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Research Paper

# Long-term outcome in outpatients with depression treated with acute and maintenance intravenous ketamine: A retrospective chart review

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ABSTRACT

*Background:* Little is known about the long-term outcomes of repeated ketamine infusions for depression. We conducted a retrospective chart review to investigate outcomes of maintenance intravenous ketamine treatment at Massachusetts General Hospital.

*Methods:* Eighty-five patients with treatment-resistant depression (TRD) who started intravenous ketamine from October 2018 to November 2019 were examined. Symptom severity was evaluated with the 16-item Quick Inventory of Depressive Symptomatology-Self Report scale (QIDS-$SR_{16}$) at every visit prior to administration. The initial ketamine dose was usually 0.5 mg/kg infused over 40 min. Intravenous ketamine was administered twice-weekly for three weeks in an induction phase, followed by maintenance with a variable administration schedule and dose. Response was defined as a ≥50% reduction in total QIDS-$SR_{16}$ score from baseline.

*Results:* Forty (47.1%) of the 85 patients who started treatment discontinued during or right after the induction phase; 3 (3.5%) were still on induction at the time of this report, and 42 (49.4%) transitioned to maintenance after completing induction. Among these patients, 14 (16.5%) discontinued during maintenance and 28 (32.9%) continued on maintenance. The mean ketamine dosage during maintenance was 0.91 ± 0.28 mg/kg. Fifteen out of 82 patients (18.3%) responded to induction treatment and 6 (7.3%) remained in responder status at the time of data analysis during maintenance. Three patients discontinued ketamine due to side-effects.

*Conclusions:* Despite the apparently low response rate in QIDS-$SR_{16}$ scores and considerable out-of-pocket costs, almost half of real-world outpatients with TRD decided to continue with maintenance ketamine treatment due to perceived significant improvement.

## 1. Introduction

Ketamine, an N-methyl-D-aspartate receptor antagonist, has been shown in short-term studies to be effective for patients with treatment-resistant depression (TRD) and for patients with suicidal ideation (Wilkinson and Sanacora, 2016). Multiple clinical trials have demonstrated that even a single subanesthetic dose of intravenous ketamine has a rapid-acting antidepressant effect (Cusin et al., 2017; Diamond et al., 2014; Fava et al., 2018; Singh et al., 2016).

However, the long-term outcome of patients treated repeatedly with intravenous ketamine has been reported only through case series. Wilkinson et al. summarized intravenous ketamine treatment with a 4-infusion protocol for 44 patients with mood disorder at Yale Psychiatric Hospital and published the outcome of maintenance treatment for 14 of them who were followed for up to two years (Wilkinson et al., 2018). Archer et al. in a retrospective study of 30 patients treated with an induction course reported on 11 patients with refractory major depressive disorder (MDD) and bipolar depression (BD) who received maintenance intravenous ketamine treatment for up to one year (Archer et al., 2018). Riva-Posse et al. examined cardiovascular safety in 66 patients with TRD who had received maintenance ketamine treatment for up to 2 years (Riva-Posse et al., 2018).

The major concerns about long-term safety and efficacy of ketamine treatment derive primarily from the literature on patients with ketamine use disorder, which reports major adverse effects such as persisting psychotic and dissociative symptoms, impaired cognition, and

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interstitial cystitis (Liang et al., 2013; Morgan et al., 2012; Myers et al., 2016). In 2019, Janssen published controlled data regarding long-term efficacy and safety of administration of intranasal esketamine in 297 patients with TRD, followed for up to 92 weeks (Daly et al., 2019). In this study, the patients who were maintained on esketamine frequently reported transient dysgeusia, vertigo, dissociation, somnolence, and dizziness (Daly et al., 2019) but there was no report of persistent cognitive disturbances or urinary problems. In another 56-week open-label maintenance study with esketamine, 9.5% of the patients with TRD who were initially considered responders discontinued the drug due to adverse events such as anxiety, depression, blood pressure increased, dizziness, suicidal ideation, and dissociation (The U.S. Food and Drug Administration, 2019).

The Intravenous Ketamine Clinic for Depression at Massachusetts General Hospital opened in late 2018 and has treated patients with TRD. In the present report, we present the long-term clinical and dispositional outcome of all patients with TRD who started intravenous ketamine treatment at our facility over a continuous period of 13 months through a retrospective chart review.

## 2. Methods

### 2.1. Clinical procedures

At MGH ketamine treatment is offered to patients with severe and refractory MDD or BD with at least two or more adequate antidepressant treatment failures (however, they were referred to the clinic after an average of 7.4 ± 3.7 previous antidepressant trials), while patients with history of psychosis, current substance use disorder, or uncontrolled medical illness are not eligible for ketamine treatment. After psychiatric consultation and medical assessment, patients review and sign a consent for ketamine treatment that emphasizes that ketamine is not approved by the US FDA and is provided off-label for depression, in addition to potential risks and benefits. Patients are required to pay out of pocket for each infusion due to lack of insurance coverage for the procedure. At each visit, patients are evaluated and monitored by a staff psychiatrist, a nurse, and an anesthesiologist. Symptom severity is evaluated with the 16-item Quick Inventory of Depressive Symptomatology-Self Report scale (QIDS-$SR_{16}$) (Rush et al., 2003) and Clinical Global Impression-Severity/Improvement scales (CGI-S/I) before administration and at every subsequent visit. The initial ketamine dose is usually 0.5 mg/kg infused over 40 min. Patients who experience transient dissociative symptoms or anxiety during the infusions can receive intravenous lorazepam 1 mg to improve tolerability of the infusion. Patients who experience nausea can receive intravenous ondansetron or/and prochlorperazine. Blood pressure is monitored at regular intervals during the infusions and for 30 min afterwards and patients with clinically significant increase in blood pressure can be received intravenous labetalol. Criteria for discharge readiness include return to baseline mental status, absence of gait disturbance and nausea, and normal blood pressure. All administrations are provided between the hours of 5:30pm and 8pm. Any administration requires the patient to be discharged to the care of an adult escort, and driving is not permitted in the evening post administration until the following day. Intravenous ketamine is administered with a twice-weekly schedule for three weeks as an induction phase, followed by maintenance with variable administration schedule (i.e. every 2–6 weeks) based on duration of effect. Depending on response and tolerability, the dose during the induction can be individually adjusted up to 1.2 mg/kg. The dose in the maintenance phase remains stable, with exceptions in cases of major changes in medical condition or concomitant medications. Other pharmacological and psychotherapeutic treatments are continued as part of the usual regimen.

In the present report, patients with depression who started ketamine treatment from October 2018 to November 2019 were included. This retrospective data analysis was approved by the Institutional Review Board (IRB) of the Massachusetts General Hospital. The following information was collected from patient charts: age, sex, race, ethnicity, diagnosis, concomitant psychiatric disorder, number of depressive episodes, duration of current episode, history of suicide attempts, treatment history, marital status, employment status, used ketamine dose, total duration of ketamine treatment, adverse events during ketamine administration, and reasons for discontinuation. Response to intravenous ketamine was defined as a ≥50% reduction in the QIDS-$SR_{16}$ total score from baseline. Presence of suicidal ideation was defined as a score of ⩾1 on the suicidal ideation item of the QIDS-$SR_{16}$. Logistic regression analysis was performed to evaluate associations between non-response and the following variables: age, sex, employment status, primary diagnosis (i.e. MDD or BD), psychiatric comorbidities, duration of current episode, history of suicide attempt, history of psychiatric hospitalization, number of lifetime antidepressant trials, history of failed lifetime electroconvulsive therapy (ECT) trials, and the QIDS-$SR_{16}$ total score at baseline. A two-tailed P value of $<0.05$ was considered statistically significant. Statistical analysis was conducted using Statistical Package for Social Science (SPSS) version 23.0 for Windows (IBM Corporation, Armonk, NY).

## 3. Results

### 3.1. Subject characteristics

A total of 87 outpatients were treated at the MGH ketamine clinic from October 25th, 2018 to November 30th, 2019. Table 1 shows baseline demographic and clinical characteristics of these patients.

### 3.2. Treatment outcome

Of the 87 outpatients who began intravenous ketamine treatment, 2 patients were enrolled directly in the maintenance phase, due to prior history of good response to ketamine treatment received elsewhere. Among the 85 patients who were ketamine naive, 59 (69.4%) completed the induction series of 6 ketamine infusions, 23 (27.1%) discontinued before the sixth infusion, and 3 (3.5%) were still in the induction phase at the time of this report (Fig. 1). Reasons for early discontinuation of treatment included insufficient improvement ($n=11$), side-effects ($n=3$) including dissociative symptoms, agitation, and migraine, transition to intranasal ketamine treatment ($n=3$) and lost to follow-up ($n=3$). The mean number of infusions received in these patients was 3.0 ± 1.3 administrations. The mean ketamine dose was 61.1 ± 27.0 mg (0.77 ± 0.19 mg/kg) in the discontinued patients and 76.4 ± 24.4 mg (0.97 ± 0.24 mg/kg) in completers. If the patient did not tolerate the most recent dose increase, the dose returned to the previous level (18 patients, 21.2%). Three patients did not complete QIDS-$SR_{16}$ at baseline. Among the 82 patients who had QIDS-$SR_{16}$ data at baseline, 15 (18.3%) achieved response by infusion 6 (Fig. 2), and 29 (35.4%) had improved by 35% or more in the QIDS-$SR_{16}$ total score. On logistic regression analyses only short duration of the current depressive episode significantly predicted subsequent non-response (OR = 0.944, 95% CI = 0.893-0.997, $p=0.040$), although this result did not remain significant after correction for multiple testing, while that other variables including age, sex, unemployment, primary diagnosis, psychiatric comorbidity, history of suicide attempt, history of psychiatric hospitalization, number of failed lifetime antidepressant trials, history of failed lifetime ECT trials, and the QIDS-$SR_{16}$ total score at baseline were not associated with outcome (Table 2). No statistically significant difference was found in the response rate between those who received intravenous lorazepam to improve tolerability of infusion and those who did not (13.6% (6/44) vs. 23.7% (9/38), $\chi^2(1)=1.38$, $p=0.24$). Among the 67 patients who had a suicidal ideation score $>0$ on the QIDS-$SR_{16}$ at baseline, 12 (17.9%) achieved complete absence of suicidal ideation by infusion 6, and 25 (37.3%) decreased the score by at least 1 level (e.g. from 2 to 1 or from 2 to 0) from baseline. One

**Table 1**
Baseline demographic and clinical characteristics.

| Characteristics | Patients (n = 87) |
|---|---|
| Age in years, mean ± SD (range) | 46.0 ± 19.1 (17-81) |
| Female, n (%) | 48 (55.2%) |
| Race/Ethnicity, n (%) | |
| Caucasian | 79 (90.8%) |
| Asian | 2 (2.3%) |
| Others | 6 (6.9%) |
| Education completed, n (%) | |
| Grade 6-12 or graduated high school | 6 (6.9%) |
| Some college | 18 (20.7%) |
| Graduated 4-year college | 30 (34.5%) |
| Graduate/professional degree | 31 (35.6%) |
| Unknown | 2 (2.3%) |
| Current marital status, n (%) | |
| Single, never married | 42 (48.3%) |
| Married, civil union, cohabitating | 35 (40.2%) |
| Separated, divorced, widowed | 10 (11.5%) |
| Current employment status, n (%) | |
| Full-time | 30 (34.5%) |
| Part-time | 5 (5.7%) |
| Not employed | 32 (36.8%) |
| Student | 20 (23.0%) |
| Primary diagnosis, n (%) | |
| MDD | 78 (89.7%) |
| BD, depressed | 9 (10.3%) |
| Current concomitant psychiatric disorder, n (%) | 58 (66.7%) |
| GAD | 32 (36.8%) |
| PTSD | 12 (13.8%) |
| OCD | 6 (6.9%) |
| ADHD | 17 (19.5%) |
| Others | 22 (25.3%) |
| Concomitant medications in 78 patients with MDD, n (%) | |
| Antidepressant drug | 72 (92.3%) |
| Antidepressant combination | 35 (44.9%) |
| Mood stabilizer | 30 (38.5%) |
| Antipsychotic drug | 28 (35.9%) |
| Concomitant medications in 9 patients with BD, n (%) | |
| Antidepressant drug | 7 (77.8%) |
| Antidepressant combination | 4 (44.4%) |
| Mood stabilizer | 9 (100.0%) |
| Antipsychotic drug | 7 (77.8%) |
| Multiple episodes, n (%) | 58 (66.7%) |
| Duration of current episode, years, mean ± SD | 6.7 ± 11.1 |
| History of suicide attempt, n (%) | 26 (29.9%) |
| Lifetime mean number of failed antidepressant trials, mean ± SD | 7.4 ± 3.7 |
| Treatment history with ECT, n (%) | 29 (33.3%) |
| Treatment history with TMS, n (%) | 24 (27.6%) |
| CGI-S, mean ± SD | 5.2 ± 0.7 |
| QIDS-$SR_{16}$, mean ± SD | 17.0 ± 5.1 |

ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; CGI-S, Clinical Global Impressions-Severity of Illness; ECT, electroconvulsive therapy; GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; QIDS-$SR_{16}$, Quick Inventory of Depressive Symptomatology Self Report; SD, standard deviation; TMS, transcranial magnetic stimulation

patient committed suicide approximately 10 days after the fourth treatment of the induction phase (the reasons for delaying the last two infusions are not known), possibly in the context of severe life stressors, even though his score of suicidal ideation had decreased from 2 to 1 on the fourth infusion and his QIDS-$SR_{16}$ total score marginally decreased from 22 to 19. Three patients were referred for inpatient treatment during the induction phase for lack of improvement and persistent suicidal ideation. There was no report of cognitive disturbance or urinary problems on periodic review of symptoms.

After the completion of the induction phase, 17 patients (20.0% of those who started with induction treatment) discontinued ketamine because of insufficient improvement ($n = 12$), transition to intranasal ketamine treatment ($n = 3$), lost to follow-up ($n = 1$), and unknown reasons ($n = 1$). One patient who experienced no improvement in suicidal ideation or depressive symptoms after the sixth infusion attempted suicide by overdose and was hospitalized. The remaining 42 patients (49.4% of those who started induction treatment) continued with maintenance intravenous ketamine, with the longest follow up being 11 months, and they were analyzed together with the 2 patients who entered directly in the maintenance phase as described above. Among these 44 patients, 15 discontinued during maintenance and 29 patients were still on maintenance at the time of data analysis. Reasons for discontinuation included insufficient improvement ($n = 7$), transition to intranasal ketamine treatment ($n = 5$), financial reasons ($n = 1$), moving to another country ($n = 1$), and lost to follow-up ($n = 1$). For the patients who discontinued during maintenance treatment, the mean number of infusions received was 2.3 ± 1.5 after the initial six. The mean dosages of ketamine during maintenance treatment were 77.4 ± 18.6 mg (1.00 ± 0.26 mg/kg) in the discontinued patients and 75.5 ± 25.9 mg (0.93 ± 0.23 mg/kg) in completers. The mean intervals between ketamine infusions during maintenance treatment were 3.4 ± 3.9 weeks in the discontinued patients and 4.0 ± 3.3 weeks in the continued patients. One patient decided to continue maintenance treatments at a different facility. Among the 15 patients who responded to induction treatment, 6 (7.3% of those who started induction treatment) also remained as responders at the time of data analysis during the maintenance phase. Out of the 29 patients who improved by 35% or more in the QIDS-$SR_{16}$ total score during the induction phase, 13 (15.9%) remained the similar improvement at the time of data analysis during the maintenance phase. Among the 12 patients who achieved complete absence of suicidal ideation during the induction phase, 5 (7.4% of those who reported suicidal ideation at baseline) still reported no suicidal ideation at the time of data analysis during the maintenance phase. Out of the 25 patients who decreased the suicidal ideation score by at least 1 level on the QIDS-$SR_{16}$ during the induction phase, 13 (19.4%) remained the equivalent reduction at the time of data analysis during the maintenance phase. None of the patients needed to be admitted to the hospital during the maintenance phase. There was no report of cognitive disturbance or urinary problems.

### 3.3. Ketamine treatment switch- intravenous to intranasal

A total of 11 patients who started intravenous ketamine were switched to racemic ketamine intranasal (i.e. 5 during the induction phase, 3 after the completion of the induction phase, and 3 during the maintenance phase). In our clinical practice, the off-label intranasal racemic ketamine was started at 50 mg every week, with the frequency and dose adjusted individually up to 200 mg every 2–3 days depending on the duration of antidepressant response in the following days. It is likely that all the patients had significant concerns about the out of pocket cost of intravenous ketamine that provided benefit only for a few days, while they were interested in continuing with an intranasal treatment that could provide similar or slightly lower benefit for a fraction of the cost. Among these patients, 4 discontinued ketamine treatment after an average 3.8 ± 1.9 months because of insufficient improvement ($n = 3$) or side-effects (unpleasant feelings) ($n = 1$). Their CGI-I scores at the endpoint were 4 ($n = 2$) and 3 ($n = 2$). On the other hand, 7 patients continued to receive ketamine for an average of 9.3 ± 3.1 months. Their CGI-I scores at the time of analysis were 2 ($n = 4$), 3 ($n = 2$), and 4 ($n = 1$).

## 4. Discussion

To our knowledge, this is the largest reported investigation of intravenous ketamine treatment for 85 consecutive patients with TRD in a clinical treatment setting. Despite the apparent low response rate on the QIDS-$SR_{16}$ score (18.3%), more than one third of patients displayed reduction in suicidality. Furthermore, almost 50% of patients transitioned to maintenance treatment, which might a proportion similar to other studies (31–37%) (Archer et al., 2018; Wilkinson et al., 2018).

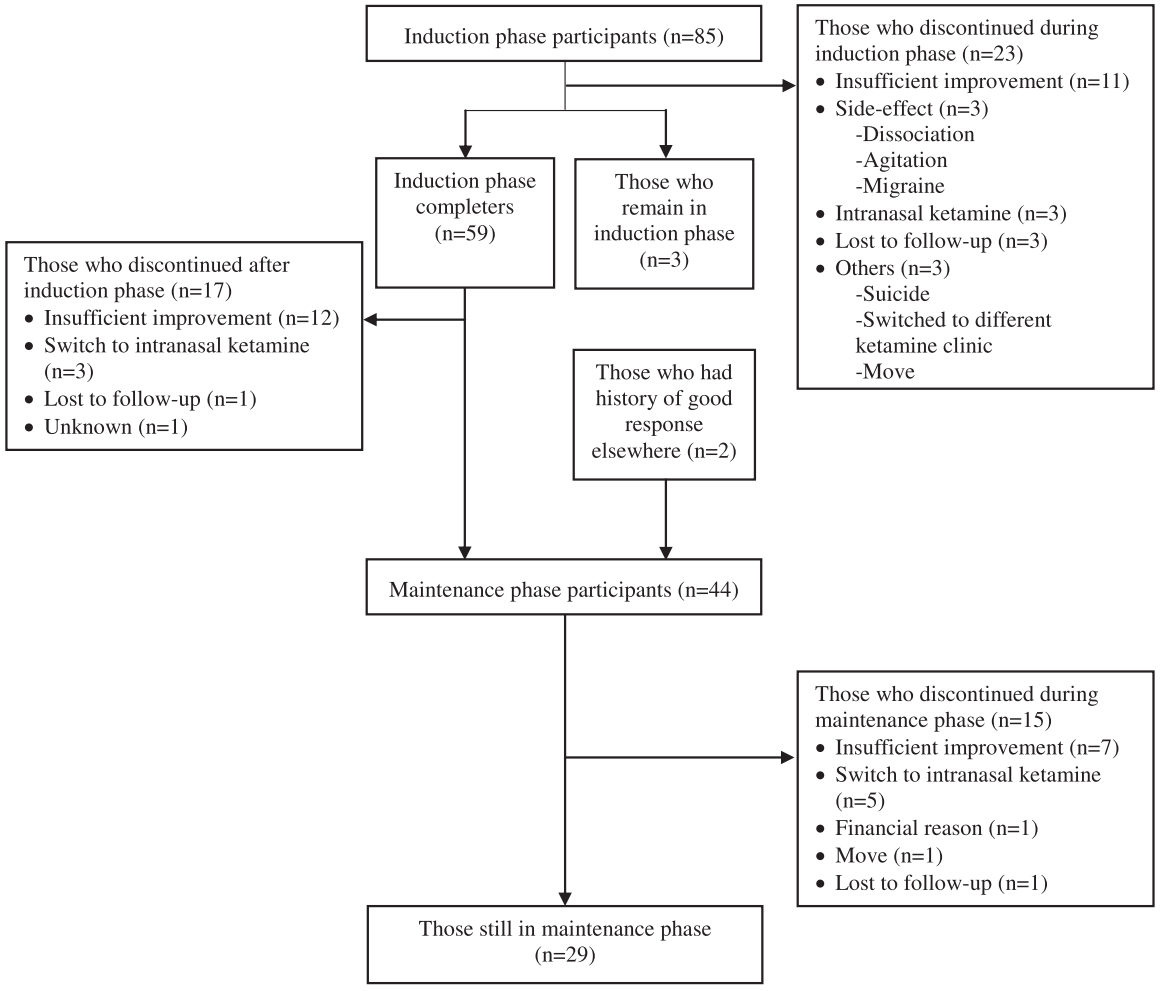


**Fig. 1.** Patient flow.

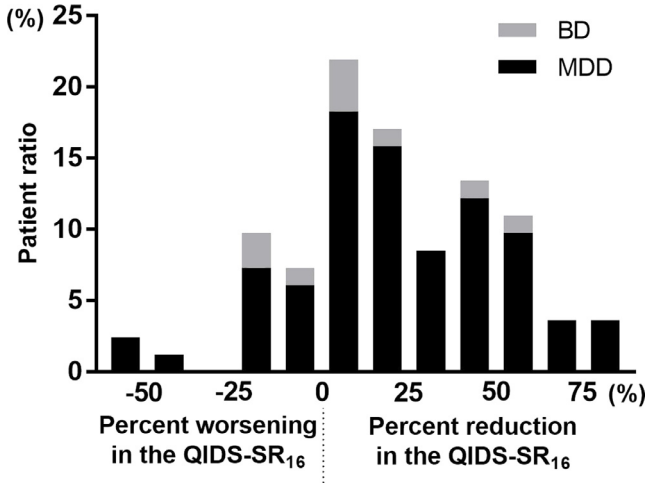


**Fig. 2.** Percentage Reduction in the QIDS-$SR_{16}$ during Ketamine Induction Treatment, Abbreviations: BD, bipolar disorder; MDD, major depressive disorder; QIDS-$SR_{16}$, 16-item Quick Inventory of Depressive Symptomatology-Self Report scale.

These findings indicate that they had experienced a level of improvement sufficient to justify continuing ketamine treatment despite side effects experienced during the infusion and costs of the treatment.

The response rate to intravenous ketamine in our clinic appears significantly lower compared to rates published in randomized controlled trials (RCTs), which range from 30% to 70% on day 1 (Aan Het Rot et al., 2012; Fava et al., 2018; Grunebaum et al., 2018). Similarly, the decrease in suicidal ideation severity after initial series of infusions was observed in a relatively low percentage of patients, compared with the reported effectiveness of ketamine treatment for decreasing suicidal ideation in the literature (Grunebaum et al., 2017). Participants in clinical trials do not usually reflect patients seen in clinical practice because of strict selection criteria (Zimmerman et al., 2004). Indeed, patients in our sample had an average duration of current episode of 6.7 ± 11.1 years, 69.0% had at least one comorbid psychiatric disorder, and had at least 7.4 ± 3.7 lifetime failed antidepressant trials, which reflects a high level of treatment resistance of our population. In addition, because ketamine infusions are currently not covered by insurance, the high cost of repeated intravenous ketamine ($530/infusion at our clinic) is a major contributor to early discontinuation if the perceived benefit is not sufficient to justify continuing treatment.

Furthermore, the present response rate to intravenous ketamine was also lower than that of the Wilkinson et al.'s case series, which was 45.5% with a 4-infusion protocol at fixed dose of 0.5 mg/kg (Wilkinson et al., 2018). One possible explanation for this discrepancy is the difference in dosing schedule. In our clinical procedure, the ketamine dose was adjusted individually up to 1.2 mg/kg, with clinical outcome assessed in the following days with frequent remote contacts with the primary psychiatrist, therapist, and ketamine clinicians. For example, the starting dose was with 0.5 mg/kg and increased to 0.6 mg/kg at the second infusion, 0.75 mg/kg at the third, and 1.0 mg/kg at the fourth if a patient without significant side effects reported no

**Table 2**
Association between clinical variables and non-response.

| | β | Odds ratio | 95% CI | P value |
|---|---|---|---|---|
| Age | 0.001 | 1.001 | 0.956-1.049 | 0.953 |
| Female sex | 1.270 | 3.562 | 0.739-17.170 | 0.113 |
| Unemployment | 0.043 | 1.044 | 0.181-6.006 | 0.961 |
| Primary diagnosis BD | 0.210 | 1.234 | 0.096-15.869 | 0.872 |
| Psychiatric comorbidity | -1.015 | 0.363 | 0.067-1.956 | 0.238 |
| **Duration of current episode** | **-0.058** | **0.944** | **0.893-0.997** | **0.040** |
| Prior suicide attempt | -1.355 | 0.258 | 0.057-1.168 | 0.079 |
| History of hospitalization | -0.543 | 0.581 | 0.112-3.003 | 0.517 |
| Number of failed antidepressant trials | -0.004 | 0.996 | 0.818-1.211 | 0.966 |
| History of ECT | 0.893 | 2.443 | 0.359-16.638 | 0.361 |
| QIDS-$SR_{16}$ at baseline | 0.077 | 1.080 | 0.943-1.237 | 0.266 |

BD, bipolar disorder; CI, confidence interval; ECT, electroconvulsive therapy; QIDS-$SR_{16}$, 16-Item Quick Inventory of Depressive Symptomatology, Self-Reported

change in their mood or suicide ideation in the following days after ketamine infusion. We are aware that in pre-clinical studies, there is data considering that ketamine may have a U-shaped antidepressant effect and that higher doses may be less effective for depression-like behaviors in rodents (Chowdhury et al., 2017; Li et al., 2010). However, taking account of the high out of pocket costs of ketamine infusions and our prior experience in a similar population of highly treatment-resistant patients who were showing minimal improvement with three infusions at the same dose of 0.5 mg/kg and partial improvement with dose increment to 0.75 mg/kg for the following three infusions (Cusin et al., 2017), we needed to balance costs for the patient and the need to try different doses to help with their severe depression. Another possible explanation for discrepancy in results is that we administer the QIDS-$SR_{16}$ prior to each infusion in our clinical setting, not at a pre-specified endpoint. While in research studies the outcome measure is usually administered 1–7 days after the infusion, as it was in the case series, such difference in the timing of evaluation might contribute to the difference in apparent response rate. Finally, some patients sustain response or remission from one visit to the next during maintenance phase while others experienced a period of progressively worsening mood over days at the end of the cycle, just before the next scheduled infusion. Lower response rates at follow up may especially be influenced by this pattern.

Our results suggest that repeated administrations of intravenous ketamine were well tolerated without serious adverse events. Only 3 of 85 patients (3.5%) dropped out during the induction phase because of side effects, and this finding is consistent with previous reports (aan het Rot et al., 2010; Wilkinson et al., 2018). While 81 patients (93.1%) experienced transient dissociative symptoms and 31 (35.6%) experienced anxiety during the infusions, 45 (51.7%) of them were treated with intravenous lorazepam 1 mg to improve tolerability of the infusion. Although it has been reported that concomitant benzodiazepine use might attenuate ketamine response (Frye et al., 2015), in our sample intravenous lorazepam use was not significantly associated with response rate to the induction treatment. Thirty-nine patients (44.8%) received intravenous ondansetron or prochlorperazine because of nausea during the infusions. Only one patient (aged 78 years, with history of poorly controlled hypertension) required administration of labetalol 5 mg.

This study has several limitations. First, this is a retrospective chart review and patients were followed naturalistically, with the possibility to continue or change antidepressants and psychotherapy regimen according to recommendations from the treating psychiatrist. The effect of concomitant treatments for medical or psychiatric conditions on ketamine efficacy has not been thoroughly investigated, and some medications may interfere with the effect of ketamine, thus impacting treatment outcomes. However, it would not be feasible or safe for most patients to taper off and discontinue concurrent psychiatric treatments for the purpose of undergoing ketamine therapy. Second, the high drop-out rate observed in our sample may have been influenced by the cost of ketamine infusions, since this treatment is not currently covered by insurance. Third, drug screening test was not conducted. However, after patients are referred to our clinic by their long-term provider, we discuss the referral with the primary psychiatrist, including the exclusion of patients with current substance use disorder. Besides, in addition to the detailed review on drug use history at the initial visit, patients are strongly advised to avoid marijuana and alcohol during induction treatment as they may interfere with the antidepressant effect of ketamine. Finally, there is the (albeit unlikely) possibility that some adverse events, including mild cognitive disturbances and urinary problems went undetected without screening tools. However, patients report marked improvement in concentration, motivation, and social functioning that correlated with decrease in depression severity, and were able to resume the previous level of functioning (work or college classes) that preceded the severe depression. Overall, the cost of infusions and presence of short-term side effects did not deter a large proportion of patients from continuing with ketamine infusions because of perceived benefit on depression and quality of life that may not have been fully captured by the QIDS-$SR_{16}$ scores.

In conclusion, long-term ketamine treatment was well tolerated and produced modest improvement on QIDS-$SR_{16}$ score in real-world outpatients with TRD, and almost 50% of patients elected to continue with this relatively expensive treatment because of perceived benefit on depression and suicidal ideation. At present, we are lacking guidelines for pharmacological treatment of patients with MDD who failed more than 5-6 antidepressants trials. For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Level 4 trial, the cumulative response rates after up to 14 weeks of tranylcypromine and combination treatment with venlafaxine and mirtazapine on the QIDS-$SR_{16}$ scale were 12.1% and 23.5%, respectively (McGrath et al., 2006). In an observational study to examine the effectiveness of adjunctive Vagal Nerve Stimulation (VNS), the cumulative response rate of treatment-as-usual at 3 months was less than 10% for those who had 7.3 failed treatments for depression (Aaronson et al., 2017). Large, pragmatic comparative effectiveness studies are urgently needed to identify the role of ketamine in the depression treatment algorithm, as well as to better characterize the optimal dosing and frequency of ketamine treatment for TRD.

## Declaration of Competing Interest

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Hitoshi Sakurai: Statistical analysis, interpretation of data, and writing first draft of the article.

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Paola Pedrelli: Interpretation of data and co-writing of article.

David Mischoulon: Interpretation of data and co-writing of article.

Maurizio Fava: Interpretation of data and co-writing of article.

Cristina Cusin: Study design, PI of current report, interpretation of data and co-writing of article.

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## References


Aan het Rot, M., Collins, K.A., Murrough, J.W., Perez, A.M., Reich, D.L., Charney, D.S., Mathew, S.J., 2010. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol. Psychiatry 67, 139–145. https://doi.org/10.1016/j.biopsych.2009.08.038.

Aan Het Rot, M., Zarate, C.A., Charney, D.S., Mathew, S.J., 2012. Ketamine for depression: where do we go from here? Biol. Psychiatry 72, 537–547. https://doi.org/10.1016/j.biopsych.2012.05.003.

Aaronson, S.T., Sears, P., Ruvuna, F., Bunker, M., Conway, C.R., Dougherty, D.D., Reimherr, F.W., Schwartz, T.L., Zajecka, J.M., 2017. A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: comparison of response, remission, and suicidality. Am. J. Psychiatry 174, 640–648. https://doi.org/10.1176/appi.ajp.2017.16010034.

Archer, S., Chrenek, C., Swainson, J., 2018. Maintenance Ketamine Therapy for Treatment-Resistant Depression. J. Clin. Psychopharmacol. 38, 380–384. https://doi.org/10.1097/JCP.0000000000000894.

Chowdhury, G.M.I., Zhang, J., Thomas, M., Banasr, M., Ma, X., Pittman, B., Bristow, L., Schaeffer, E., Duman, R.S., Rothman, D.L., Behar, K.L., Sanacora, G., 2017. Transiently increased glutamate cycling in rat PFC is associated with rapid onset of antidepressant-like effects. Mol. Psychiatry 22, 120–126. https://doi.org/10.1038/mp.2016.34.

Cusin, C., Ionescu, D.F., Pavone, K.J., Akeju, O., Cassano, P., Taylor, N., Eikermann, M., Durham, K., Swee, M.B., Chang, T., Dording, C., Soskin, D., Kelley, J., Mischoulon, D., Brown, E.N., Fava, M., 2017. Ketamine augmentation for outpatients with treatment-resistant depression: Preliminary evidence for two-step intravenous dose escalation. Aust. N. Z. J. Psychiatry 51, 55–64. https://doi.org/10.1177/0004867416631828.

Daly, E.J., Trivedi, M.H., Janik, A., Li, H., Zhang, Y., Li, X., Lane, R., Lim, P., Duca, A.R., Hough, D., Thase, M.E., Zajecka, J., Winokur, A., Divacka, I., Fagiolini, A., Cubala, W.J., Bitter, I., Blier, P., Shelton, R.C., Molero, P., Manji, H., Drevets, W.C., Singh, J.B., 2019. Efficacy of Esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. https://doi.org/10.1001/jamapsychiatry.2019.1189.

Diamond, P.R., Farmery, A.D., Atkinson, S., Haldar, J., Williams, N., Cowen, P.J., Geddes, J.R., McShane, R., 2014. Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. J. Psychopharmacol. Oxf. Engl. 28, 536–544. https://doi.org/10.1177/0269881114527361.

Fava, M., Freeman, M.P., Flynn, M., Judge, H., Hoeppner, B.B., Cusin, C., Ionescu, D.F., Mathew, S.J., Chang, L.C., Iosifescu, D.V., Murrough, J., Debattista, C., Schatzberg, A.F., Trivedi, M.H., Jha, M.K., Sanacora, G., Wilkinson, S.T., Papakostas, G.I., 2018. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Mol. Psychiatry. https://doi.org/10.1038/s41380-018-0256-5.

Frye, M.A., Blier, P., Tye, S.J., 2015. Concomitant benzodiazepine use attenuates ketamine response: implications for large scale study design and clinical development. J. Clin. Psychopharmacol. 35, 334–336. https://doi.org/10.1097/JCP.0000000000000316.

Grunebaum, M.F., Ellis, S.P., Keilp, J.G., Moitra, V.K., Cooper, T.B., Marver, J.E., Burke, A.K., Milak, M.S., Sublette, M.E., Oquendo, M.A., Mann, J.J., 2017. Ketamine versus midazolam in bipolar depression with suicidal thoughts: a pilot midazolam-controlled randomized clinical trial. Bipolar Disord. 19, 176–183. https://doi.org/10.1111/bdi.12487.

Grunebaum, M.F., Galfalvy, H.C., Choo, T.-H., Keilp, J.G., Moitra, V.K., Parris, M.S., Marver, J.E., Burke, A.K., Milak, M.S., Sublette, M.E., Oquendo, M.A., Mann, J.J., 2018. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. Am. J. Psychiatry 175, 327–335. https://doi.org/10.1176/appi.ajp.2017.17060647.

Li, N., Lee, B., Liu, R.-J., Banasr, M., Dwyer, J.M., Iwata, M., Li, X.-Y., Aghajanian, G., Duman, R.S., 2010. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329, 959–964. https://doi.org/10.1126/science.1190287.

Liang, H.J., Lau, C.G., Tang, A., Chan, F., Ungvari, G.S., Tang, W.K., 2013. Cognitive impairments in poly-drug ketamine users. Addict. Behav. 38, 2661–2666. https://doi.org/10.1016/j.addbeh.2013.06.017.

McGrath, P.J., Stewart, J.W., Fava, M., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Thase, M.E., Davis, L., Biggs, M.M., Shores-Wilson, K., Luther, J.F., Niederehe, G., Warden, D., Rush, A.J., 2006. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. Am. J. Psychiatry 163, 1531–1541. https://doi.org/10.1176/ajp.2006.163.9.1531. quiz 1666.

Morgan, C.J.A., Curran, H.V., Independent Scientific Committee on Drugs, 2012. Ketamine use: a review. Addict. Abingdon Engl. 107, 27–38. https://doi.org/10.1111/j.1360-0443.2011.03576.x.

Myers, F.A., Bluth, M.H., Cheung, W.W., 2016. Ketamine: a cause of urinary tract dysfunction. Clin. Lab. Med. 36, 721–744. https://doi.org/10.1016/j.cll.2016.07.008.

Riva-Posse, P., Reiff, C.M., Edwards, J.A., Job, G.P., Galendez, G.C., Garlow, S.J., Saah, T.C., Dunlop, B.W., McDonald, W.M., 2018. Blood pressure safety of subanesthetic ketamine for depression: a report on 684 infusions. J. Affect. Disord. 236, 291–297. https://doi.org/10.1016/j.jad.2018.02.025.

Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., Markowitz, J.C., Ninan, P.T., Kornstein, S., Manber, R., Thase, M.E., Kocsis, J.H., Keller, M.B., 2003. 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 54, 573–583. https://doi.org/10.1016/s0006-3223(02)01866-8.

Singh, J.B., Fedgchin, M., Daly, E.J., De Boer, P., Cooper, K., Lim, P., Pinter, C., Murrough, J.W., Sanacora, G., Shelton, R.C., Kurian, B., Winokur, A., Fava, M., Manji, H., Drevets, W.C., Van Nueten, L., 2016. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am. J. Psychiatry 173, 816–826. https://doi.org/10.1176/appi.ajp.2016.16010037.

The U.S. Food and Drug Administration, 2019. Esketamine. Maryland.

Wilkinson, S.T., Katz, R.B., Toprak, M., Webler, R., Ostroff, R.B., Sanacora, G., 2018. Acute and longer-term outcomes using ketamine as a clinical treatment at the Yale Psychiatric Hospital. J. Clin. Psychiatry 79. https://doi.org/10.4088/JCP.17m11731.

Wilkinson, S.T., Sanacora, G., 2016. Ketamine: a potential rapid-acting antisuicidal agent? Depress. Anxiety 33, 711–717. https://doi.org/10.1002/da.22498.

Zimmerman, M., Chelminski, I., Posternak, M.A., 2004. Exclusion criteria used in antidepressant efficacy trials: consistency across studies and representativeness of samples included. J. Nerv. Ment. Dis. 192, 87–94. https://doi.org/10.1097/01.nmd.0000110279.23893.82.