Acute and Longer-Term Outcomes Using Ketamine as a Clinical Treatment at the Yale Psychiatric Hospital

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ABSTRACT

Objective: Ketamine has emerged as a rapid-acting antidepressant, though controversy remains whether sufficient data exist to justify its use outside of research protocols. In October 2014, the authors' institution began providing ketamine as an off-label therapy on a case-by-case basis for patients unable to participate in research protocols. Here, the participant experience during 29 months of providing ketamine as a clinical treatment for severe and treatment-resistant mood disorders through February 2017 is described.

Methods: Patients were initially treated with a single- or double-infusion protocol (0.5 mg/kg for 40 minutes intravenously) and were later transitioned to a 4-infusion protocol over 2 weeks.

Results: Fifty-four patients received ketamine, with 518 total infusions performed. A subset of 44 patients with mood disorders initiated the 4-infusion protocol, of whom 45.5% responded and 27.3% remitted by the fourth infusion. A subsample (n = 14) received ketamine on a long-term basis, ranging from 12 to 45 total treatments, over a course of 14 to 126 weeks. No evidence was found of cognitive decline, increased proclivity to delusions, or emergence of symptoms consistent with cystitis in this subsample.

Conclusions: In general, ketamine infusions were tolerated well. The response and remission rates in this clinical sample were lower than those observed in some research protocols. The small number of patients who were treated on a maintenance schedule limits the conclusions that can be drawn regarding the long-term safety of ketamine; however, no long-term adverse effects were observed in this sample.

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Several small clinical trials[1–5] have shown that subanesthetic doses of ketamine have rapid-acting antidepressant effects in patients with treatment-resistant mood disorders. Additional studies[6–10] suggest the relative safety of repeated (up to 6) doses. Due to the great unmet need for improved therapeutics in treatment-resistant mood disorders, the off-label clinical use of ketamine for the treatment of psychiatric disorders has grown rapidly since 2012.[11] Nonetheless, controversy remains about whether ketamine should be used outside of research protocols due to concerns regarding potential negative clinical outcomes from repeated use, including impaired cognition, delusions, and interstitial cystitis.[12–15] In October 2014, our institution began providing ketamine as an off-label therapeutic agent on a case-by-case basis for patients who were unable to participate in ongoing research protocols. This article describes our experience during 29 months of providing ketamine as a clinical treatment to participants with severe and treatment-resistant mood disorders.

METHODS AND CLINICAL PROTOCOL

Ketamine treatments, as part of the Interventional Psychiatry Service at Yale Psychiatric Hospital, are given in an electroconvulsive therapy (ECT) suite. After psychiatric consultation, signed informed consent, and medical clearance (including basic laboratory work, urine toxicology, electrocardiogram, history, and physical examination), patients began intravenous infusions. As emphasized in the written consent form, patients understood that this treatment was not approved by the US Food and Drug Administration and was given off-label for depression.

Patients were instructed to fast for approximately 8 hours (starting at midnight) prior to each infusion. On the patient's arrival to the treatment suite, baseline blood pressure, heart rate, pulse oxygenation, respiratory rate, and temperature were recorded and a peripheral intravenous catheter inserted. Ketamine was administered at a dose of 0.5 mg/kg (based on standard research protocols[4,16]), mixed in 500 mL of 0.9% normal saline and infused over 40 minutes. For patients with a body mass index ≥ 30 kg/m^2, we initially adjusted the dose based on ideal body weight (see Appendix 1). During the infusion, blood pressure was monitored at least every 10 minutes and heart rate and pulse oxygenation were monitored continuously. We continued to monitor vital signs every 10 minutes following the completion of the infusion. If nausea occurred during or shortly after an infusion, we offered patients intravenous ondansetron prophylactically at the next infusion. Psychotropic medications were not controlled, and washouts were not done routinely prior to initiation of therapy. In general, we avoided use of benzodiazepines in the 8–12 hours prior to dosing, based on theoretical concerns[17] and limited prior evidence suggesting an attenuation of the antidepressant effects of ketamine when it is given concomitantly with benzodiazepines.[18] Patients were instructed to hold psychotropic medications until after ketamine

Clinical Points

- Ketamine shows promise as a potential treatment for refractory mood disorders; however, evidence to date is mostly limited to short-term (≤ 1 month) outcomes. The field urgently awaits long-term data on the efficacy and safety of ketamine as a treatment for psychiatric disorders.
- Ketamine treatment was generally well tolerated in patients who received infusions on a long-term basis.
- Longer-term treatment strategies should be considered prior to initiation of ketamine treatment.

on the days of treatment, but were instructed to take other medications (ie, for blood pressure, heart rate, diabetes, etc) prior to dosing.

Initially, patients were treated with a single- or double-infusion protocol (1 or 2 doses during 1 week). In early 2015, as several studies emerged showing the safety of a multiple-infusion protocol,[6,8,9] we transitioned to a 4-dose protocol given twice per week. We based this protocol on evidence presented at professional meetings in 2014[8] which showed that thrice-weekly was no better than twice-weekly dosing.

Initially, symptom severity was tracked with the Quick Inventory of Depressive Symptomatology-Self Report scale (QIDS-SR),[19] which was administered at each visit. In addition, the QIDS-SR was given to outpatients to fill out 24 hours following each infusion. The Clinician-Administered Dissociative State Scale (CADSS)[20] was given at the completion of each infusion (40 minutes) as well as immediately prior to discharge (to ensure discharge readiness criteria) or return to the inpatient unit. As the service grew, we implemented the Montgomery-Asberg Depression Rating Scale (MADRS)[21] to track outcomes at each visit prior to treatment.

The service has treated both inpatients and outpatients. Similar to our ECT guidelines, outpatients were not permitted to drive on days of infusion and were discharged to the care of a responsible adult. Criteria for discharge readiness were (1) a return to predose hemodynamic parameters, (2) a CADSS score of 0 (or equal to or below pretreatment score), and (3) at least 30 minutes of observation following the completion of the infusion. The Institutional Review Board granted a waiver of full review for a medical record review. Yale-New Haven Hospital approved the written consent form (see Appendix 2).

For patients with meaningful clinical improvement, we attempted to maintain this improvement using various pharmacologic or psychotherapeutic strategies based on individual treatment history. A portion of the patients treated (n = 16) have undergone open-label cognitive-behavioral therapy in an effort to sustain ketamine's antidepressant effects, the results of which have been published previously.[10] For patients who have been unable to sustain response, we have provided continuation/maintenance ketamine treatments with ongoing informed consent of the risks and benefits of continued treatment. We have instituted a flexible, symptom-triggered tapering schedule, which we modeled after a continuation/maintenance ECT schedule.[22] We attempted to spread the frequency of treatments to every 3 or 4 weeks while still maintaining response.

There is concern for cognitive deterioration with repeated exposure to ketamine.[13] Consequently, we have instituted regular cognitive assessments for all patients who receive ketamine in our program. We used the CogState battery (www.cogstate.com), which includes tasks assessing attention, working memory, visual memory, processing speed, and verbal memory with delayed recall. Further description of these tasks can be found elsewhere.[23,24] Cognitive assessments are done at baseline and thereafter every 6–12 treatments. A subsample of our cohort (n = 14) have received ketamine for at least 14 weeks. Because the patients in this ongoing cohort have received a differing number of treatments to date, we approached this analytically by correlating the total number of treatments with the paired difference (age-adjusted *z*-score) of the first and most recent cognitive assessments.

Table 1. Demographic and Clinical Characteristics (N = 54)[a]

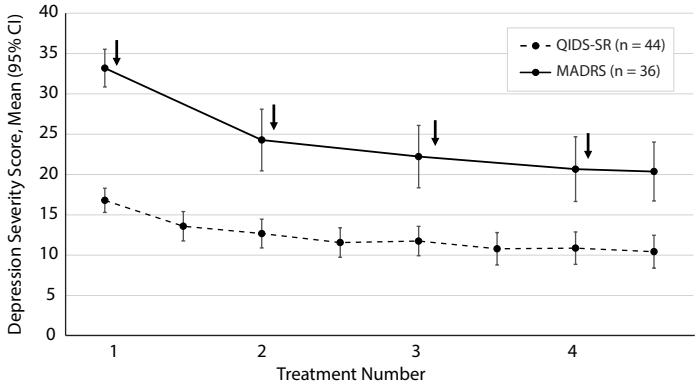
Variable	Value
Age, mean (SD); range, y	46.7 (18.0); 16–87
Male	21 (38.9)
Marital status	
Single	25 (46.3)
Married	18 (33.3)
Divorced/separated	5 (9.3)
Other	6 (11.1)
Disabled	2 (4.7)[b]
Race	
White	52 (96.3)
African American	1 (1.9)
Other	1 (1.9)
Diagnosis	
Major depressive disorder	44 (81.5)
Bipolar disorder	6 (11.1)
Schizoaffective disorder	3 (5.6)
Catatonia	1 (1.9)
History of electroconvulsive therapy	27 (50.0)
History of hospitalization	40 (74.1)
History of hospitalization for suicidal ideation or attempt	35 (64.8)
History of suicide attempt	23 (46.9)[c]
Inpatient status at first infusion	21 (38.9)
Baseline QIDS-SR score, mean (SD)	19.8 (6.0)
Baseline MADRS score, mean (SD)	33.1 (6.9)

[a]Values shown as n (%) unless otherwise noted.
[b]Missing data for 11 patients.
[c]Missing data for 5 patients.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report.

RESULTS

In total, 54 patients were treated with at least 1 ketamine infusion from October 2014 through February 2017. In total, 518 infusions were given. Table 1 shows the demographic and baseline clinical characteristics of these patients. Three patients with schizoaffective disorder were treated. The rationale for including 1 of these patients has been described previously.[25,26] The other 2 patients had failed ECT and were suffering from severe functional limitations due to the current depressive episode.

Figure 1. Depression Severity Over Time in a 4-Infusion Ketamine Protocol[a]



[a]Last observation carried forward was used for missing data. A mixed-effects, general linear model showed a main effect of time using the QIDS-SR (main effect of time: $t = -7.72$, $P < .001$) as well as the MADRS ($t = -8.48$, $P < .001$). Treatments were given twice weekly. Time points between treatments were 2–4 days; the QIDS-SR was administered 24 hours following each treatment. Arrows indicate ketamine infusions.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report.

Outcomes Following Acute Treatment Period

Of 54 total patients treated, 44 patients had a primary mood disorder and began a 4-infusion protocol, with treatment given twice weekly over 2 weeks. Using a self-report measure (QIDS-SR), patients showed a significant reduction in symptoms over time in a general linear mixed model (main effect of time: $t = -7.72$, $P < .001$; Figure 1). Overall, mean QIDS-SR score decreased from 16.8 to 10.4, a 37.9% reduction. The majority of the improvement (64.7% of total improvement, or a reduction of 4.12 QIDS-SR points) occurred between the first and second infusions (a 2- to 4-day time period). MADRS data were collected on 36 of these subjects and showed a similar pattern (Figure 1), with a significant effect of time in a general linear, mixed model ($t = -8.48$, $P < .001$). Overall, mean MADRS score decreased from 32.8 to 20.4, a 37.8% reduction. The majority of improvement (68.5% of total improvement, or a reduction of 8.5 MADRS points) occurred between the first and second infusions. Using a general linear mixed model, we adjusted for peak CADSS score (at 40 minutes), age, sex, and history of failed ECT. None of these variables moderated the effect of time on the MADRS or QIDS-SR scores.

Dichotomous Outcomes

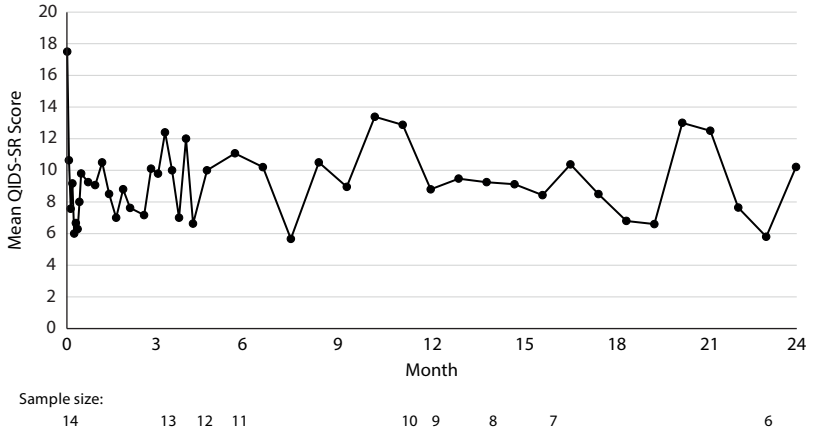
We calculated dichotomous outcomes from the sample of patients with mood disorders who began a 4-infusion protocol (n = 44). Following the first infusion, 31.8% of patients (n = 14) were classified as responders (50% or greater improvement in QIDS-SR). By the fourth infusion, 45.5% of patients (n = 20) were responders. Prior to our instituting a 4-infusion protocol, we treated 6 patients with mood disorders with single- or double-infusion protocols. Of these 6, 5 experienced a 50% improvement in mood symptoms following the first treatment. Hence, 50.0% of patients (n = 25) with mood disorders responded to a protocol of infusions ranging from 1 to 4. Following a single infusion, 11.4% of patients (n = 5) were classified as remitters (QIDS-SR score ≤ 5); following 4 infusions, 27.3% of patients (n = 12) were classified as remitters.

When MADRS data were used on a smaller sample (n = 36), 22.2% of patients (n = 8) responded following the first infusion. By the fourth infusion, 38.9% (n = 14) responded. We did not perform MADRS assessments for the 6 patients with mood disorders treated before we instituted a 4-infusion protocol. Following a single infusion, 13.9% of patients (n = 5) remitted (MADRS score ≤ 10); by the fourth infusion, 25.0% of patients (n = 9) remitted.

Discontinuation of Acute-Phase Treatment

Of the 44 patients with mood disorders who began the 4-infusion protocol, 5 did not complete all treatments. Reasons for discontinuation were lack of efficacy (n = 4) and lack of tolerability of infusions (n = 1). Of the 518 total infusions (N = 54), 2 were discontinued midinfusion. In a 48-year-old woman with MDD, type 1 diabetes, and hypertension, the first infusion was stopped early due to elevated blood pressure (maximum = 181/72 mm Hg). Within 10 minutes of stopping the infusion, blood pressure was 168/69 mm Hg and by 30 minutes was 149/64. This subject received low-dose (50–100 mg) oral labetalol pretreatment prior to subsequent infusions with good effect (maximum blood pressures of 161/79, 141/61, and 152/69 mm Hg for the second, third, and fourth infusions, respectively). The subject experienced remission following the first infusion. The other early termination occurred during the first infusion for a 78-year-old woman with MDD who was hospitalized. The infusion was stopped 10 minutes early due to intolerable dissociative side effects. The patient was able to tolerate all 3 subsequent infusions but did not show clinical improvement. Of the 54 patients who received ketamine, 16 (29.6%) experienced

Figure 2. Longer-Term (2-year) Outcomes of Patients Who Received Continuation/Maintenance Ketamine Treatment for Treatment-Resistant Depression (n = 14)[a]



[a]The sample size decreases over time, reflecting that patients are at different stages of continuation/maintenance therapy and not reflecting patient dropout. Data for 1 of the patients were previously published in a case report.[27]
Abbreviation: QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report.

mild nausea and received prophylactic ondansetron for subsequent infusions. No patient vomited during treatment. Two patients (3.7%) received pretreatment, low-dose oral labetalol prophylactically based on blood pressure elevations during prior treatments.

Long-Term Outcomes

Figure 2 shows long-term outcomes over 2 years for all patients (n = 14) from our program who have received continuation/maintenance ketamine treatments for at least 14 weeks.[27] Overall, these patients have received 351 treatments, with a mean (SD) of 25.1 (10.5) treatments per patient and a median of 27 treatments per patient (range, 12–45 treatments). The mean (SD) length of course of therapy among these patients was 75.7 (39.2) weeks, with a median of 84 weeks (range, 14–126 weeks). Of these 14 patients, 3 initiated therapy on a single- or double-infusion protocol. Not including acute course of 4 treatments given twice per week, the mean (SD) time between treatments was 22.3 (22.7) days, with a median time between treatments of 21 days (range, 2–189 days). Among the 14 longer-term patients, we observed 1 case of tachyphylaxis. A 16-year-old male with MDD who failed ECT and had recurrent hospitalizations showed remission following 4 treatments (MADRS score was 4 at this time point). After an attempt to taper the treatments to every 2 weeks, his MADRS score rose to 28. Additional infusions given twice weekly did not lead to clinical improvement. Two patients relapsed resulting in suicide attempts and hospitalizations during long-term follow-up. Both were able to regain response status after resumption of ketamine treatment (infusions twice weekly). Seven additional patients relapsed (depression score showing < 25% improvement from baseline) during the 2-year follow-up period but were all able to regain response status. One patient relapsed after a 6-month hiatus (living in another state) and was able to regain a partial but not full response to treatment after a second acute series of ketamine treatments. Three patients did not relapse during longer-term follow-up. Qualitatively, 7 of these long-term patients reported that the antidepressant effect of ketamine started to fade approximately 3 weeks following exposure.

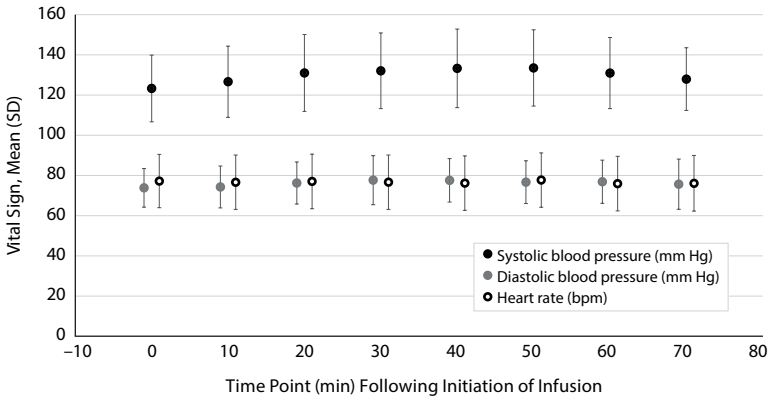
Concomitant Medications

Among the full sample, the majority of patients (96.3%; n=52) were taking at least 1 psychotropic medication (Supplementary Table 1). The most common medication type was an antidepressant, taken by 72.2% of patients (n=39). This was followed by antipsychotic (53.7%; n=29), sedative/hypnotic (50.0%; n=27), mood stabilizer/anticonvulsant (37.0%; n=20), stimulant (22.2%; n=12), and lithium (18.5%; n=10). There was no moderating effect of any class of psychotropic medication, including benzodiazepines, on antidepressant effect as measured by the MADRS or QIDS-SR. Among the 14 longer-term patients, changes in concomitant medications can be found in Supplementary Table 2.

Safety

One of our patients, an adolescent with multiple hospitalizations who failed ECT prior to beginning ketamine, was surreptitiously using cannabis on a frequent basis. He had a history of intermittent cannabis use prior to beginning treatment, though this was not disclosed. His urine toxicology screen prior to initiating therapy was negative. Upon discovery of his use, further ketamine treatments were contingent on his abstinence, which he was not able to maintain. Hence ketamine treatments were discontinued.

Figure 3. Vital Sign Monitoring During and 30 Minutes After a 40-Minute Infusion Protocol of 0.5 mg/kg Intravenous Ketamine[a]



[a]Data represent 54 patients with 210 total infusions.

Table 2. Cognitive Outcomes of Long-Term Ketamine Treatment (n = 14)[a]

Cognitive Domain	Mean Paired Difference Between First and Most Recent Cognitive Assessment (age-adjusted *z*-score)	Correlation Between Paired Difference (age-adjusted *z*-score) and No. of Ketamine Treatments	
		r^2 Value	*P* Value
Processing speed	0.330	0.035	.538
Attention	–0.187	0.042	.500
Visual memory	0.126	0.008	.771
Verbal memory	0.361	0.021	.635
Verbal memory, delayed recall	0.316	0.099	.297
Working memory	0.807	0.143	.203

[a]Paired differences between the first and most recent cognitive assessments were calculated for each subject and then correlated with the total number of treatments between assessments. A positive difference indicates improved performance at second assessment compared to baseline. Tasks included are as follows: Identification Task (attention), One-Back Task (working memory), One Card Learning Task (visual memory), International Shopping List and Delayed Recall (verbal memory, with delayed recall), and Detection Task (processing speed). Further description of these tasks can be found elsewhere.[23,24]

Two patients who received treatment later committed suicide. One experienced significant clinical improvement after 4 treatments given over 2 weeks. She received 1 maintenance treatment 2 months following the acute course of treatments but no further ketamine treatments following this. She committed suicide by hanging 4 months after her last dose of ketamine. Another patient committed suicide by hanging approximately 10 months after receiving his final ketamine treatment. He had been seen in psychiatric follow-up the week of his death and had been in a heated argument with an ex-spouse the day of his suicide. He had experienced a partial improvement from the ketamine following 4 treatments (35.6% improvement).

Acute Dissociative Effects

Following the first treatment, the mean (SD) CADSS score was 6.79 (8.51), at 40 minutes and had nearly returned to zero at 70–80 minutes (mean [SD] score = 0.12 [0.32]). Following the second, third, and fourth infusions, mean (SD) CADSS scores at 40 minutes were 5.86 (6.25), 4.52 (5.03), and 4.53 (7.16), respectively. Following the second, third, and fourth infusions, mean CADSS scores at 70–80 minutes were 0.07 (0.26), 0.04 (0.19), and 0.00 (0.00), respectively.

Vital Sign Monitoring

When data are collapsed across the 4 acute infusions, mean (SD) systolic blood pressure (SBP) increased from a baseline value of 123.3 (16.6) mm Hg to a peak of 133.5 (19.0) mm Hg at 50 minutes (10 minutes following completion of infusion). By 70 minutes, mean (SD) SBP was 127.9 (15.6) mm Hg (Figure 3). Mean (SD) diastolic blood pressure (DBP) increased from 73.8 (9.6) mm Hg at baseline to a peak of 77.6 (10.8) at 40 minutes. By 70 minutes, mean (SD) DBP was 75.6 (12.5) mm Hg. Mean (SD) heart rate remained between 75 (13.3) and 78 (13.8) beats per minute throughout the infusion and recovery time. Mean (SD) pulse oximetry readings ranged from 98.1% (1.5%) to 98.4% (2.0%) throughout the infusion period and recovery time. Five patients experienced SBP elevated over 180 mm Hg during their first infusion, though 4 of these elevations were transient. One patient consistently had a SBP of 180 mm Hg or greater at the last time point (40 minutes) of his second, third, and fourth infusions, which normalized within 30 minutes following treatment. During the first infusion, 1 patient transiently had a DBP of 110 mm Hg, which normalized within 30 minutes postinfusion. No patient had DBP values of 110 mm Hg or greater during the second, third, or fourth infusions.

Cognitive Outcomes

Among the subsample of patients receiving ketamine long-term (n = 14), there was no correlation between number of treatments received and paired change in cognitive measures of attention, processing speed, working memory, verbal memory, and visual memory (Table 2). The mean paired difference for each domain was positive, except for the measure of attention. The median time between assessments was 331 days (range, 49–522 days). Among the full sample, baseline measures of cognition did not correlate with improvement in depressive symptoms.

DISCUSSION

From October 2014 through February 2017, our service provided ketamine as a clinical treatment to 54 patients, 14 of whom have received long-term infusions of 12 treatments or more. Infusions given at 0.5 mg/kg over 40 minutes are generally well tolerated, with 1 patient requiring premature cessation of infusion prior to completion due to intolerable dissociative effects and 1 for transient hypertension. Notably, our response (45.5%) and remission (27.3%) rates following a 4-infusion protocol are lower than those reported in most clinical trials.[1,3–5,9] We found no effect of acute dissociative symptoms, age, sex, and history of failed or inability to tolerate ECT on response. Among the subsample receiving long-term treatment, there was no correlation between number of infusions and change in cognition.

Many potential reasons exist for the discrepancy between the relatively lower rates of response and remission in this sample compared to research settings. There is often an "efficacy-effectiveness" gap as new treatments move from research to clinical settings.[28] Considerably less attention is paid to patients outside of research protocols compared to research subjects. Part of the large effect of ketamine observed in research trials may be due to these nonspecific, supportive effects. Randomized trials with ketamine compared to saline placebo may also result in artificially large effect sizes due to functional unblinding because of psychoactive properties of the drug. Compared to samples from prior research trials, our patient sample may also represent a more ill and complicated population. As noted in the Introduction, most of the subjects receiving open-label clinical treatment in our program were considered for clinical trial enrollment but were not appropriate for participation for various reasons, including disallowed comorbid conditions (general medical and/or psychiatric), evidence of ultra-refractoriness (failing numerous previous treatment trials or ECT), current hospitalization, inability to delay treatment long enough to complete required study procedures (medication washout, observation periods), presence of significant suicidal ideation or behavior, and age outside of protocol limits. As one example, almost 40% of our patients began treatment as inpatients. Whereas some research protocols required patients to be hospitalized overnight as part of the research protocol,[1,29] the hospitalized patients from our sample were admitted for clinical reasons of suicide risk or inability to function. Nonetheless, in this sample of complicated and severely ill patients (50% who had failed or not tolerated ECT and 38.9% who were inpatients), we believe a 50% response rate within 2 weeks of treatment is a significant outcome.

While we did not document potential adverse events with the same level of scrutiny afforded in sponsored clinical trials, we did not observe gross decrements in cognition, an increased propensity for delusions, or emergent symptoms indicative of cystitis over time. Beyond the 1 adolescent with continued cannabis use, we saw no evidence of patients showing signs of substance abuse or increased drug seeking in our sample of patients. It should be emphasized, however, that our sample of patients receiving long-term treatment (n = 14) is very small and does not provide statistical power sufficient to detect subtle changes in cognition, delusions, or bladder function. The field urgently awaits further and more powerful long-term safety data on ketamine and related compounds.

Overall, in the 29-month history of our program, 2 former patients committed suicide. One did so 10 months after last contact with our program, and the suicide was judged not to be related to ketamine treatment. The other suicide occurred 4 months after last contact with our program. In this case, the patient's health maintenance organization did not refer the patient back to our institution for consideration of further treatment. Both of these patients had a history of hospitalization for suicide attempts. It is noteworthy that almost half (46.9%) of the patients in our sample had a history of attempted suicide while nearly two-thirds (64.8%) had been hospitalized for suicidal ideation or suicide attempts. In light of this history, we believe it is unlikely that ketamine exposure increased their propensity toward suicide, especially given the long period between the time of death and last ketamine exposure. However, given the severity of illness of patients with treatment-resistant depression,[7] these cases highlight the critical need for consideration of longer-term strategies prior to treatment initiation, especially given the lack of long-term data on ketamine use.[30,31]

The small size and racial homogeneity of our sample limit the generalizability of our results. However, given the paucity of data on long-term safety, our results provide the first signal of long-term safety in a small sample. There remains an urgent need for more powerful and comprehensive long-term safety data on ketamine from much larger samples. This need is underscored by the rapid growth in the number of providers offering ketamine outside of research protocols for the treatment of psychiatric disorders.[11] Given that racemic ketamine hydrochloride no longer has patent protections, it is unlikely that large and long-term clinical trials will be conducted to provide such long-term safety data. The formation of a registry combining data from community and academic sites is therefore the most realistic way of capturing long-term data on the effectiveness and safety of ketamine as a treatment for mood disorders.[32]

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Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. 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(10):1134–1142.
2. Sos P, Klirova M, Novak T, et al. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. *Neuroendocrinol Lett*. 2013;34(4):287–293.
3. Zarate CA Jr, Brutsche NE, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry*. 2012;71(11):939–946.
4. 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(8):856–864.
5. Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. 2010;67(8):793–802.
6. Shiroma PR, Johns B, Kuskowski M, et al. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. *J Affect Disord*. 2014;155:123–129.
7. Vande Voort JL, Morgan RJ, Kung S, et al. Continuation phase intravenous ketamine in adults with treatment-resistant depression. *J Affect Disord*. 2016;206:300–304.
8. Singh JB, Fedgchin M, Daly EJ, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *Am J Psychiatry*. 2016;173(8):816–826.
9. Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry*. 2013;74(4):250–256.
10. Wilkinson ST, Wright D, Fasula MK, et al. Cognitive behavior therapy may sustain antidepressant effects of intravenous ketamine in treatment-resistant depression. *Psychother Psychosom*. 2017;86(3):162–167.
11. Wilkinson ST, Toprak M, Turner MS, et al. A survey of the clinical, off-label use of ketamine as a treatment for psychiatric disorders. *Am J Psychiatry*. 2017;174(7):695–696.
12. Morgan CJ, Muetzelfeldt L, Curran HV. Ketamine use, cognition and psychological wellbeing: a comparison of frequent, infrequent and ex-users with polydrug and non-using controls. *Addiction*. 2009;104(1):77–87.
13. 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.
14. Schobel SA, Chaudhury NH, Khan UA, et al. Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and implicates glutamate as a driver. *Neuron*. 2013;78(1):81–93.
15. Morgan CJ, Curran HV; Independent Scientific Committee on Drugs. Ketamine use: a review. *Addiction*. 2012;107(1):27–38.
16. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47(4):351–354.
17. Duman RS, Aghajanian GK, Sanacora G, et al. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med*. 2016;22(3):238–249.
18. Frye MA, Blier P, Tye SJ. Concomitant benzodiazepine use attenuates ketamine response: implications for large scale study design and clinical development. *J Clin Psychopharmacol*. 2015;35(3):334–336.
19. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-item Quick Inventory of Depressive Symptomatology (QIDS), Clinician rating (QIDS-C), and Self-Report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.
20. 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(1):125–136.
21. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
22. Lisanby SH, Sampson S, Husain MM, et al. Toward individualized post-electroconvulsive therapy care: piloting the Symptom-Titrated, Algorithm-Based Longitudinal ECT (STABLE) intervention. *J ECT*. 2008;24(3):179–182.
23. Maruff P, Thomas E, Cysique L, et al. Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. *Arch Clin Neuropsychol*. 2009;24(2):165–178.
24. Fredrickson J, Maruff P, Woodward M, et al. Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. *Neuroepidemiology*. 2010;34(2):65–75.
25. Ostroff R, Gonzales M, Sanacora G. Antidepressant effect of ketamine during ECT. *Am J Psychiatry*. 2005;162(7):1385–1386.
26. Ribeiro CM, Sanacora G, Hoffman R, et al. The use of ketamine for the treatment of depression in the context of psychotic symptoms: to the editor. *Biol Psychiatry*. 2016;79(9):e65–e66.
27. Dwyer JB, Beyer C, Wilkinson ST, et al. Ketamine as a treatment for adolescent depression: a case report. *J Am Acad Child Adolesc Psychiatry*. 2017;56(4):352–354.
28. Eichler HG, Abadie E, Breckenridge A, et al. Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. *Nat Rev Drug Discov*. 2011;10(7):495–506.
29. Feder A, Parides MK, Murrough JW, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry*. 2014;71(6):681–688.
30. Sanacora G, Frye MA, McDonald W, et al; American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*. 2017;74(4):399–405.
31. Wilkinson ST, Sanacora G. Considerations on the off-label use of ketamine as a treatment for mood disorders. *JAMA*. 2017;318(9):793–794.
32. Sanacora G, Heimer H, Hartman D, et al. Balancing the promise and risks of ketamine treatment for mood disorders. *Neuropsychopharmacology*. 2017;42(6):1179–1181.

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Supplementary Material

Article Title: Acute and Longer-Term Outcomes Using Ketamine as a Clinical Treatment at the Yale Psychiatric Hospital

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Appendix 1

Methods

Ketamine Dosing
Ketamine dosing is 0.5mg/kg. If BMI > 30, we initially use adjusted body weight for this calculation, which is calculated as follows:

Adjusted body weight = ideal body weight + 40% * (actual body weight – ideal body weight)

Ideal body weight is calculated according to the formula below:

For males: 50kg + (2.3 kg*inches for every inch in height above 5 feet)
For females: 45.5kg + (2.3 kg*inches for every inch in height above 5 feet)

For individuals who are < 5 feet in height, use actual weight unless weight is > 50kg for men or > 45.5kg for women; in this case, we use 50kg for men and 45.5kg for women as ideal body weight.

Appendix 2

Consent Form: "Off-label use of ketamine for the Treatment of a Major Depressive Episode"

I authorize Dr. _____ and assistants of his/her choice to administer intravenous (IV) ketamine to _____ (name of patient) and to continue this treatment at such intervals, as they may deem advisable.

I understand the US Food and Drug Administration have not approved ketamine for the treatment of depression. Ketamine is being administered "off-label" based on several small clinical trials that suggest the medication has rapid acting antidepressant effects in some patients that have not responded to standard antidepressant treatments. I also understand that the longer-term benefits of the treatments on depression have not yet been evaluated. I have discussed the above with my physician and understand these issues to my satisfaction.

I understand that before IV ketamine is given, there will be a complete physical examination, which may include an electrocardiogram, and chest x-rays if indicated. I understand that there may be cardiologic, neurologic, or anesthesiology consults requested if indicated.

I understand that there are acute risks of ketamine administration.

- I may have a dissociative experience, which may consist of a distorted sense of time, a feeling I am detached from own body, or an altered sense of perception (hearing, vision, etc.) that may be uncomfortable and cause some anxiety. The infusion may be stopped if there are any concerns about my safety.
- I may experience changes in my blood pressure or heart rate. Although it is highly unlikely, these physiological effects could cause serious unwanted consequences including stroke and death. The occurrence of significantly increased blood pressure and/or heart rate could necessitate stopping the ketamine infusion as a safety concern. To prevent this during future treatments, I may be given a low-dose of oral blood pressure medication.

I understand that during the infusion and for the period during which I am regaining a normal mental status, I will be closely observed.

I understand that heavy and chronic ketamine use may cause unwanted side effects, including impaired cognition, inflammation of the bladder, delusions, and/or addiction/dependence. I also understand that moderate quantities of ketamine, administered in a time-limited fashion, may have side effects that are currently unknown.

I understand that I will not be able to drive for 24 hours after completing a ketamine treatment, and I will need to have a responsible adult accompany me to home on each treatment day.

Alternative methods of treatment have been explained to me and I understand them. I have been given the opportunity to ask about potential risks and benefits and alternative treatment options, and my concerns have been answered to my satisfaction. I understand my decision to agree to ketamine is made on a voluntary basis, and that I may withdraw my consent at any time.

Signed:

Physician's Note

I have informed _____ (name of patient, parent or guardian) of the purpose, potential benefits and possible risks of ketamine infusion, which is to be performed under my direction. Alternative methods of treatment have been discussed and I have answered the patient's questions.

Additional physician comments:

Printed name of physician:
Signature of physician:

Supplementary Table 1. Concomitant medications during acute course.

Psychotropic Medication Class	N (%)
Any antidepressant (%)	39 (72.2)
SSRI	12 (22.2)
SNRI	11 (20.4)
TCA	4 (7.4)
MAOI	5 (9.3)
Other (Bupropion, mirtazapine, vortioxetine)	14 (25.9)
Antipsychotic	29 (53.7)
Mood stabilizer/anticonvulsant	20 (37.0)
Valproic acid	2 (3.7)
Lamotrigine	13 (24.1)
Gabapentin	5 (9.3)
Other (Topiramate, Oxcarbezapine)	2 (3.7)
Lithium	10 (18.5)
Sedative/hypnotic	27 (50.0)
Benzodiazepine	25 (46.3)
Zolpidem	5 (9.3)
Stimulant	12 (22.2)
Any psychotropic	52 (96.3)

Supplementary Table 2. Concomitant medications for longer-term patients.

Time Point	Medications
Patient 1, baseline	Tranylcypromine 20mg, lurasidone 40mg, lamotrigine 100mg
3 months	Tranylcypromine 40mg, lurasidone 60mg, lamotrigine 200mg, lorazepam 1mg
6 months	Tranylcypromine 40mg, lurasidone 80mg, lamotrigine 300mg, lorazepam 1mg
12 months	Tranylcypromine 40mg, lurasidone 60mg, lamotrigine 300mg, riluzole 100mg
18 months	Tranylcypromine 40mg, lurasidone 60mg, lamotrigine 300mg
24 months	Tranylcypromine 60mg, lurasidone 20mg, quetiapine 25mg, lamotrigine 300mg
Patient 2, baseline	Buspirone 60mg, clozapine 250mg, lamotrigine 300mg, lorazepam 2mg, lithium 300mg, benztropine 1mg, glycopyrrolate 2mg, prazosin 4mg
3 months	Buspirone 60mg, clozapine 250mg, lamotrigine 350mg, lorazepam 2mg, lithium 300mg, benztropine 1mg, glycopyrrolate 2mg, prazosin 4mg
6 months	Buspirone 60mg, clozapine 250mg, lamotrigine 350mg, lorazepam 2mg, lithium 300mg, benztropine 1mg, glycopyrrolate 2mg, prazosin 4mg
12 months	Buspirone 60mg, clozapine 250mg, lamotrigine 350mg, lorazepam 2mg, lithium 300mg, benztropine 1mg, glycopyrrolate 2mg, prazosin 4mg
18 months	Buspirone 30mg, clozapine 250mg, lamotrigine 350mg, lorazepam 2mg, lithium 300mg, benztropine 1mg, glycopyrrolate 2mg, prazosin 4mg
24 months	Clozapine 250mg, lamotrigine 350mg, lithium 300mg, benztropine 1mg, glycopyrrolate 2mg, prazosin 4mg
Patient 3, baseline	Venlafaxine 150mg, bupropion 100mg, lorazepam 1mg, zolpidem 10mg
3 months	Venlafaxine 150mg, bupropion 100mg, lorazepam 1mg, zolpidem 10mg
6 months	Venlafaxine 150mg, bupropion 100mg, lorazepam 1mg, zolpidem 10mg
12 months	Venlafaxine 225mg, bupropion 100mg, lorazepam 1mg, zolpidem 10mg, trazodone 100mg
18 months	Venlafaxine 225mg, bupropion 100mg, lorazepam 1mg, zolpidem 10mg, trazodone 100mg
24 months	Venlafaxine 225mg, bupropion 100mg, lorazepam 1mg, zolpidem 10mg
Patient 4, baseline	Lamotrigine 400mg, clonazepam 2mg, lithium 900mg, methylphenidate 60mg
3 months	Lamotrigine 400mg, clonazepam 2mg, lithium 900mg, methylphenidate 60mg

6 months	Lamotrigine 400mg, clonazepam 2mg, lithium 1200mg, methylphenidate 60mg
12 months	Lamotrigine 150mg, clonazepam 2mg, lithium 1200mg, methylphenidate 60mg
18 months	Lamotrigine 150mg, clonazepam 2mg, lithium 1200mg, methylphenidate 30mg
24 months	Lamotrigine 150mg, clonazepam 2mg, lithium 1200mg, methylphenidate 30mg
Patient 5, baseline	Tranylcypromine 30mg, hydroxyzine 25mg, lorazepam .5mg, temazepam 15mg, lithium 600mg, gabapentin 600mg
3 months	Tranylcypromine 50mg, hydroxyzine 25mg, lorazepam .5mg, lithium 600mg, gabapentin 600mg
6 months	Tranylcypromine 60mg, lorazepam 1mg, lithium 600mg, gabapentin 600mg
12 months	Tranylcypromine 60mg, clozapine 100mg, risperidone 3mg, lorazepam 1mg, temazepam 15mg, gabapentin 600mg
18 months	Tranylcypromine 60mg, clozapine 100mg, risperidone 4mg, lorazepam 2mg, temazepam 15mg, gabapentin 600mg
24 months	Tranylcypromine 40mg, perphenazine 32mg, lorazepam 2mg, temazepam 15mg, gabapentin 200mg
Patient 6, baseline	Aripiprazole 15mg, lithium 300mg, amphetamine salts 40mg, trazodone 50mg
3 months	Aripiprazole 15mg, lithium 450mg, amphetamine salts 40mg
6 months	Aripiprazole 15mg, lithium 750mg, amphetamine salts 40mg
12 months	Risperidone 2mg, lithium 1200mg
Patient 7, baseline	Fluoxetine 80mg, quetiapine 50mg
3 months	Fluoxetine 80mg, quetiapine 50mg
6 months	Fluoxetine 80mg, quetiapine 50mg
12 months	Fluoxetine 80mg, quetiapine 50mg
Patient 8, baseline	Quetiapine 400mg, oxcarbazepine 600mg, lamotrigine 150mg
3 months	Quetiapine 400mg, oxcarbazepine 600mg, lamotrigine 150mg, Liothyronine 10mcg
6 months	Quetiapine 400mg, oxcarbazepine 350mg, lamotrigine 75mg, Liothyronine 10mcg
12 months	Quetiapine 275mg, oxcarbazepine 350mg, lamotrigine 75mg, Liothyronine 10mcg
18 months	Quetiapine 275mg, oxcarbazepine 350mg

Patient 9, baseline	Duloxetine 60mg, bupropion 150mg, gabapentin 400mg, lorazepam 1mg
3 months	Duloxetine 60mg, bupropion 150mg, gabapentin 400mg, lorazepam 1mg
6 months	Duloxetine 60mg, bupropion 300mg, gabapentin 400mg, lorazepam 1mg
12 months	Duloxetine 60mg, bupropion 300mg, gabapentin 400mg, lorazepam 1mg, modafinil 100mg
Patient 10, baseline	Phenelzine 45mg, alprazolam 2mg
3 months	Phenelzine 45mg, liothyronine 5mcg, alprazolam 2mg,
6 months	Venlafaxine 150mg, liothyronine 5mcg, alprazolam 2mg, gabapentin 200mg
12 months	Protriptyline 20mg, alprazolam 1mg
18 months	Pramipexole .125mg, alprazolam .25mg
24 months	Pramipexole .5mg
Patient 11, baseline	Desvenlafaxine 100mg, bupropion 300mg, buspirone 30mg, mirtazapine 30mg, lamotrigine 300mg
3 months	Desvenlafaxine 100mg, bupropion 300mg, buspirone 30mg, mirtazapine 30mg, lamotrigine 300mg
Patient 12, baseline	Fluvoxamine 200mg, clonidine .1mg, lurasidone 80mg, lithium 450mg
3 months	Buproprion 200mg, lurasidone 80mg, clonazepam .5mg, lithium 450mg,
Patient 13, baseline	Bupropion 150mg, trazodone 150mg, amphetamine salts 30mg, liothyronine 5mg, nortriptyline 75mg
3 months	Bupropion 150mg, trazodone 150mg, amphetamine salts 30mg, liothyronine 5mg
6 months	Bupropion 150mg, trazodone 50mg, amphetamine salts 30mg, liothyronine 5mg
Patient 14, baseline	Bupropion 450mg, methylphenidate 36mg, venlafaxine 75mg
3 months	Bupropion 450mg, methylphenidate 36mg, duloxetine 60mg
6 months	Bupropion 300mg, methylphenidate 54mg, duloxetine 120mg
12 months	Bupropion 300mg, methylphenidate 54mg, duloxetine 120mg