Clinical Outcomes of Intravenous Ketamine Treatment for Depression in the VA Health System

Paul N. Pfeiffer, MD; Jamarie Geller, MD; Dara Ganoczy, MPH; Jennifer Jagusch, MSW; John Carty, MD; Fe Erlita D. Festin, MD; William S. Gilmer, MD; Brian Martis, MD; Mohini Ranganathan, MD; Ilse R. Wiechers, MD; and Avinash Hosanagar, MD

Abstract

Objective/Background: Intravenous (IV) ketamine is effective for reducing symptoms of major depressive disorder in short-term clinical trials; this study characterized clinical outcomes of repeated infusions in routine clinical practice and the frequency and number of infusions used to sustain symptom improvement.

Methods: Records of IV ketamine infusions for depression and associated Patient Health Questionnaire-9 (PHQ-9) scores were identified from Veterans Health Administration (VA) electronic medical records for patients treated in Fiscal Year 2020 and up to 12 months following the date of their first infusion.

Results: Sample patients (n = 215) had a mean baseline PHQ-9 score of 18.6 and a mean of 2.1 antidepressant medication trials in the past year and 6.1 antidepressant trials in the 20 years prior to their first ketamine infusion. Frequency of infusions decreased from every 5 days to every 3–4 weeks over the first 5 months of infusions, with a mean of 18 total infusions over 12 months. After 6 weeks of treatment, 26% had a 50% improvement in PHQ-9 score (response) and 15% had PHQ-9 score ≤ 5 (remission). These improvements were similar at 12 and 26 weeks. No demographic characteristics or comorbid diagnoses were associated with 6-week PHQ-9 scores.

Conclusions: While only a minority of patients treated with IV ketamine for depression experienced response or remission, symptom improvements achieved within the first 6 weeks were sustained over at least 6 months with decreasing infusion frequency. Further study is needed to determine optimal infusion frequency and potential for adverse effects with repeated ketamine infusions for depression.

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Author affiliations are listed at the end of this article.

Major depressive disorder (MDD) is a leading cause of disability worldwide with an estimated annual prevalence of 10% in the general US population.[1,2] The prevalence of an MDD diagnosis is 17%[3] among Veterans Health Administration (VA) patients, with whom it is associated with increased morbidity from general medical conditions, such as diabetes and myocardial infarction, an increase in all-cause premature mortality, and increased suicide mortality.[4–7]

While remission was achieved in over half of individuals with depression following two different antidepressant medication trials in the pragmatic Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[8] among VA patients the majority of depression has been observed to be chronic (eg, duration of > 2 years), with remission relatively difficult to achieve.[9] In a large clinical trial of VA patients who started a new antidepressant medication after at least one prior treatment attempt,[10] remission rates across 6 months were 16%. Additionally, VA patients with treatment-resistant depression (TRD) incur substantially greater all-cause health care costs than those with non-TRD MDD.[11]

In addition to the poor overall remission rates for oral antidepressant medications among VA patients, these medications also take several weeks to achieve response (50% reduction in symptoms).[12] These factors can result in lengthy series of dose titrations and medication switches, limiting utility in patients with severe symptoms and those at imminent risk for suicide due to depression. Electroconvulsive therapy (ECT) has consistently been shown to be more effective than oral antidepressant medications[13]; however, cognitive side effects, access

Clinical Points

- Intravenous (IV) ketamine has been shown to be effective for depression in short-term clinical trials; this study assessed longer-term outcomes among Veterans Health Administration patients treated under routine care conditions for up to 1 year.
- About one-fourth of patients achieved a 50% reduction in depression symptoms, and symptom improvement tended to plateau after 6 weeks of repeated infusions. Symptom improvement was maintained for several months as infusion frequency decreased from about twice weekly to every 3 to 4 weeks.
- Veterans who received IV ketamine had extensive prior antidepressant treatment use and high rates of comorbid posttraumatic stress disorder, alcohol and substance use disorders, and chronic pain, which may explain lower response rates compared to prior studies.

barriers, and poor acceptability limit widespread use for VA patients with chronic, treatment-resistant depression.[14–16]

Ketamine, approved by the US Food and Drug Administration (FDA) in 1970 as an anesthetic agent, is an emerging treatment for depression that has not responded to other antidepressant medications. Although the exact mechanisms of ketamine's antidepressant effects are not known, ketamine blocks *N*-methyl-D-aspartate receptors, resulting in complex downstream effects that represent novel mechanisms compared to conventional antidepressant medications.[17] Ketamine administered intravenously has been shown to rapidly and effectively reduce depression symptoms, though symptom reduction lasts on average several days to a week when patients are administered only a single infusion. In clinical trials of repeated infusions, ketamine continues to be effective up to 3 weeks,[18] and a meta-analysis of naturalistic samples[19] found an overall 30% remission rate with no loss of antidepressant effect with repeated dosing over time. However, few studies have characterized the effects of ketamine beyond several weeks of repeated infusions.[20]

On the basis of positive short-term clinical trial data for intravenous (IV) ketamine and the FDA approval of intranasal esketamine (Spravato), the VHA Office of Mental Health and Suicide Prevention (OMHSP) developed a community of practice in 2019 to support implementation of these two treatments for interested psychiatric providers. Additionally, the 2022 update of the VA/Department of Defense (DoD) Clinical Practice Guideline for the Management of Major Depressive Disorder[3] included IV ketamine as a recommend treatment option for treatment-resistant depression. Given the scarcity of long-term clinical trial or naturalistic study data, there is limited guidance regarding how long IV ketamine treatment should continue and what frequency of infusions is used to sustain response. Predictors of treatment response are also not well understood. Ketamine may be more effective when used in earlier stages of depression treatment, as measured by fewer number of failed antidepressant trials and shorter duration of symptoms.[21] However, whether these or other patient characteristics, such as age or psychiatric comorbidities, predict response among Veterans is not known.

To inform the clinical management of depression with IV ketamine, we analyzed VA medical record data to (1) describe the demographic and clinical characteristics of patients that have received IV ketamine for depression; (2) characterize the frequency, duration, and dose of IV ketamine infusions when used to treat depression; and (3) assess depression symptom outcomes following IV ketamine treatment and whether patient or treatment factors are associated with differences in outcomes.

METHODS

Data Source

We accessed data from the VA's Corporate Data Warehouse (CDW), the central repository for all VA electronic medical record data, including patient demographic information, diagnosis and procedure codes, medications, and the text of progress notes. CDW data were accessed via the VA Informatics and Computing Infrastructure (https://www.research.va.gov/programs/vinci/default.cfm). The study was approved by the VA Ann Arbor Institutional Review Board.

Cohort

We identified all patients who received IV ketamine for depression in Fiscal Year 2020 (FY20) by first identifying all patients with a depressive disorder diagnosis at an outpatient encounter. We then searched all of the progress notes of these patients for instances of the word *ketamine* appearing in close proximity to terms related to depression or mental health (eg, *depression*, *mood*, *psych*), excluding notes with terms indicating a nonpsychiatric use of ketamine. Receipt of IV ketamine treatments for depression among these patients was then confirmed via manual electronic medical record review. Patients were neither included nor excluded based on any other diagnostic or other criteria. We compared the counts of patients who received IV ketamine treatment to individual facility field reports and reconciled any discrepancies by modifying our search strategy (eg, by searching for uniquely identifying progress note titles).

Variable Definitions

Patient characteristics. From CDW data fields, we obtained patient age, gender, race, ethnicity, and whether they had a military service-connected disability. We obtained all diagnoses recorded at

clinical encounters for the 12 months prior to each patient's first IV ketamine infusion date and their past-year treatments, including outpatient mental health encounters, psychiatric hospitalizations, number of antidepressant medications prescribed, medications that may be used to augment antidepressant treatment (atypical antipsychotics, lithium, buspirone, liothyronine [T_3]), oral benzodiazepines, repetitive transcranial magnetic stimulation (rTMS), and ECT. We also assessed medication use during IV ketamine treatment and the number of different antidepressant medications trialed since 1999 to encompass at least the past 20 years of treatment. Use of other psychotropic medication classes was measured in supplementary analyses.

Treatment characteristics and outcomes. For each patient identified as having received IV ketamine for depression in (October 1, 2019 to September 30, 2020), using manual electronic chart review we determined the date of their first IV ketamine infusion, including if that infusion occurred in FY19. If a patient's first infusion occurred prior to FY19, they were excluded from analyses in order to ensure equal follow-up treatment time across patients. After determination of the date of the first IV ketamine infusion, all subsequent infusions were identified over the next 12 months. For each infusion, we extracted the date of infusion, dose of IV ketamine, and any Patient Health Questionnaire-9 (PHQ-9)[22] scores collected at the time of infusion.

Analyses

Means and frequencies were used to describe patient and treatment characteristics and PHQ-9 scores at each infusion. Using the last observation carried forward, we calculated improvement in PHQ-9 scores at weeks 6, 12, and 24. For each time point, we applied 3 metrics: minimally clinically important difference (MCID), measured as at least a 5-point decrease in score from baseline; response, measured by 50% reduction; or remission, measured by a score of 5 or less.[23,24] We used bivariate regression to assess whether patient demographic characteristics, mental health diagnoses, or number of infusions in the 6 weeks from the first infusion were associated with the change in PHQ-9 score at 6 weeks. Six weeks was chosen as the primary endpoint for these analyses, based on visual inspection of trends in symptom improvement which indicated that the majority of improvement occurred within 6 weeks from the first infusion.

RESULTS

Patient Characteristics

We identified 215 patients who received IV ketamine for depression in VA in FY20. A total of 19 VA facilities delivered ketamine for depression to at least 1 patient, though only 7 facilities treated 10 or more patients, and 50% of the patients were treated at the 2 highest volume facilities. Patients had a mean (SD) age of 50 (14) years (15% over the age of 65 years); 18% were female, 83% were White, 4% were Black, 2% were Asian American/Pacific Islander/Native Hawaiian, 2% were American Indian/Alaskan Native, 9% were multiracial or of unknown race, and 10% were of Hispanic ethnicity (Table 1). Overall, 89% had a service-connected disability.

Table 1.
Characteristics of Patients Treated With IV Ketamine for Depression (N = 215)

Characteristic	n	%
Age, y		
18–25	1	0.5
26–45	93	43
46–65	89	41
66–75	27	13
76+	5	2
Gender		
Female	38	18
Male	177	82
Race/ethnicity		
White	178	83
Black	9	4
Asian American, Pacific Islander	4	2
American Indian, Alaskan Native	5	2
Unknown/multiracial	19	9
Hispanic	22	10
Comorbid diagnoses		
Posttraumatic stress disorder	150	70
Other anxiety disorder	108	50
Bipolar disorder	37	17
Major depressive disorder with psychotic features	26	12
Other psychotic disorder	6	3
Attention-deficit/hyperactivity disorder	13	6
Alcohol use disorder	58	27
Other substance use disorder	59	27
Personality disorder	25	12
Pain	169	79

Abbreviation: IV = intravenous.

The prevalence of a past-year diagnosis of major depressive disorder was 98%; 12% had at least 1 MDD diagnosis with a psychotic features specifier, and 2% had some other depressive disorder (eg, dysthymic disorder). Bipolar disorder was diagnosed in 17% of patients (thus these patients had been diagnosed with both unipolar and bipolar mood disorders), and the rates of comorbid mental health diagnoses were 70% for posttraumatic stress disorder (PTSD); 50% for other anxiety disorders; 3% for schizophrenia, schizoaffective, and other psychotic disorders (excluding depression with psychotic features); 6% for attention-deficit/hyperactivity disorder; 12% for personality disorders; 27% for alcohol use disorders; and 27% for other substance use disorders.

In the 12 months prior to their first ketamine infusion, patients had completed a mean of 39 (SD = 42,

Figure 1.
Days to Last Ketamine Infusion

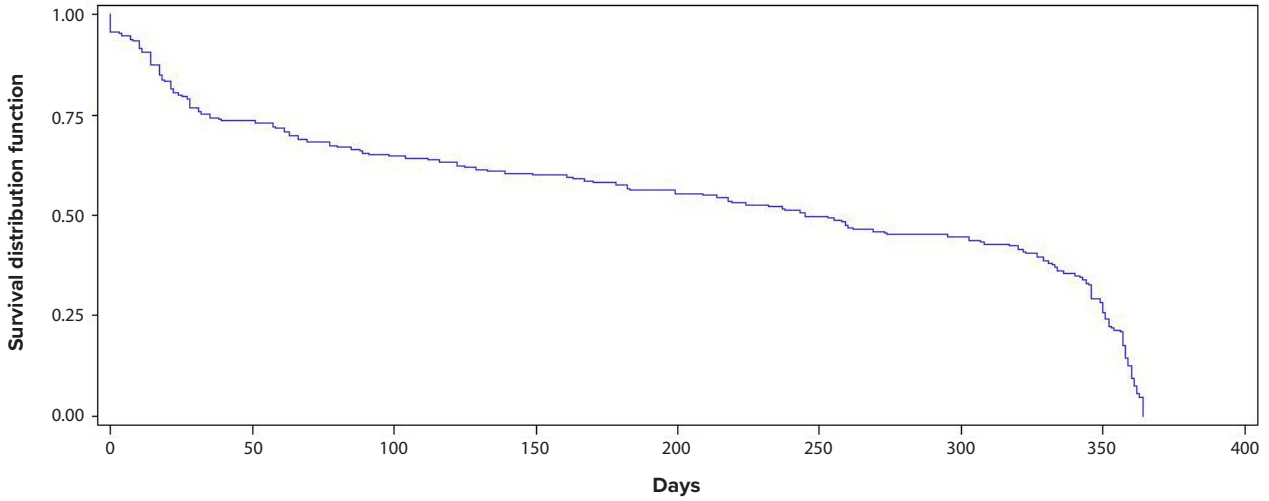
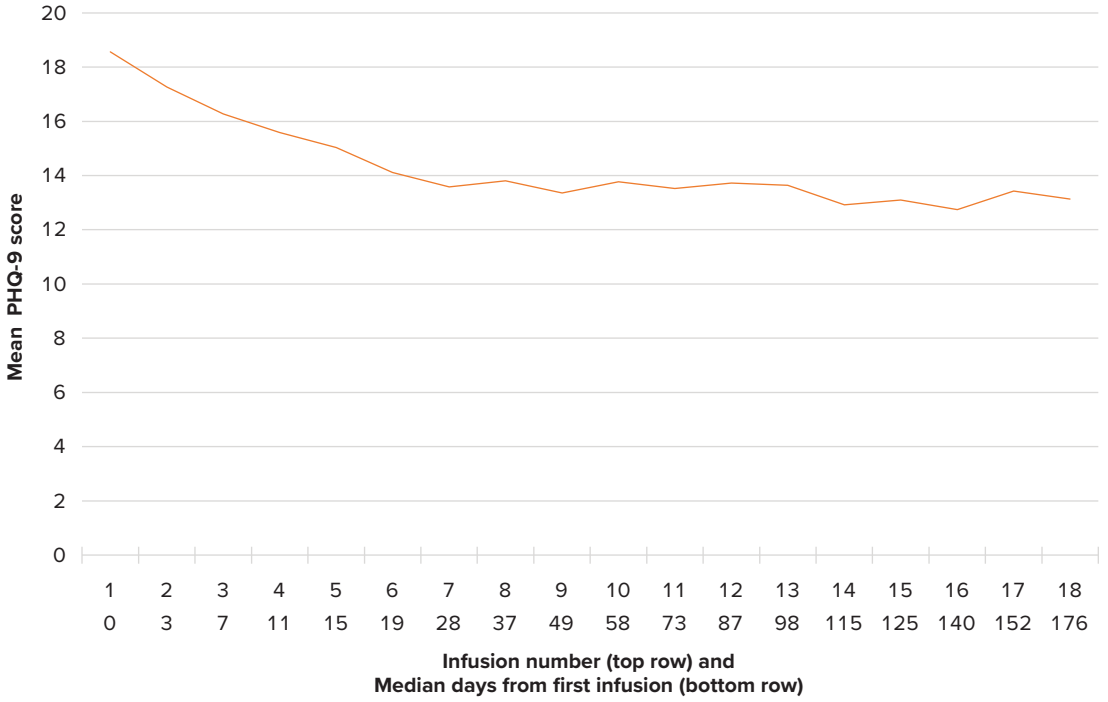


Figure 2.
PHQ-9 Score by Median Days From First Ketamine Infusion



Abbreviation: PHQ-9 = Patient Health Questionnaire-9.

median = 24) mental health visits, 22% had received inpatient psychiatric treatment, 13% had received rTMS, and 18% had received ECT. Medications prescribed in the year prior to and during IV ketamine, respectively, were 83% and 63% for antidepressants, 45% and 27% for atypical antipsychotics, 15% and 7% for lithium, 8% and 7% for buspirone, 3% and 1% for T_3, and 33% and 27% for benzodiazepines (see Supplementary Table 1, which also includes other medication classes). Among those prescribed an antidepressant, the mean number of different antidepressant trials was 2.1 (SD = 1.3, median = 2) in the past year, 6.1 (SD = 2.7, median = 6) in the past 20 years, and 1.5 (SD = 0.6, median = 1) during ketamine treatment.

Treatment Characteristics and Outcomes

In the 12 months following their initial infusion, 96% received additional infusions, with a mean total of 18 treatments (SD = 13, median = 16). The survival curve from first to last infusion is depicted in Figure 1, noting data were censored at 12 months. The mean number of days between first and last infusion was 207 (SD = 145, median = 245). The interval between infusions increased from a mean of 5 days during the month after the first infusion to 12–17 days during months 2 to 4 and to 23–28 days during months 5 to 12. The mean dose of ketamine over all infusions was 59 mg (SD = 25, median = 54 mg), with a mean of 45 mg (SD = 14, median = 43 mg) at the first infusion and 66 mg (SD = 32, median = 60 mg) at patients' last infusion.

Patients had mean PHQ-9 score of 18.6 (SD = 5.7, median = 20.0) at their first infusion. Patients' PHQ-9 scores by subsequent infusion number and time from first infusion over the initial 6 months are depicted in Figure 2. At 6, 12, and 26 weeks, respectively, the mean improvement in PHQ-9 scores was 4.6 (SD = 6.8, median = 3.0; n = 164), 4.4 (SD = 6.5, median = 4.0; n = 169), and 4.7 (SD = 6.7, median = 4.0 n = 171); the percent with MCID was 47%, 44%, and 50%; the percent with response was 26%, 25%, and 28%; and the percent with remission was 15%, 12%, and 13%. Among those who ever met criteria for an improvement outcome, the mean time and number of infusions, respectively, to reach each outcome were 51 days and 9 infusions (median of 37 days, and 8 infusions) for MCID (n = 97), 56 days and 9 infusions (median of 37 days, and 9 infusions) for response (n = 63), and 56 days and 10 infusions (median of 37 days, and 9 infusions) for remission (n = 35).

In bivariate regression models, the only variable associated with change in PHQ-9 score at 6 weeks was the number of infusions the patients received over that time with a β coefficient of 0.7 ($P = .002$) for number of infusions, indicating that each additional infusion was associated with a mean 0.7-point greater improvement in the 6-week PHQ-9 score.

DISCUSSION

Intravenous ketamine was rarely used to treat depression in VA in FY2020, with less than one-fifth of VA medical centers administering the treatment and only 215 patients out of hundreds of thousands with depression receiving the treatment. Patients who received ketamine for depression had highly treatment-resistant depression with an average baseline PHQ-9 score in the moderately severe range despite an average of 6 prior antidepressant medication trials and frequent past-year use of outpatient mental health services. Clinicians appear to have appropriately selected patients for ketamine who had not benefitted from less costly and more accessible treatment options.

Patients who received IV ketamine generally found the treatment acceptable, as evidenced by only 4% of patients receiving only 1 treatment and receipt of an average of 18 treatments within 1 year. The total number of infusions and decreasing infusion frequency suggests a clinical practice of an initial acute phase of more frequent treatments followed by a longer-term phase of maintenance treatments every 3 to 4 weeks. While the effectiveness of long-term IV ketamine maintenance treatments has not been established in clinical trials, the SUSTAIN trial of intranasal esketamine (Spravato) showed that discontinuation of esketamine (vs continued treatment) was more likely to result in relapse among those who had stable response or remission after 16 weeks of esketamine treatments.[25] However, given differences between racemic ketamine and esketamine and routes of administration, controlled trials of IV ketamine are yet needed to confirm the effectiveness of current practices of maintenance treatment for relapse prevention.

We found nearly half of patients experienced a minimally clinically important difference in depression symptoms following 6 weeks of IV ketamine treatment and 26% achieved the threshold for response to treatment. These findings are similar to those from a Canadian study of treatment-resistant patients in a real-world clinical setting that showed a short-term response rate of 27% and remission rate of 13% following 4 infusions. While we found mean symptom improvements among those who continued treatment remained stable for up to 6 months, the overall response rates in our sample were lower than those reported from a large private ketamine practice, which showed that while only 14% of patients responded after 3 infusions, nearly 72% responded after 10 infusions.[20] Our study sample consisted of Veterans with high rates of antidepressant treatment failures and psychiatric comorbidity. These factors along with sociodemographic differences, such as the older age of VA patients, could explain the lower response rates among VA patients.[26] Response rates of VA patients treated with ketamine were similar to the 31% response rate for receipt of rTMS in an observational study of VA patients, although those who received 30 rTMS treatments (45% of the total sample) had a 40% response rate.[27] Ketamine patients in our sample had higher rates of PTSD, alcohol use disorder, and substance use disorder comorbidities when compared to those in the rTMS study by Madore et al.[27] Head-to-head effectiveness trials comparing IV ketamine and rTMS that control for differences in patient characteristics and that account for treatment acceptability and potential for sustained improvement with or without maintenance treatments are therefore needed.

Although remission from depression is associated with greater functioning and reduced risk of relapse compared to response,[8] overall remission rates with IV ketamine treatment in our study sample were low. Our

finding that patients continued to engage in treatment despite incomplete remission suggests patients may experience benefits not captured well by the PHQ-9. Conventional depression severity measures that are sensitive to changes from monoamine-based treatments may not be equally valid for antidepressants with different mechanisms of action.[28] A recent qualitative study of IV ketamine treatment found many of the non-remitters reported experiencing partial recovery and substantial benefit from ketamine infusions despite non-remission status on scale measures.[29] Other quantitative measures (eg, functional status, quality of life, suicide risk) should be considered when assessing the clinical benefits of ketamine treatment for depression. Future studies should also evaluate the therapeutic context in which IV ketamine is provided, including the integration of psychotherapy and the impact of contextual factors (eg, treatment environment) on outcomes.

Our finding that patient demographic and diagnostic characteristics were not related to 6-week PHQ-9 outcomes is consistent with prior IV ketamine studies.[30] The lack of a diminished effect for patients with comorbid PTSD, 70% of our sample, contrasts with VA studies of oral antidepressant medications and rTMS that found depressed Veterans were less likely to experience remission if they had comorbid PTSD.[31] Though data on PTSD symptoms were not routinely collected in the current study sample, repeated infusions of IV ketamine were effective for improving PTSD symptoms in a small RCT,[32] further indicating IV ketamine may be of particular clinical utility in patients with depression and PTSD. The association between the number of infusions within 6 weeks and greater PHQ-9 improvement supports the current practice of higher frequency treatments in the initial 6 weeks; however, clinical trials testing different dosing frequencies and taper strategies are needed to clarify optimal practice.

Although a systematic review of clinical trials and case reports has shown few adverse effects of maintenance IV ketamine treatment,[33] our study is limited by not including an assessment of safety, such as the incidence of cardiac events, interstitial cystitis, or substance use disorders. Validated electronic medical record measures of ketamine-related adverse outcomes were not available but are critically needed to inform risk-benefit clinical decision-making. This study is also limited by the absence of PHQ-9 data outside of the dates of ketamine infusions. Patients who continued with IV ketamine treatment in our sample may have been those with less sustained improvement in symptoms compared to those who terminated treatment, and thus our findings may underestimate rates of longer-term response. Medical record diagnoses used to characterize patients may not be as accurate as those obtained through structured diagnostic interviews. Structured diagnostic interviews and standardized assessments of concurrent symptoms, treatment history, and social factors would strengthen the ability to identify predictors of treatment response in future studies. While it is a strength that our sample of VA patients included patients with high rates of comorbid PTSD and chronic pain and with other characteristics often excluded from clinical trials—such as psychosis, alcohol and substance use disorders, and age over 65 years—findings may not generalize to other patient populations or health systems.

Given the short-term RCT evidence for IV ketamine, the long-term RCT evidence for esketamine, prior observational studies of longer-term treatment, and our added observational finding that patients who received repeated ketamine infusions as part of routine VA care experienced stable symptom improvement, clinicians should continue to consider repeated IV ketamine infusions as a treatment option for patients who have failed multiple oral antidepressant medications and/or rTMS. Additional controlled trials of repeated infusions are needed to establish safety and effectiveness; to identify optimal dosing and infusion frequency; and to compare the costs and effectiveness of IV ketamine to other routes of administration (eg, intramuscular, oral), other advanced treatments for treatment-resistant depression (such as repetitive transcranial magnetic stimulation and electroconvulsive therapy), or augmentation of oral antidepressant medications (such as with atypical antipsychotic medications or psychotherapy).

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Author Affiliations: VA Center for Clinical Management Research, VA Ann Arbor Healthcare System, Ann Arbor, Michigan (Pfeiffer, Ganoczy, Jagusch); Department of Psychiatry, University of Michigan Medical School, Ann Arbor, Michigan (Pfeiffer, Geller, Hosanagar); Albuquerque VA Medical Center, Albuquerque, New Mexico (Carty); University of New Mexico School of Medicine Albuquerque, New Mexico (Carty); VA Boston Healthcare System, Boston, Massachusetts (Festin); Harvard Medical School, Boston, Massachusetts (Festin); Boston University School of Medicine, Boston, Massachusetts (Festin); Edward Hines Jr VA Hospital, Hines, Illinois (Gilmer); Northwestern University Feinberg School of Medicine, Chicago, Illinois (Gilmer); VA San Diego Healthcare System, San Diego, California (Martis); University of San Diego School of Medicine, San Diego, California (Martis); VA Connecticut Healthcare System, West Haven, Connecticut (Ranganathan); Yale School of Medicine, New Haven, Connecticut (Ranganathan, Wiechers); VA Office of Mental Health and Suicide Prevention, Washington, DC (Wiechers); University of California San Francisco School of Medicine, San Francisco, California (Wiechers); Mental Health Service, VA Ann Arbor Healthcare System, Ann Arbor, Michigan (Hosanagar).

Corresponding author: Paul N. Pfeiffer, MD; VA Center for Clinical Management Research, 2800 Plymouth Road, Building 16, Ann Arbor, MI 48109 (Paul.Pfeiffer@va.gov).

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Supplementary Material

Article Title: Clinical Outcomes of Intravenous Ketamine Treatment for Depression in the VA Health System

Author(s): Paul N. Pfeiffer, MD; Jamarie Geller, MD; Dara Ganoczy, MPH; Jennifer Jagusch, MSW; John Carty, MD; Fe Erlita D. Festin, MD; William S. Gilmer, MD; Brian Martis, MD; Mohini Ranganathan, MD; Ilse R. Wiechers, MD; and Avinash Hosanagar, MD

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. Table 1 Medication use before and during IV ketamine treatment

DISCLAIMER

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Supplementary Table 1. Medication use before and during IV ketamine treatment

	Period relative to IV ketamine			
	Year prior		During	
Medication or class	**N**	**%**	**N**	**%**
Antidepressant	179	83	136	63
Atypical antipsychotic	97	45	57	27
Lithium	32	15	15	7
Buspirone	18	8	14	7
Liothyronin (T3)	6	3	3	1
Benzodiazepine	70	33	58	27
1st generation antipsychotic	10	5	6	3
Stimulant	38	18	27	13
Anticonvulsant mood stabilizer	63	29	43	20
Gabapentinoid	67	31	46	21
Selective NRI	2	1	2	1
Hypnotic/sleep medication	111	52	94	44
Non-benzodiazepine / Z-drug	30	14	23	11
Melatonin agonist	51	24	41	19
Orexin receptor antagonist	0	0	0	0
Hypnotic antidepressant	68	32	52	24
Hydroxyzine	51	24	27	13

Class definitions:

Antidepressants: BUPROPION, CITALOPRAM, DESVENLAFAXINE, DULOXETINE, ESCITALOPRAM, FLUOXETINE, FLUVOXAMINE, LEVOMILNACIPRAN, MIRTAZAPINE, NEFAZODONE, PAROXETINE, SERTRALINE, VENLAFAXINE, VILAZODONE, VORTIOXETINE, AMITRIPTYLINE, AMOXAPINE, CLOMIPRAMINE, DESIPRAMINE, DOXEPIN > 10mg, IMIPRAMINE, MAPROTILINE, NORTRIPTYLINE, PROTRIPTYLINE, TRIMIPRAMINE, ISOCARBOXAZID, PHENELZINE SULFATE, TRANYLCYPROMINE, SELEGILINE,TRAZODONE > 150mg

Atypical antipsychotics: ARIPIPRAZOLE, CLOZAPINE, OLANZAPINE, QUETIAPINE, RISPERIDONE, ZIPRASIDONE, PALIPERIDONE, ASENAPINE, ILOPERIDONE, LURASIDONE, BREXPIPRAZOLE, CARIPRAZINE, LUMATEPERONE

Benzodiazepines (long-acting): ALPRAZOLAM, CHLORDIAZEPOXIDE, CLONAZEPAM, DIAZEPAM, ESTAZOLAM, LORAZEPAM, OXAZEPAM, PRAZEPAM, TEMAZEPAM

1st generation antipsychotics: CHLORPROMAZINE, CHLORPROTHIXENE, FLUPHENAZINE, HALOPERIDOL, LOXAPINE, MESORIDAZINE, MOLINDONE, PERPHENAZINE, PIMOZIDE, THIORIDAZINE, THIOTHIXENE, TRIFLUOPERAZINE, DROPERIDOL, PROCHLORPERAZINE, TRIFLUPROMAZINE

Stimulants: AMPHETAMINE, DEXTROAMPHETAMINE, METHYLPHENIDATE, AMPHETAMINE/DEXTROAMPHETAMINE, LISDEXAMPHETAMINE,DEXMETHYLPHENIDATE

Anticonvulsant mood stabilizers: DIVALPROEX, VALPROIC ACID, LAMOTRIGINE, CARBAMAZEPINE, OXCARBAZEPINE, TOPIRAMATE

Gabapentinoids: GABAPENTIN, PREGABALIN

Selective norepinephrine reuptake inhibitors (NRIs): ATOMOXETINE, VILOXAZINE

Hypnotic/sleep medications: any non-benzodiazepine, melatonin receptor agonist, orexin receptor antagonist, or hypnotic antidepressant

Non-benzodiazepines / Z-drugs: ZOLPIDEM, ZALEPLON, ESZOPICLONE

Melatonin receptors agonists: MELATONIN, RAMELTEON

Orexin receptor antagonists: SUVOREXANT, DARIDOREXANT, LEMBOREXANT

Hypnotic antidepressants: TRAZODONE ≤ 150mg, DOXEPIN ≤ 10mg