israel

**Corresponding author:* John G. Keilp, PhD, Box 42, NYSPI, 1051 Riverside Dr, New York, NY 10032 (jgk13@cumc.columbia.edu).

Intravenous ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has robust therapeutic effects on both depression and suicidal ideation within hours to days in some depressed patients.[1–4] However, its impact on neurocognition, particularly aspects of neurocognition associated with suicidal behavior,[5–7] is not well understood.

The effects of ketamine on neurocognition within hours after administration are largely detrimental in healthy volunteers, including adverse effects on attention,[8] episodic memory,[9] working memory,[10,11] semantic processing and priming,[12,13] verbal fluency,[11] and executive function.[11] These effects are dose-dependent.[14,15] Deficits appear to resolve within days following ketamine administration in healthy individuals[9] and persist only with chronic ketamine use and abuse.[15,16]

There is evidence in depressed patients, however, that neurocognitive functioning improves within the first few days after infusion, after the resolution of any acute transitory, negative neurocognitive effects and during the period of peak antidepressant effect. Permoda-Osip and colleagues[17] observed improvement in performance on the Trail Making Test and a Stroop task 3 days after ketamine infusion in an open study. Murrough and colleagues[18] observed general cognitive improvement at 7 days after infusion in a randomized clinical trial comparing ketamine and midazolam for treatment of refractory depression, though improvement was not specific to either drug and uncorrelated with improvement in depressive symptoms. Zheng and colleagues[19] observed improvement in speed of processing and verbal learning 1 day after completion of a 12-day course of 6 intravenous infusions of ketamine that was mediated by improvement in depressive symptoms. Effects of ketamine infusion on neurocognition in depressed patients with moderate to severe suicidal ideation, however, are presently unknown.

This study reports neurocognitive results from a randomized trial of ketamine vs midazolam in a sample of depressed patients with clinically significant suicidal ideation. Clinical findings from this study have been reported previously.[1] The primary goal was to measure neurocognitive changes from baseline to 24 hours after treatment and to investigate relationships of these changes in neurocognitive performance to changes in depressive symptoms and suicidal thinking. We hypothesized that neurocognitive performance on a standard battery of tests would improve globally with effective treatment, given previous open-label[17] and controlled clinical trials,[18] and do so within a time period consistent with its clinical effects.

Clinical Points

- Ketamine has been found to reduce suicidal ideation in at-risk depressed patients, but its effects on neurocognition are not clear.
- Ketamine produced improvement in suicidal thinking, as well as improvement in measures of reaction time and interference processing/cognitive control, in both blinded and open phases of this study.
- Ketamine improved neurocognitive functioning associated with suicidal behavior, beyond its effects on suicidal thinking alone.

Secondarily, we examined correlations between neurocognitive performance and measures of clinical response. Previous studies have found an association between baseline cognitive slowing and therapeutic response to ketamine.[18,20] We hypothesized that performance on measures of reaction time, processing speed, and timed language fluency would correlate with clinical response. Changes in neurocognitive performance were also examined in relation to clinical response.

Third, a subset of those patients who (*a*) initially received blinded midazolam, (*b*) did not show a predefined remission of suicidal thoughts, and (*c*) chose to receive open-label ketamine (per protocol) were assessed a third time, 1 day after infusion. This assessment was introduced later in the study (on the last 60% of the sample) and was done to determine if neurocognitive functions affected by ketamine during the blinded infusion were similarly affected after open ketamine in those who initially received blinded midazolam and failed to show a clinical response. If these patients did not also show an improvement in neurocognitive performance after midazolam, later administration of ketamine might augment any changes in neurocognitive performance, consistent with the initial effects of the blinded ketamine administration.

METHODS

Subjects

Participants were 78 individuals with major depressive disorder and clinically significant suicidal ideation (out of 80 participants in the full clinical trial), as described in our clinical efficacy paper.[1] Two subjects from the full trial sample were dropped for neuropsychological analyses, one who spoke limited English and could not be tested and another who was not cooperative with the testing. Characteristics of participants are presented in Table 1. Registration for the full clinical trial may be found at ClinicalTrials.gov (NCT01700829). The study was approved by the New York State Psychiatric Institute Institutional Review Board, and all participants signed informed consent.

Instruments

Clinical response measures included the 24-item Hamilton Depression Rating Scale (HDRS) and Beck Scale for Suicidal Ideation (SSI).[1] The Profile of Mood States (POMS) was administered at the time of each of the neuropsychological assessments.

Neuropsychological measures assessed 10 core functions: reaction time (computerized 4 button Choice Reaction Time task[21]), psychomotor speed (Wechsler Adult Intelligence Scale—III [WAIS-III] Digit Symbol[22] subtest, a timed paper-and-pencil transcription task), attention (computerized Continuous Performance Test [CPT], Identical Pairs version[23]; 4-digits fast condition, identifying rapidly presented sequential pairs of 4-digit number strings), cognitive control/interference processing (computerized Stroop Task[21,24]), immediate memory (Buschke Selective Reminding Test [SRT], Total Immediate Recall[25] for a 12-item word list, over 12 trials), delayed memory (Buschke SRT, Delayed Recall[25] of word list at 30 minutes), working memory/reasoning speed (computerized A Not B Timed Reasoning Task,[21] rapidly solving syllogisms based on letter order), letter (phonemic) fluency (Controlled Oral Word Association Test, Letters,[26] generating words beginning with specific letters with a minute), category (semantic) fluency (Controlled Oral Word Association Test, Animal naming,[26] generating as many animals as possible within 1 minute), and inhibitory control (computerized Go–No Go Task,[21] a computerized bimodal matching [auditory tone and location on screen], target identification task). The battery was designed to assess processing speed, attention, memory, concentration, language skills, and impulse control—all of which may be affected by depression and/or suicide risk[5,6]—before and after treatment. Primary outcome measures for each task are listed in Table 2. Alternate forms of Digit Symbol, CPT, Buschke SRT, and Letter Fluency were used in repeated assessments to reduce practice effects. Choice Reaction Time and Go–No Go measures used randomized and counterbalanced item order within each administration. Scores were converted to age, sex, and/or education adjusted *z* scores based on published normative data or archived normative data from our laboratory,[21] consistent with prior publications.[5,6,27] Conversion of performance measures to a common *z* score metric allowed for the use of all neuropsychological measures in an omnibus analysis and for direct comparison of changes across tasks in *z*-score units.

Procedures

Participants were recruited by advertisement and clinician referral. All met criteria for current *DSM-5* major depressive disorder, with a minimum 17-item HDRS score ≥ 16 and SSI score ≥ 4—a clinically significant cutoff. All participants were admitted to an inpatient research unit at the New York State Psychiatric Institute for acute treatment and discharged when judged not an imminent safety risk. Exclusion criteria were described previously.[1] Current psychiatric medications were continued at stable doses with the exception of benzodiazepines, which were discontinued at least 24 hours prior to infusion and neuropsychological testing.

Participants, raters, and physicians were blind to randomization to 0.5 mg/kg racemic ketamine or 0.02 mg/

kg midazolam iv infusion. Blood pressure, pulse oxygenation saturation, and heart and respiratory rates were monitored continuously during the 40-minute infusion by a study psychiatrist.

Baseline neurocognitive assessment was completed 1–3 days prior to blinded infusion (referred to below as day minus-1), and participants were reassessed approximately 24 hours after this infusion (day 1; infusion day designated as day 0).

To provide all patients a chance to receive ketamine, nonremitters at day 1 after blinded infusion (remission defined as a decline in SSI of at least 50% below baseline *and* below the eligibility cutoff of 4) had their blind broken. Those who had received midazolam were offered an open ketamine infusion the next day. In the full clinical trial, a total of 35 patients who had not responded to midazolam received this open ketamine infusion. Because the neuropsychological assessment after open ketamine was not begun until approximately 40% of the sample had been recruited, 22 subjects were available for this third neuropsychological assessment; 21 completed the assessment.

The study was conducted between November 2012 and January 2017.

Statistical Analyses

Baseline clinical and demographic data were compared between patients randomized to midazolam or ketamine via *t* test for continuous variables or χ^2 for categorical variables.

Treatment-related changes in depression severity (HDRS), suicidal ideation (SSI), and mood (POMS) were compared in repeated measures analyses of variance.

The primary analysis of neurocognitive performance was an omnibus comparison of performance across the full neuropsychological battery, in the two drug assignment groups, from baseline (day minus-1) to the day after the blinded infusion (day 1). Analysis was undertaken via a general linear model, with main effects for assessment point (baseline vs day 1), drug assignment (midazolam vs ketamine), and test (10 levels, corresponding to the primary outcome measure for each test) and all interactions. Following this omnibus analysis, significant main effects and interactions were examined in univariate comparisons of individual tests, across assessment point and drug assignment. Analyses were performed in a hierarchical fashion, with individual test comparisons uncorrected for multiple comparisons if omnibus analysis including all test measures was significant.

Correlations were then computed between (*a*) baseline neuropsychological test performance and change in primary clinical outcome measures, including HDRS, SSI, and POMS total score, and (*b*) change in neuropsychological test performance and the change in these primary clinical outcome measures.

For midazolam nonremitters who received open ketamine and completed the third neuropsychological assessment, performance was compared across 3 time points (day minus-1 baseline, day 1 post–blinded infusion, and day 3 post–open ketamine). A significant omnibus effect for assessment point (3 levels) or an assessment point × test interaction led to follow-up univariate comparisons of individual tests. A significant univariate effect for assessment point in univariate comparisons was then followed by pairwise post hoc comparison of each assessment day. The pairwise difference in performance between the post–blinded infusion day (day 1) and the post–open ketamine day (day 3) was the critical planned pairwise comparison, as it reflected change after open ketamine accounting for any practice effect after the blinded midazolam infusion.

RESULTS

Baseline Characteristics

Treatment groups were comparable at baseline in demographics, clinical characteristics, and concomitant medications (Table 1). Both had an average estimated intelligence in the superior range (≥ 90th percentile of population).

Clinical Changes After Blinded Infusion

For those receiving neurocognitive assessment, HDRS score improved in both treatment groups (assessment point effect, $F_{1, 76} = 63.27$, $P < .001$) but did not significantly favor ketamine (assessment point × drug interaction, $F_{1, 76} = 2.91$, $P = .092$; see Table 2). SSI improved in both groups ($F_{1, 76} = 63.10$, $P < .001$), but to a greater degree with ketamine compared to midazolam ($F_{1, 76} = 7.31$, $P = .008$). POMS scores obtained at the time of neuropsychological testing also improved in both groups ($F_{1, 74} = 86.04$, $P < .001$), but more so with ketamine ($F_{1, 74} = 9.91$, $P = .002$).

Neurocognitive Changes After Blinded Infusion

Omnibus analysis of all neuropsychological test scores revealed a significant effect of assessment point ($F_{1, 76} = 15.83$, $P < .001$), a marginal assessment point × drug interaction ($F_{1, 76} = 3.58$, $P = .062$), and a significant assessment point × drug × test interaction ($F_{9, 684} = 2.75$, $P = .004$).

Performance on the battery overall improved regardless of drug assignment on day 1 (Figure 1). While favoring ketamine relative to midazolam at a trend level ($P = .062$), overall change was not uniform across the entire battery.

There was a significant interaction of assessment point × drug × test due to greater relative improvement with ketamine compared to midazolam on 3 tasks: Choice RT (assessment point × drug interaction, $F_{1, 75} = 4.21$, $P = .044$), Stroop Interference ($F_{1, 76} = 4.43$, $P = .039$), and Buschke Delayed Recall ($F_{1, 76} = 5.91$, $P = .017$). Choice RT and Stroop Interference improved after ketamine ($t_{37} = 3.85$, $P < .001$ for Choice RT; $t_{38} = 2.85$, $P = .007$ for Stroop), with no change after midazolam ($t_{38} = 0.82$, $P = .419$; $t_{38} = 0.28$, $P = .780$). However, for Buschke Delayed Recall, improvement after ketamine was nonsignificant ($t_{38} = 1.66$, $P = .106$), with a trend toward worsening after midazolam ($t_{38} = 1.80$, $P = .081$).

Including a covariate for baseline medication status (yes/no) did not alter the significant assessment point × drug × test interaction ($F_{9, 675} = 2.80$, $P = .003$).

Table 1. Demographic and Clinical Characteristics

Variable	Midazolam treated (n = 39) Mean	Midazolam treated (n = 39) SD	Ketamine treated (n = 39) Mean	Ketamine treated (n = 39) SD	*P* value
Age, y	39.6	13.0	37.2	12.9	.429
Education, y	15.7	2.4	16.1	1.9	.437
WAIS-III Vocabulary subtest	14.4	2.9	14.6	2.7	.687
BMI	29.1	8.6	26.6	5.6	.135
Age at onset of first episode of MDD, y	17.7	10.3	17.6	9.9	.969
Number of episodes of MDD	11.3 [median = 3]	18.3	17.2 [median = 5]	20.8	.178
Duration of current episode of MDD, wk	354.8 [median = 52]	622.0	120.4 [median = 60]	152.6	.351
Rating scale scores (baseline)					
HDRS-24	30.0	5.9	29.1	5.9	.494
SSI	15.4	6.7	14.4	6.4	.503
POMS	110.6	38.5	107.3	33.0	.687
	n	%	n	%	
Sex, female	25	64.1	22	56.4	.488
Native language					
English	39	100.0	37	94.9	.152
Race					
European-American	37	97.4	34	87.2	.128
Black or African-American	1	2.6	1	2.6	
Asian	0	0.0	4	10.3	
Ethnicity: Hispanic	2	5.1	0	0.0	.308
At least 1 prior hospitalization	28	71.8	26	66.7	.624
Concurrent medications					
None	12	30.8	12	30.8	…
Any medication	27	69.2	27	69.2	1.000
Antidepressants	22	56.4	20	51.3	.650
Anticonvulsants	9	23.1	10	25.6	.792
Antipsychotics	5	12.8	8	20.5	.362
Benzodiazepines	11	28.2	15	38.5	.337
Lithium	1	2.6	1	2.6	1.000
Suicide attempt history—past suicide attempt	21	53.8	17	43.6	.365
Psychopathology					
Any personality disorder	12	34.3	15	42.1	.492
Past history of substance abuse	8	20.5	7	17.9	.774

Abbreviations: BMI = body mass index, HDRS-24 = Hamilton Depression Rating Scale 24-item, MDD = major depressive disorder, POMS = Profile of Mood States, SSI = Scale for Suicide Ideation, WAIS-III = Wechsler Adult Intelligence Scale—III.

Table 2. Clinical Severity and Neurocognitive Performance Across Treatment Conditions and Assessment Time Points

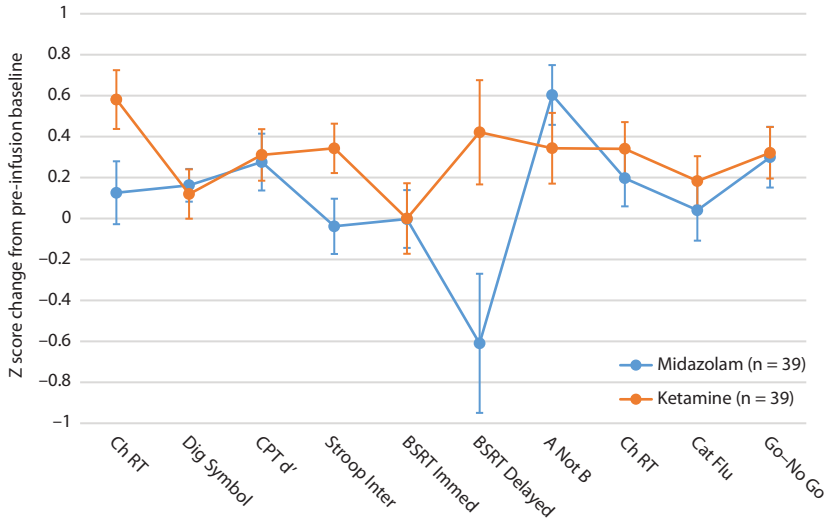
Test[a]	Midazolam baseline	Midazolam post-infusion	Ketamine baseline	Ketamine post-infusion	*P* value: Time effect	Drug effect	Time × drug
HDRS-24	30.0 (5.9)	23.8 (8.9)	29.1 (5.9)	19.5 (9.4)	< .001	.072	.092
SSI	15.4 (6.7)	11.4 (7.3)	14.4 (6.4)	6.1 (5.6)	< .001	.014	.008*
POMS Total	110.6 (38.5)	82.9 (45.5)	106.7 (33.2)	50.5 (42.6)	< .001	.027	.002*
Choice RT	−0.21 (1.16)	−0.09 (1.65)	−0.73 (1.50)	−0.17 (1.43)	.002	.337	.044*
Digit Symbol	−0.63 (1.05)	−0.47 (1.22)	−0.33 (1.01)	−0.22 (0.91)	.056	.226	.769
CPT d'	−0.15 (1.10)	0.19 (1.04)	0.03 (1.13)	0.33 (0.87)	.001	.467	.846
Stroop Interference	−0.23 (1.03)	−0.27 (1.04)	−0.31 (1.09)	0.04 (1.13)	.096	.604	.039*
Buschke SRT Immediate	−0.16 (1.41)	−0.16 (1.50)	−0.02 (1.28)	−0.02 (1.22)	.991	.639	.992
Buschke SRT Delayed	0.21 (1.94)	−0.40 (2.27)	0.02 (1.61)	0.44 (1.70)	.658	.385	.017*
A Not B RT	−0.35 (1.35)	0.24 (1.16)	−0.33 (1.10)	0.01 (1.11)	< .001	.672	.297
Letter Fluency	0.31 (1.16)	0.50 (1.14)	0.01 (1.09)	0.35 (0.87)	.006	.312	.450
Category Fluency	0.04 (0.94)	0.08 (1.14)	−0.12 (1.02)	0.06 (0.92)	.246	.685	.460
Go–No Go Commission Error	−0.42 (0.87)	−0.11 (1.11)	−0.23 (1.09)	0.06 (1.02)	.003	.395	.885

[a]HDRS-24, SSI, and POMS values reflect mean (SD) total scores. All neurocognitive test scores are *z* scores adjusted for age, sex, and/or education.

*$P < .05$ for time × drug interaction.

Abbreviations: Buschke SRT = Buschke Selective Reminding Test, CPT = Continuous Performance Test, HDRS-24 = Hamilton sDepression Rating Scale 24-item, POMS = Profile of Mood States, RT = reaction time.

Figure 1. Change at 24 Hours in Neuropsychological Test Performance After Blinded Infusion in Patients Randomized to Midazolam and Patients Randomized to Ketamine (Mean ± SEM)



Abbreviations: A Not B = A Not B Timed Reasoning Test response time score; BSRT Delayed = Buschke Selective Reminding Test Delayed Recall; BSRT Immed = Buschke Selective Reminding Test Immediate Recall; Cat Flu = Controlled Oral Word Association Test, words produced to category of animals; Ch RT = Choice Reaction Time; CPT d' = Continuous Performance Test d-prime; Dig Symbol = WAIS-III Digit Symbol subtest; Go–No Go = Go–No Go task commission error score; Lett Flu = Controlled Oral Word Association Test, words produced to specific letters; Stroop Inter = Stroop Interference score.

Table 3. Clinical Severity and Neurocognitive Performance of Midazolam Nonresponders Receiving Open Ketamine

				P value			
Test[a]	Baseline	Post–blind midazolam	Post–open ketamine	Time effect	Baseline vs post–blind midazolam	Baseline vs post–open ketamine	Post–blind midazolam vs post–open ketamine
HDRS-24	31.1 (6.3)	25.1 (7.2)	18.3 (9.6)	<.001	.002	<.001	.002*
SSI	18.2 (6.7)	13.9 (6.8)	6.9 (8.3)	<.001	.003	<.001	<.001*
POMS Total	116.4 (35.2)	95.1 (38.5)	57.6 (53.0)	<.001	<.001	<.001	<.001*
Choice RT	−0.33 (0.84)	−0.20 (0.67)	0.18 (0.73)	<.001	.332	<.001	.002*
Digit Symbol	−0.50 (0.99)	−0.28 (1.09)	0.01 (0.93)	<.001	.059	<.001	.016*
CPT d'	0.06 (1.29)	0.47 (1.14)	0.43 (1.10)	.078	.027	.161	.795
Stroop Interference	−0.15 (0.97)	−0.03 (0.98)	0.35 (0.81)	.008	.459	.005	.024*
Buschke SRT Immediate	−0.09 (1.64)	−0.12 (1.63)	0.02 (1.21)	.835	.857	.700	.609
Buschke SRT Delayed	0.18 (2.31)	−0.48 (2.43)	−0.78 (1.49)	.054	.100	.022	.460
A Not B RT	−0.54 (1.47)	0.31 (1.25)	0.42 (1.00)	<.001	<.001	<.001	.414
Letter Fluency	0.50 (1.31)	0.77 (1.30)	1.17 (1.38)	.002	.188	.002	.003*
Category Fluency	0.33 (1.02)	0.46 (1.14)	1.16 (1.17)	<.001	.566	.001	<.001*
Go–No Go Commission Error	−0.69 (0.70)	−0.25 (1.02)	0.06 (1.00)	.003	.058	.002	.127

[a]HDRS-24, SSI, and POMS values reflect mean (SD) total scores. All neurocognitive test scores are *z* scores adjusted for age, sex, and/or education.
*$P < .05$ for post–blind midazolam vs post–open ketamine.
Abbreviations: Buschke SRT = Buschke Selective Reminding Test, CPT = Continuous Performance Test, HDRS-24 = Hamilton Depression Rating Scale 24-item, POMS = Profile of Mood States, RT = reaction time.

Correlations With Clinical Response

Baseline Buschke SRT immediate performance correlated with the decline in HDRS score ($r = -0.39$, $P = .016$), but was only 1 of 30 correlations to fall below a nominal significance level of $P < .05$.

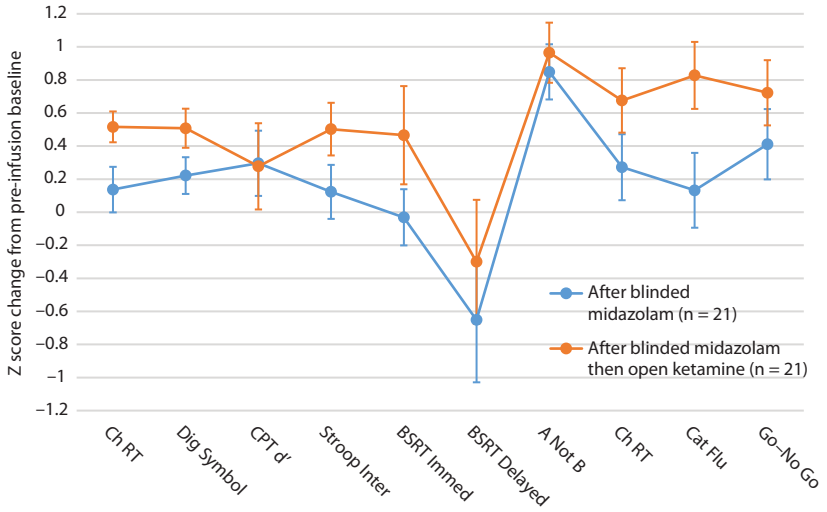
We did not find associations between slower baseline processing speed and change in the HDRS (Choice RT, $r = 0.09$, $P = .579$; Digit Symbol, $r = 0.10$, $P = .559$; Letter Fluency, $r = -0.07$, $P = .665$; Category Fluency, $r = -0.05$, $P = .766$), the SSI (respectively, $r = 0.10$, $P = .564$; $r = 0.06$, $P = .725$; $r = 0.02$, $P = .915$; $r = -0.07$, $P = .690$), or the POMS (respectively, $r = 0.08$, $P = .476$; $r = 0.05$, $P = .786$; $r = 0.05$, $P = .786$; $r = -0.08$, $P = .651$).

Change in neuropsychological performance after the blinded ketamine infusion (ketamine group only) was not significantly correlated with change on any clinical severity measure.

Clinical Changes After Open Ketamine

The subsample of midazolam nonremitters who received open ketamine and neuropsychological testing (n = 21) improved clinically on the HDRS ($F_{2, 40} = 19.94$, $P < .001$),

Figure 2. Change at 24 Hours in Neuropsychological Test Performance in Midazolam Nonresponders, After Initial Blinded Infusion, and Then Following an Open Ketamine Infusion (Mean ± SEM)



Abbreviations: A Not B = A Not B Timed Reasoning Test response time score; BSRT Delayed = Buschke Selective Reminding Test Delayed Recall; BSRT Immed = Buschke Selective Reminding Test Immediate Recall; Cat Flu = Controlled Oral Word Association Test, words produced to category of animals; Ch RT = Choice Reaction Time; CPT d' = Continuous Performance Test d-prime; Dig Symbol = WAIS-III Digit Symbol subtest; Go–No Go = Go–No Go task commission error score; Lett Flu = Controlled Oral Word Association Test, words produced to specific letters; Stroop Inter = Stroop Interference score.

the SSI ($F_{2, 40} = 20.59$, $P < .001$), and the POMS ($F_{2, 40} = 24.31$, $P < .001$; Table 3). All scores on day 3 reflected significant improvement relative to the post–blinded midazolam day 1 assessment (as well as to baseline).

Neurocognitive Changes After Open Ketamine

In the omnibus comparison of performance across all tests and all assessment days in this subgroup, there was overall improvement across the 3 assessment points ($F_{2, 40} = 18.40$, $P < .001$; see Figure 2). Average *z* score across all tests by day 3 (+0.30 ± 0.63) was significantly better than at either baseline (–0.22 ± 0.76, $P < .001$) or day 1 (–0.04 ± 0.80, $P < .001$).

Day 3 (post–open ketamine) performance was improved relative to both day 1 and baseline on Choice RT ($F_{2, 40} = 10.86$, $P < .001$), WAIS-III Digit Symbol ($F_{2, 40} = 10.18$, $P < .001$), Stroop Interference ($F_{2, 40} = 5.40$, $P = .008$), and both Letter ($F_{2, 40} = 7.50$, $P = .002$) and Category Fluency ($F_{2, 40} = 10.13$, $P < .001$). Performance on either the Buschke SRT Immediate or Delayed did not improve after open ketamine.

After open ketamine, improvements in neuropsychological test performance again were not correlated with clinical improvement.

DISCUSSION

In the context of a modest general improvement of cognition 24 hours after infusion in both treated groups, Choice Reaction Time and Stroop Interference, measures of response time and interference processing/cognitive control, improved selectively after subanesthetic ketamine in depressed patients with clinically significant suicidal ideation. Changes in these test scores were not correlated with one another ($r = –0.06$, $P = .72$), making it unlikely that improvement in cognitive control was simply a function of faster response times. These same tests also improved significantly within the same timeframe after open ketamine treatment in the subgroup of nonremitters to blinded midazolam, suggesting a ketamine-specific effect. Improvement of approximately a third of a standard deviation across all tests during this open phase is unlikely due to practice effects.

Relative drug-related changes favoring ketamine were observed on delayed memory performance after blinded infusion but appeared to reflect a decline in performance after midazolam rather than improvement after ketamine.

Neurocognitive performance generally improved 1 day after blinded infusion with either ketamine or midazolam, suggesting that most acute negative effects of these drugs had dissipated by this time—the exception being the marginal decline in memory retention 24 hours after midazolam, consistent with known acute benzodiazepine effects on memory[28,29] despite the relatively short half-life of midazolam.[30]

Consistent with other research, neurocognitive changes observed in our study were not associated with clinical changes after a single infusion,[18] although such correlations were found in at least 1 study that assessed neurocognition after multiple infusions and more extensive clinical change.[19]

The lack of association between clinical change and ketamine's effects on response time and interference processing/cognitive control suggests a potential additive feature of ketamine's antisuicide properties beyond its

effects on suicidal ideation itself. Measures of interference processing/attentional control, assessed here via a computerized Stroop, have been associated with past suicide attempt in our[5,6] and others' previous research[7]—though not with suicidal ideation[5,6] or even depression severity as assessed on standard rating scales.[31] Our finding of improvement in Stroop task performance after both blinded and open ketamine infusion is consistent with at least 1 other report assessing Stroop performance.[17] To the degree that such neuropsychological performance deficits constitute an independent risk factor for suicide attempt, improvement after ketamine may reduce suicide risk in ways other than reduction in ideation and depressive symptoms alone. It is unclear whether these neurocognitive effects might dissipate at the same rate as other global antidepressant effects.

The mechanisms underlying any specific neurocognitive effects are unclear. Li and colleagues[32] had demonstrated a link between subanesthetic ketamine administration and activation of the mTOR pathway, leading to rapid synapse formation and signaling in medial prefrontal cortex in rodents, suggesting the possibility of a link to effects on neurocognitive tasks sensitive to prefrontal function, though other animal studies suggest this effect may be occurring in other brain regions as well, such as hippocampus.[33,34] In human studies with substance abusing populations, ketamine reduces cravings for both cocaine[35] and alcohol[36] in clinical laboratory paradigms, an effect attributed in part to improved decision making. The role that improved cognitive control plays in such resistance to urges and cravings is unclear, though psychological theories of self-regulation place central importance on this cognitive capability for managing urges and cravings.[37–39]

We did not observe an association between baseline slowed processing speed and reduction in depression severity, overall mood disturbance, or suicidal ideation—as reported elsewhere.[18,20] This may be due in part to the high estimated intelligence of the sample, which we have previously found to attenuate patient/non-patient differences in processing speed.[40] Recruitment of such a sample may have resulted from a reliance on online advertising of the study, rather than direct referral from clinicians.

The lack of an untreated or placebo-treated sample limited our ability to determine the precise degree to which neuropsychological changes reflect practice effects rather than treatment effects. However, in a prior study[27] comparing neuropsychological performance after 6 weeks of treatment with bupropion or paroxetine, both treatment groups exhibited clinical improvement but no change in Stroop Interference using the same task employed in this study. Similarly, internal laboratory data in a sample of healthy volunteers (described previously[21]; data available from the corresponding author on request) revealed no practice effect on the interference measure of this task when repeated after 1 week. The prevalence of concurrent medications may have attenuated some clinical and neuropsychological effects, though no differences were observed in neurocognitive change between those who were and were not taking other medications.

All conclusions drawn here are based on the effects of a single treatment, but at a time when repeated treatment is becoming more common,[41] particularly with approval of an intranasal form of ketamine designed to be administered as a maintenance treatment.[42]

Overall, in this sample of depressed adults with suicidal ideation, neurocognitive improvement at 24 hours after a single, subanesthetic ketamine infusion appeared specific to response time and interference processing/attention control tasks. These improvements were independent of reductions in depression severity or suicidal ideation, suggesting that ketamine-related therapeutic effects on neurocognition may be orthogonal to ketamine's effects on mood symptoms. Neuropsychological risks of long-term, repeated therapeutic ketamine treatment are unknown but warrant further study given that heavy, chronic use, as in addiction, is associated with neurocognitive impairment,[15,16] with some impairment persisting even when use is discontinued.[43]

Submitted: February 8, 2021; accepted June 7, 2021.

Published online: November 2, 2021.

Potential conflicts of interest: **Dr Keilp** and his spouse hold stock in Pfizer, Inc. and Zoetis, Inc. **Drs Burke** and **Mann** receive royalties for commercial use of the Columbia-Suicide Severity Rating Scale, which was not used in this study. The other authors report no other relevant funding or any potential conflicts of interest regarding this study.

Funding/support: Supported by R01 MH096784 from the National Institute of Mental Health, Bethesda, MD.

Role of the sponsor: The funding source approved the initial design of the study and monitored safety and progress of the clinical trial. It had no role in the management, analysis, or interpretation of the data.

Acknowledgments: The authors thank the inpatient staff of the Clinical Research Unit at the New York State Psychiatric Institute for their support during this study. They also thank the individuals who participated in this study at a difficult point in their lives.

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(4):327–335.
2. Sinyor M, Williams M, Belo S, et al. Ketamine augmentation for major depressive disorder and suicidal ideation: preliminary experience in an inpatient psychiatry setting. *J Affect Disord*. 2018;241:103–109.
3. Ballard ED, Yarrington JS, Farmer CA, et al. Characterizing the course of suicidal ideation response to ketamine. *J Affect Disord*. 2018;241:86–93.
4. Witt K, Potts J, Hubers A, et al. Ketamine for suicidal ideation in adults with psychiatric disorders: a systematic review and meta-analysis of treatment trials. *Aust N Z J Psychiatry*. 2020;54(1):29–45.
5. Keilp JG, Gorlyn M, Russell M, et al. Neuropsychological function and suicidal behavior: attention control, memory and executive dysfunction in suicide attempt. *Psychol Med*. 2013;43(3):539–551.
6. Keilp JG, Beers SR, Burke AK, et al. Neuropsychological deficits in past suicide attempters with varying levels of depression severity. *Psychol Med*. 2014;44(14):2965–2974.
7. Richard-Devantoy S, Berlim MT, Jollant F. A meta-analysis of neuropsychological markers of vulnerability to suicidal behavior in mood disorders. *Psychol Med*. 2014;44(8):1663–1673.
8. Passie T, Karst M, Wiese B, et al. Effects of different subanesthetic doses of *S*-ketamine on neuropsychology, psychopathology, and state of consciousness in man. *Neuropsychobiology*. 2005;51(4):226–233.
9. Morgan CJ, Mofeez A, Brandner B, et al. Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. *Neuropsychopharmacology*. 2004;29(1):208–218.
10. Honey RA, Turner DC, Honey GD, et al. Subdissociative dose ketamine produces a deficit in manipulation but not maintenance of

the contents of working memory. *Neuropsychopharmacology*. 2003;28(11):2037–2044.
11. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994;51(3):199–214.
12. Morgan CJ, Mofeez A, Brandner B, et al. Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose-response study. *Psychopharmacology (Berl)*. 2004;172(3):298–308.
13. Morgan CJ, Rossell SL, Pepper F, et al. Semantic priming after ketamine acutely in healthy volunteers and following chronic self-administration in substance users. *Biol Psychiatry*. 2006;59(3):265–272.
14. Hayley A, Green M, Downey L, et al. Neurocognitive and behavioural performance of healthy volunteers receiving an increasing analgesic-range infusion of ketamine. *Psychopharmacology (Berl)*. 2018;235(4):1273–1282.
15. Ke X, Ding Y, Xu K, et al. The profile of cognitive impairments in chronic ketamine users. *Psychiatry Res*. 2018;266:124–131.
16. Morgan CJ, Muetzelfeldt L, Curran HV. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. *Addiction*. 2010;105(1):121–133.
17. Permoda-Osip A, Kisielewski J, Bartkowska-Sniatkowska A, et al. Single ketamine infusion and neurocognitive performance in bipolar depression. *Pharmacopsychiatry*. 2015;48(2):78–79.
18. Murrough JW, Burdick KE, Levitch CF, et al. Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: a randomized controlled trial. *Neuropsychopharmacology*. 2015;40(5):1084–1090.
19. Zheng W, Zhou YL, Liu WJ, et al. Neurocognitive performance and repeated-dose intravenous ketamine in major depressive disorder. *J Affect Disord*. 2019;246:241–247.
20. Romeo B, Choucha W, Fossati P, et al. Clinical and biological predictors of ketamine response in treatment-resistant major depression: review [in French]. *Encephale*. 2017;43(4):354–362.
21. Keilp JG, Sackeim HA, Mann JJ. Correlates of trait impulsiveness in performance measures and neuropsychological tests. *Psychiatry Res*. 2005;135(3):191–201.
22. Wechler D. *Wechler Adult Intelligence Scale*. 3rd ed. The Psychological Corporation; 1997.
23. Cornblatt BA, Risch NJ, Faris G, et al. The Continuous Performance Test, identical pairs version (CPT-IP), I: new findings about sustained attention in normal families. *Psychiatry Res*. 1988;26(2):223–238.
24. MacLeod CM. Half a century of research on the Stroop effect: an integrative review. *Psychol Bull*. 1991;109(2):163–203.
25. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology*. 1974;24(11):1019–1025.
26. Benton AL, Hamsher K, Sivan AB. *Multilingual Aphasia Examination*. 3rd ed. AJA Associates; 1983.
27. Gorlyn M, Keilp J, Burke A, et al. Treatment-related improvement in neuropsychological functioning in suicidal depressed patients: paroxetine vs bupropion. *Psychiatry Res*. 2015;225(3):407–412.
28. Kanto J, Allonen H. Pharmacokinetics and the sedative effect of midazolam. *Int J Clin Pharmacol Ther Toxicol*. 1983;21(9):460–463.
29. Crowe SF, Stranks EK. The residual medium and long-term cognitive effects of benzodiazepine use: an updated meta-analysis. *Arch Clin Neuropsychol*. 2018;33(7):901–911.
30. Lister RG. The amnesic action of benzodiazepines in man. *Neurosci Biobehav Rev*. 1985;9(1):87–94.
31. Keilp JG, Madden SP, Gorlyn M, et al. The lack of meaningful association between depression severity measures and neurocognitive performance. *J Affect Disord*. 2018;241:164–172.
32. Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010;329(5994):959–964.
33. Ardalan M, Rafati AH, Nyengaard JR, et al. Rapid antidepressant effect of ketamine correlates with astroglial plasticity in the hippocampus. *Br J Pharmacol*. 2017;174(6):483–492.
34. Clarke M, Razmjou S, Prowse N, et al. Ketamine modulates hippocampal neurogenesis and pro-inflammatory cytokines but not stressor induced neurochemical changes. *Neuropharmacology*. 2017;112(pt A):210–220.
35. Dakwar E, Nunes EV, Hart CL, et al. A single ketamine infusion combined with mindfulness-based behavioral modification to treat cocaine dependence: a randomized clinical trial. *Am J Psychiatry*. 2019;176(11):923–930.
36. Dakwar E, Levin F, Hart CL, et al. A single ketamine infusion combined with motivational enhancement therapy for alcohol use disorder: a randomized midazolam-controlled pilot trial. *Am J Psychiatry*. 2020;177(2):125–133.
37. Kaplan S, Berman MG. Directed attention as a common resource for executive functioning and self-regulation. *Perspect Psychol Sci*. 2010;5(1):43–57.
38. Hofmann W, Freise M, Roefs A. Three ways to resist temptation: the independent contributions of executive attention, inhibitory control, and affect regulation to the impulse control of eating behavior. *J Exp Soc Psychol*. 2009;45(2):431–435.
39. Kotabe HP, Hofmann W. On integrating the components of self-control. *Perspect Psychol Sci*. 2015;10(5):618–638.
40. Venezia RG, Gorlyn M, Burke AK, et al. The impact of cognitive reserve on neurocognitive performance in major depressive disorder. *Psychiatry Res*. 2018;270:211–218.
41. Phillips JL, Norris S, Talbot J, et al. Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. *Neuropsychopharmacology*. 2020;45(4):606–612.
42. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2019;76(9):893–903.
43. Morgan CJ, Monaghan L, Curran HV. Beyond the K-hole: a 3-year longitudinal investigation of the cognitive and subjective effects of ketamine in recreational users who have substantially reduced their use of the drug. *Addiction*. 2004;99(11):1450–1461.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.