Real-world patient characteristics, treatment patterns, efficacy and safety of intramuscular ketamine treatment: a retrospective cohort study

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Abstract

Background

Ketamine has emerged as a promising pharmacotherapy for depression and other mental illnesses, and the intramuscular (IM) administration of ketamine is now offered at many North American outpatient psychiatric clinics. However, a characterization of the outpatient population receiving IM ketamine treatment, and an evaluation of the real-world efficacy and safety of long-term IM ketamine treatment, has not been reported. This study aimed to evaluate the clinical characteristics, treatment patterns, clinical outcomes, and adverse events of patients receiving IM ketamine treatment.

Methods

Patient data from the electronic health records of a private outpatient psychiatric clinic network in the United States were collected and analyzed retrospectively. Adults who received ketamine treatment only by IM administration from January 2018 to June 2021 were included; a total of 452 patients were included in the cohort.

Results

Patients receiving IM ketamine treatment had a mean of 2.8 (SD 1.4) psychiatric diagnoses. 420 (93%) patients had a diagnosis of major depressive disorder, 243 (54%) patients had a diagnosis of generalized anxiety disorder, and 126 (28%) patients had a diagnosis of post-traumatic stress disorder. Thirty-seven percent (42/114) of patients reported a history of a previous suicide attempt, and patients had an average of 3.1 (SD 2.9) psychiatric medication prescriptions at baseline. Patients received between 1 and 48 IM ketamine treatments. Average depression and anxiety symptoms both significantly improved by 34% ($p < .001$) from baseline (PHQ-9: mean=16.3, SD=6.7; GAD-7: mean=12.8, SD=5.7) to patients' last treatment (PHQ-9: mean=10.8, SD=5.9; GAD-7: mean=8.4, SD=5.5), and suicidal ideation scores also significantly improved ($p < .001$) . With maintenance ketamine treatments, median improvements in depression and anxiety of at least 21% and 19% were maintained for over 13 months. An adverse event occurred during 59 of 2,532 treatments (2.3%).

Conclusions

IM ketamine is being utilized to treat psychiatric outpatients with a moderate-to-severe mental health history and multiple mental illnesses not limited to depression. Average depression and anxiety levels significantly improve throughout IM ketamine treatment and do not regress to baseline for over one year with maintenance treatments. Prospective studies are recommended to confirm the long-term efficacy and safety of IM ketamine.

Background

Major depressive disorder (MDD) is a common psychiatric disorder with a lifetime prevalence of 15% [1], and is projected to be the global leading cause of burden of disease by 2030 [2]. The currently recommended first-line treatment options for MDD, which include second-generation antidepressants and psychotherapy [3, 4], have limitations. Firstly, patients' initial response to antidepressants can take two to four weeks [5], and up to 70% of patients are noncompliant to antidepressant prescriptions most commonly due to their side effects [6]. Forms of psychotherapy have shown effectiveness in reducing depression severity, but evidence regarding comparative effectiveness of various psychotherapy modalities is lacking [7]. Clinically efficacious somatic therapy options exist for MDD such as repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT) [8, 9]. However, limitations of these treatments include that rTMS is costly and time consuming [10], and ECT can cause the rare adverse effect of retrograde amnesia [11].

Ketamine is a glutamatergic n-methyl-$_D$-aspartate receptor antagonist. Ketamine was originally approved in 1970 as an anesthetic [12], and behaves as an anesthetic agent at doses of 2 to 10 mg/kg depending on the route of administration [13]. Over the past two decades however, low-dose ketamine has emerged as a pharmacological treatment option for MDD due to its rapid antidepressant and antisuicidal effects [14–18] and good safety and tolerability profile [19, 20]. Ketamine treatment has also demonstrated efficacy for patients with other psychiatric disorders. It has been shown to reduce anxiety symptoms in patients with generalized anxiety disorder (GAD) and/or social anxiety disorder (SAD) [21–23], and evidence suggests that these anxiolytic effects can be maintained for over three months with weekly ketamine treatments [24]. Ketamine also shows potential efficacy for the reduction of symptoms of substance use disorders [25–28], post-traumatic stress disorder (PTSD) [29], bipolar depression [30], and eating disorders [31].

Racemic ketamine, or ketamine's S-enantiomer "esketamine", can be administered via intravenous (IV), intranasal (IN), oral, sublingual (SL), anal, subcutaneous, and intramuscular (IM) routes [32]. Racemic IV ketamine has become a commonly offered off-label treatment for MDD at ketamine infusion clinics across North America and Europe [33]. While the majority of research on racemic ketamine treatment has been on IV ketamine, the IM route has a similar bioavailability of nearly 100% [5, 34]. Correspondingly, initial studies show that racemic IM ketamine treatment shows comparable mental health outcomes as IV ketamine infusions. IM and IV ketamine showed a similar 60% and 59% reduction in depression symptoms, respectively, as measured by the Hamilton Depression Rating Scale at two hours after injection, for 18 patients with treatment-refractory MDD [12]. Furthermore, a case series of 40 MDD patients receiving six IM ketamine treatments showed reductions in depression (Patient Health Questionnaire, PHQ-9), anxiety (Generalized Anxiety Disorder-7, GAD-7) and PTSD (PTSD Checklist for DSM-V) symptoms of 55%, 51% and 51% respectively, which is analogous to IV administration [35].

While IM ketamine has initially showed similar efficacy to IV ketamine, it may also be a more convenient and practical option for mental health treatment in community psychiatric clinics and primary care clinics [12]. This is because IM administration does not require the use and monitoring of an IV infusion pump [12, 36], and it is relatively less expensive than IV administration [12, 35]. Variations of IM ketamine

treatment have already begun to be offered by specialized psychiatric clinics in North America as an off-label indication to treat a variety of mental illnesses [37–42].

Only one study has described the psychiatric IM ketamine treatment provided at these outpatient clinics [32]. Dore et al. reported patient demographic, diagnosis, and depression/anxiety outcome data for 235 patients receiving IM and SL ketamine-assisted psychotherapy from three private general psychiatric practices. Given the limited data and promising potential for IM ketamine as an effective treatment option for patients with MDD and other mental illnesses, there is a need to evaluate patients receiving IM ketamine at outpatient psychiatric clinics. Specifically, the patient population currently receiving psychiatric IM ketamine treatment, including their psychiatric diagnoses, medications, and patient history, require characterization. Furthermore, evaluation of depression and anxiety outcomes and safety profile of long-term IM ketamine treatment is needed.

In this retrospective cohort study, we report the patient population and outcomes of 452 patients receiving IM ketamine treatment at a network of private outpatient psychiatric clinics. We describe the demographic characteristics, medical and social history, diagnoses, and medications of patients receiving IM ketamine therapy as well as the depression and anxiety outcome measures, adverse events (AEs), vital signs, and cost of this treatment.

Methods

This retrospective cohort study was conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices and received ethics clearance from the University of Utah Institutional Review Board.

We evaluated adults 18 years or older who received IM ketamine treatment at a private outpatient psychiatric clinic network between January 1st, 2018 and June 30th, 2021. The psychiatric clinics offer a range of mental health services, including ketamine therapy, psychotherapy, medication management, and transcranial magnetic stimulation [43]. Patients who received IV, oral, or SL ketamine, or IN esketamine from the clinics during the study period were excluded from the study.

Patients received this clinic's standard of care for IM ketamine treatment. A clinician – either a psychiatrist or physician assistant – was responsible for each patient's initial recommendation and prescription for ketamine treatment, and the ongoing management of their ketamine treatment plan including patients' ketamine dosage, treatment frequency and number of ketamine treatments. For each ketamine treatment, patients were advised to avoid food and liquids for the 6 hours preceding the treatment, and to avoid driving or the operation of heavy machinery for at least 6 hours after the treatment. During ketamine treatments, each patient was monitored using blood pressure, pulse, and direct observation for at least 60 minutes after the administration of ketamine by the prescribing clinician, with support from a medical assistant. The prescribing clinician was responsible for responding to any AEs that arose and recording the presence of AEs in the appropriate clinical notes. An effort was made by the clinic to encourage a calm set and setting for patients during their treatments. Patients received

ketamine while laying in a reclining chair in a quiet room with dim lights. During the treatments, patients wore eye shades and listened to music through headphones. Patients selected the music from a collection of playlists consisting of relaxing non-lyrical music curated by clinic staff.

Study data was collected retrospectively from the psychiatric clinic's electronic health records (EHR) system. Data was collected from the EHR through customizable reports and medical chart review. Variables collected through customizable reports include patient demographics, self-reported medical, social and family history, treatment dates, depression, suicidal ideation (SI) and anxiety outcomes, treatment payments, and insurance coverage. Some variables were not available as structured reports, so they were collected via manual chart review. These variables include patients' diagnoses, concomitant medications, AEs, vital signs, and ketamine dosage.

The primary outcomes of interest were scores from the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7) survey scores, which were administered to patients before each ketamine treatment session. The PHQ-9 and GAD-7 are valid and reliable measures to screen for MDD and GAD in clinical practice and research [44, 45]. The PHQ-9 asks patients to rate the frequency of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition's (DSM-V) symptoms of MDD over the past two weeks [44]. The PHQ-9 total score ranges from 0 to 27, with scores representing minimal depression (0-4), mild depression (5-9), moderate depression (10-14), moderately severe depression (15-19), and severe depression (20-27). Item 9 of the PHQ-9 is a brief suicidal ideation (SI) measure. This SI measure is scored on a scale of 0 to 3, and shows validity for use as a screening tool for suicide risk [46]. The GAD-7 prompts patients to rate the frequency of the DSM-V symptoms of GAD over the past two weeks [45]. The GAD-7 total score ranges from 0 to 21, and scores represent mild anxiety (0-5), moderate anxiety (6-10), moderately severe anxiety (11-15), and severe anxiety (15-21).

Statistical Analysis

Descriptive statistics were used to summarize study variables. The number of patients (*N*) with data for demographic characteristics depends on whether the corresponding data was collected and recorded by clinicians. The sample size for each medical, social and family history variable also varies based on how many patients completed the self-report forms. The number of patients with data on each variable is shown, and percentages are calculated based on the number of patients with data available.

Spearman's rank correlations were used to test the association between ketamine dose and patient weight as well as the association between the number of ketamine treatments patients received and their PHQ-9, SI and GAD-7 scores. Multiple linear regression analyses were conducted to explore potential predictors of the change in depression and anxiety measures from baseline to last ketamine treatment. Only covariates with complete data were included in the multivariable analysis. Forward selection with an entry significance level of 0.15 was utilized to determine the final covariates for predicting change in depression and anxiety scores. Both models were tested for outliers with standardized residuals, and influential values were evaluated with Cook's Distance. The variance inflation factor and condition index

were used to assess collinearity. Linearity and heteroskedasticity assumptions were assessed using residual plots. Normality was tested graphically with a histogram and Q-Q plot of the residuals. The R^2 value was calculated to determine how much variability in the change in depression score or anxiety score was accounted for by the multiple regression models. STATA version 16 and IBM SPSS version 28 were used for statistical analyses. Levels of significance in this study were defined as $p < .05$.

Results

A total of 452 patients received IM ketamine treatment from January 1st, 2018 to June 30th, 2021 and met all inclusion/exclusion criteria. 230 (51%) patients were female and patients' median age at baseline was 36.4 (IQR 20.4) years. Additionally, 95% (365/384) of patients were white, non-Hispanic, and non-Latino. For patients 30 years or older, 88% (144/164) had engaged in some post-secondary education (Table 1).

The self-reported social and mental health history of IM ketamine patients are summarized in Table 1. Of patients with self-reported data, 47% (99/210) reported being a survivor of previous physical or sexual abuse, 37% (41/112) of patients reported a history of self-harm behaviour, and 37% (42/114) of patients reported a history of one or more suicide attempts. Additionally, 31% (61/199) of patients reported a history of having received inpatient treatment at a psychiatric hospital.

Table 1

Demographic characteristics and self-reported social and mental health history of patients receiving IM ketamine therapy

	No. of patients with available data	N (%)
Demographic characteristics		
Sex, female	452	230 (51%)
Age group	452	
18-29 years		155 (34%)
30-39 years		117 (26%)
40-49 years		78 (17%)
50-59 years		62 (14%)
≥ 60 years		40 (9%)
Race	410	
American Indian or Alaska Native		2 (1%)
Asian		7 (2%)
Black or African American		3 (1%)
Native Hawaiian or Other Pacific Islander		1 (0.2%)
White		397 (97%)
Ethnicity	395	
Hispanic or Latino		16 (4%)
Utah residence	419	399 (95%)
Highest education level (30 years or older)	164	
$10^{th}/11^{th}$ grade		2 (1%)
High school graduate or GED		18 (11%)
Some college (in progress or incomplete)		52 (32%)
Undergraduate degree		63 (38%)
Graduate degree		29 (18%)
Employed	276	181 (67%)
Living status	236	
Owns house/apartment		103 (44%)
Rents house/apartment		66 (28%)
Lives with parent(s)/family		55 (23%)

Lives with friend(s)/roommate(s)		12 (5%)
Social History		
History of physical or sexual abuse	210	99 (47%)
Mental Health History		
Previous psychotherapy	197	110 (56%)
Any self-harm behaviour	85	35 (41%)
Suicide attempts	114	42 (37%)
Psychiatric hospitalizations	199	61 (31%)
Attended a drug/alcohol treatment centre	233	29 (12%)

All psychiatric diagnoses of patients are summarized in Table 2. All 452 patients had at least 1 psychiatric diagnosis, and patients had mean of 2.8 (SD 1.4) psychiatric diagnoses. Approximately 420 patients (93%) had MDD and 437 patients (97%) had any mood disorder including MDD, bipolar disorder, dysthymic disorder, cyclothymic disorder, or unspecified mood disorder. Furthermore, 288 patients (64%) had an anxiety disorder which includes GAD, anxiety disorder unspecified, panic disorder, or phobic anxiety disorder.

Table 2

Psychiatric diagnoses of patients receiving IM ketamine therapy

Total *N* = 452	N (%)
Major depressive disorder	420 (93%)
Generalized anxiety disorder	243 (54%)
Post-traumatic stress disorder	126 (28%)
Attention-deficit hyperactivity disorder	107 (24%)
Insomnia	90 (20%)
Anxiety disorder unspecified	54 (12%)
Bipolar disorder	41 (9%)
Panic disorder	38 (8%)
Other mental disorder*	35 (8%)
Substance use disorder	23 (5%)
Obsessive compulsive disorder	22 (5%)
Personality disorder	18 (4%)
Eating disorder	15 (3%)
Unspecified mood disorder	14 (3%)
Phobic anxiety disorder	13 (3%)

**Other mental disorder includes the following diagnoses: dysthymic disorder (n=8), adjustment disorder (n=6), psychotic disorder (n=6), impulse disorder (n=4), acute stress reaction (n=3), delusional disorder (n=3), autism spectrum disorder (n=3), somatoform disorder (n=3), cyclothymic disorder (n=2), and dissociative disorder (n=1).*

At baseline, patients were taking an average of 3.1 (SD 2.9) psychiatric medications other than ketamine, and 354 (78%) patients were taking at least one psychiatric medication. The most common medication class was antidepressants. For the 294 patients (65%) taking antidepressants, these patients were taking an average of 1.8 (SD 1.0) different antidepressants each (Table 3).

Table 3

Psychiatric medications at baseline for patients receiving IM ketamine therapy

Total *N* = 452	N (%) of patients	Mean (SD) prescriptions per patient
All psychiatric medications	354 (78%)	4.0 (2.7)
Antidepressant	294 (65%)	1.8 (1.0)
Stimulant	142 (31%)	1.2 (.5)
Benzodiazepine	141 (31%)	1.3 (.5)
Antipsychotic	135 (30%)	1.3 (.6)
Anticonvulsant	89 (20%)	1.1 (.3)
Sedative/hypnotic	76 (17%)	1.2 (.4)
Anticonvulsant/mood stabilizer	57 (13%)	1.0 (.2)
Azapirone	36 (8%)	1.0 (0.0)
Mood stabilizer	22 (5%)	1.0 (0.0)
Dopamine agonist	17 (4%)	1.1 (.3)
Tricyclic antidepressant	9 (2%)	1.0 (0.0)
Alcohol antagonist	5 (1%)	1.2 (.4)
Cannabis/cannabinoid	4 (1%)	1.0 (0.0)
NMDA receptor antagonist	2 (0.4%)	1.0 (0.0)
Opioid antagonist	2 (0.4%)	1.0 (0.0)

Regarding patients' self-reported history of substance use at baseline (Supplemental Table 1), 2% (6/250) of patients reported heavy alcohol consumption, 11% (32/281) of patients reported being current tobacco smokers, 4% (10/233) of patients reported current opiate use, and 20% of patients reported prior psychedelic drug use.

Of the 266 patients with completed self-report data on family mental health history (Supplemental Table 2), 236 patients (89%) had a family history of mental illness, and 37 patients (14%) had a family member who had attempted suicide. Also, 165 (62%) of patients had a family history of depression, and 132 patients (50%) had a family history of an anxiety disorder.

IM Ketamine Treatment Patterns

The number of ketamine treatments patients received ranged from 1 to 48, with a median of 4 (IQR 5) treatments. The median duration from first to last treatment was 21 (IQR 89.8) days. The frequency of acute treatments, defined as treatments one to six, was one treatment per median 5 (IQR 4) days. The

frequency of maintenance treatments, defined as treatments after treatment six, was one treatment per median 21 (IQR 35) days. We observed that treatment frequency progressively decreased after treatment 6 throughout patients' maintenance treatments (Figure 1).

Ketamine dose was positively correlated with patient weight (r(562) = 0.402, $p < .001$). Doses ranged from 0.3 mg/kg to 2.15 mg/kg. Patients were started at a median dose of 0.55 mg/kg (IQR 0.16) at their first treatment, and this median dose increased to 0.91 mg/kg (IQR 0.37) at treatment six ($p < .001$) (Figure 2). The median dose for maintenance treatments, or treatments 7 to 48 ($N = 54$ treatments), was 1.2 (IQR 0.79) mg/kg.

Depression, Suicidal Ideation, and Anxiety Outcomes

There were significant reductions in patients' depression (PHQ-9), SI (PHQ-9 item 9) and anxiety (GAD-7) scores from baseline to last ketamine treatment (Table 4). Average PHQ-9 scores decreased 34% from 16.3 (SD 6.7) or moderately severe depression at baseline, to 10.8 (SD 5.9) or moderate depression at last treatment ($p < .001$). Average GAD-7 scores decreased 34% from 12.8 (SD 5.7) or moderately severe anxiety at baseline, to 8.4 (SD 5.5) or moderate anxiety at last treatment ($p < .001$). Average SI scores significantly decreased from 1.13 (SD 1.16) at baseline to 0.58 (SD 0.76) at last treatment ($p < .001$). The percent of patients reporting any SI, defined as an SI score greater than zero, decreased from 60% (80/133) at baseline to 47% (63/133) at last treatment.

Table 4

Depression (PHQ-9), suicidal ideation (PHQ-9 item 9) and anxiety (GAD-7) scores by number of IM ketamine treatments received

**Only patients with an IM ketamine treatment duration greater than 2 weeks and survey scores available at first and last IM ketamine treatment were included. **2-sample paired t-tests were conducted*

Baseline PHQ-9 scores, but not baseline SI scores or GAD-7 scores, were positively correlated with the number of ketamine treatments patients received (Table 5). Thus, having a higher baseline PHQ-9 score significantly correlated with receiving additional ketamine treatments. The change in PHQ-9, SI, and GAD-7 scores from baseline to last treatment negatively correlated with the number of ketamine treatments patients had received. Thus, additional treatments were correlated with a larger decrease in depression, SI, and anxiety symptom severity.

Table 5

Correlations between the number of ketamine treatments patients received and their survey scores

**1-tailed Spearman's correlation; **2-tailed Spearman's correlation; df = degrees of freedom;* r_s =

	*N**	Score at Baseline Mean (SD)	Score at Last Treatment Mean (SD)	*p*-value**
Depression – PHQ-9				
All treatment lengths	112	16.3 (6.7)	10.8 (5.9)	<.001
Patients with 1 treatment	66	14.4 (7.3)	N/A	N/A
Patients with 2-4 treatments	30	14.4 (7.1)	11.4 (6.1)	<.001
Patients with 5-6 treatments	38	16.6 (6.9)	10.2 (6.1)	<.001
Patients with 7-10 treatments	29	16.3 (6.4)	11.3 (5.9)	<.001
Patients with 11-48 treatments	15	19.1 (5.4)	10.2 (5.7)	<.001
Suicidal ideation – PHQ-9 item 9				
All treatment lengths	112	1.13 (1.16)	0.58 (0.76)	<.001
Patients with 1 treatment	66	1.02 (1.06)	N/A	N/A
Patients with 2-4 treatments	30	0.90 (1.03)	0.63 (0.77)	.044
Patients with 5-6 treatments	38	1.29 (1.25)	0.63 (0.79)	<.001
Patients with 7-10 treatments	29	1.14 (1.12)	0.45 (0.63)	<.001
Patients with 11-48 treatments	15	1.13 (1.30)	0.60 (0.91)	.036
Anxiety – GAD-7				
All treatment lengths	80	12.8 (5.7)	8.4 (5.5)	<.001
Patients with 1 treatment	50	11.0 (6.1)	N/A	N/A
Patients with 2-4 treatments	24	10.8 (5.8)	9.1 (5.6)	.066
Patients with 5-6 treatments	26	14.2 (4.9)	8.3 (6.3)	<.001
Patients with 7-10 treatments	20	11.6 (6.4)	7.6 (4.5)	.004
Patients with 11-48 treatments	10	16.8 (3.0)	8.7 (5.6)	<.001

*Spearman's rank correlation coefficient; bold lettering **=** significant correlation.*

Figure 3 illustrates the change in patients' depression and anxiety symptoms throughout their treatment course. Each patient's survey scores were calculated as a percent of their baseline score, and the median of these percentages at each treatment is depicted. By treatment 6, which was median 22 (IQR 17 – 42) days after patients' first ketamine treatment, depression scores had decreased to median 64% (IQR 44% – 91%) of baseline scores, and anxiety scores had decreased to median 67% (IQR 32% – 94%) of baseline scores.

	PHQ-9			SI			GAD-7		
	df	r_s	*p*-value	df	r_s	*p*-value	df	r_s	*p*-value
Correlation between number of treatments and survey score at baseline*	255	.13	**.016**	255	.02	.353	141	.08	.187
Correlation between number of treatments and survey score at last treatment**	190	.01	.864	190	-.05	.507	139	-.02	.845
Correlation between number of treatments and change in survey score*	131	-.29	**.0003**	131	-.19	**.014**	90	-.38	**<.0001**

Figure 3 also illustrates outcome data for patients' maintenance ketamine sessions, or sessions after patients' initial course of six treatments. We end reporting at treatment 15, which was median 13 (IQR 7 – 18) months after baseline, due to the sample size decreasing to 19 patients by this treatment. From treatments 7 to 15, median depression scores fluctuated between 57% to 79% of baseline (IQR 46% – 95%) and median anxiety scores fluctuated between 51% to 81% of baseline (IQR 41% – 82%). Thus, for patients who continue with maintenance IM ketamine treatments after their acute phase, median depression and anxiety improvements of at least 21% and 19% were maintained for 13 months.

Results of the multiple linear regression analyses predicting the change in depression and anxiety scores from baseline to last treatment are reported in Supplemental Table 3. Baseline PHQ-9 scores (β = -0.53, SE = 0.07) and number of ketamine treatments (β = -0.34, SE = 0.014) were significant predictors of change in PHQ-9 scores from baseline to last treatment ($F(3, 129) = 24.3$, $p < 0.0001$, $R^2 = 0.36$). Baseline GAD-7 scores (β = -0.43, SE = 0.09) and number of ketamine treatments (β = -0.46, SE = 0.17) were significant predictors of change in GAD-7 scores from baseline to last treatment ($F(3,88) = 13.7$, $p < 0.0001$, $R^2 = 0.32$). Thus, patients who had higher baseline PHQ-9 or GAD-7 scores, and who received more treatments, showed significant decreases in PHQ-9 and GAD-7 scores, respectively.

Safety

Reported AEs during IM ketamine treatment included nausea, vomiting, abnormal vital signs, panic attacks, hallucinations, confusion, potentially unsafe movement, and bladder pain. Out of 2,532 treatments, an AE occurred during 59 (2.3%) treatments, and all AEs resolved prior to patients leaving the clinic.

Nausea and vomiting were the most common AEs recorded during ketamine treatments. Out of 2,532 ketamine treatments administered, 34 (7.5%) patients experienced nausea at 47 (1.9%) treatments, and 20 (4.4%) patients vomited at 26 (1.0%) treatments. Patients were commonly administered 8mg oral ondansetron prior to their ketamine injection to help prevent nausea and vomiting.

Patients experienced an abnormally large change in vital signs, as noted by the clinician, at 4 (0.16%) out of 2,532 treatments. For these 4 treatments, the patient's average blood pressure elevation from baseline to peak was 28.8 (systolic) and 16.5 (diastolic) mmHg, and the highest blood pressure elevation was 46 (systolic) and 30 (diastolic) mmHg. To help stabilize elevated blood pressure, two patients were administered beta-blockers. Of the four patients who had abnormal vital signs, one patient had a heart rate elevation of 10 bpm. Vital signs stabilized within 30 minutes for all four patients.

Out of 2,532 total treatments, three patients experienced a panic attack during 4 (0.16%) treatments. Two out of three of these patients had a history of panic attacks before the AE. Hallucinations occurred at 4 (0.16%) treatments, with confusion at 3 (0.12%) treatments. Also, three patients displayed potentially unsafe movement, including a fall, knocking over equipment, or hyperactivity, at 3 (0.12%) treatments. Finally, one patient reported experiencing bladder spasms and pain during 1 (0.04%) treatment, which resolved after a few minutes.

Cost of Treatment

The mean (SD) cost of a single IM ketamine treatment was $229 ($56). This included costs for mental health screening, physician and medical assistant monitoring and follow up, and drug costs including ketamine and ondansetron. Out of 2,248 visits, 2,230 (99%) were paid by the patient in full, whereas for 18 (0.8%) visits, the patients' insurance covered a portion of the cost.

Discussion

In this study, we provide a characterization of the patient population receiving IM ketamine treatment from a psychiatric outpatient clinic in the United States and describe their real-world ketamine treatment patterns. We also evaluate improvements in depression, suicidal ideation, and anxiety symptoms throughout treatment, and evaluate the safety of IM ketamine treatment.

Population

This cohort was relatively racially homogenous, had a moderate-to-severe mental health and social history, had been prescribed multiple psychiatric medications at baseline, and had multiple psychiatric comorbidities with the primary indication for treatment not limited to MDD.

Patients receiving ketamine treatment were less racially and ethnically diverse than the greater population treated by the state's mental health authority, for which 2018 data shows that 13.4% of persons were non-white and 15.8% were Hispanic or Latino (compared to 3% and 4% in this cohort) [47]. One possible explanation for this discrepancy is that the cost of racemic ketamine, which is currently rarely covered by insurance, may limit access for racial/ethnic groups with lower average income [48]. This disproportion could also be due to the relative hesitancy towards trying new prescription drugs amongst minority

patients [49]. Research on possible racial/ethnic disparities in ketamine treatment and other novel psychopharmacotherapies is warranted.

At baseline, patients in this cohort presented with a moderate-to-severe mental health history, social history, and symptom burden. This cohort showed a 37% lifetime history of suicide attempts which was equal to a 2007 characterization study of outpatient psychiatric patients [50]. This cohort had a substantial 47% prevalence of lifetime history of physical or sexual abuse, which is comparable to the 56% of psychiatric outpatients and 42% of nonpsychiatric outpatients with a history of abuse reported in 2000 [51], a point in time when abuse was more prevalent [52]. The substantial prevalence of abuse in this cohort mirrors the significant adverse childhood experiences (ACE) scores reported in ketamine-assisted psychotherapy patients by Dore et al (mean ACE score = 3.6) [32]. Furthermore, at baseline, this cohort's average symptom burden was within the moderately severe depression and anxiety ranges on the PHQ-9 and GAD-7, approximating the baseline PHQ-9 and GAD-7 scores of MDD patients in a recent IM ketamine case series of 40 patients [35].

Although racemic ketamine can be prescribed off-label as a first-line treatment for various psychiatric disorders, ketamine in this cohort was not commonly used as a first-line psychiatric treatment. In fact, the average patient in this cohort had already been prescribed 3.1 different psychiatric medications at baseline. This supports Dore et al.'s [32] view that the typical ketamine patient has tried other medications that were insufficient and comes to ketamine treatment seeking additional symptom relief to what they have previously experienced. Limitations of antidepressants and other traditional psychiatric medications are likely contributing to driving the increasing psychiatric use of ketamine.

Patients in this observational study were also clinically complex, in that they had an average of 2.8 psychiatric comorbidities each. This contrasts with cohorts in prospective trials of ketamine therapy where patients with multiple psychiatric comorbidities are either excluded or are rare [5, 14, 21]. In real-world clinical practice, IM ketamine treatment is being utilized to treat a clinically complex population. Importantly, IM ketamine was also used to treat patients with a diverse range of mental illnesses not limited to depression. In fact, since only 93% of patients carried a diagnosis of MDD, if follows that at least 7% of patients were receiving ketamine to specifically treat a mental illness other than unipolar depression.

Treatment Patterns

The treatment schedule of patients in this cohort was consistent with protocols from previous trials [53–55] and case reports [56] of ketamine therapy for treatment-resistant depression, where patients received an acute phase of up to 6 treatments within the span of one month, with some patients then receiving less frequent maintenance treatments during the subsequent months or years as determined on a case-by-case basis.

Patients received a median of four IM ketamine treatments – fewer than the typical six treatments reported in the repeated ketamine infusion literature [53–55]. However, it is unlikely that this was due to tolerability issues, given this cohort's low AE rate of 59 out of 2,532 treatments (2.3%). Instead, we report here that higher baseline depression scores correlated to a greater number of ketamine treatments. Thus, patients with lower baseline depression scores may have required fewer treatments for their depression symptoms to decrease to a manageable level and may have then decided that further treatments would not be personally cost-effective. Discontinuation of treatment at an individual patient level could have also been due to insufficient symptom improvement from initial ketamine treatments, or due to the normal attrition rate experienced in real-world clinical practice.

The ketamine dosing schedules of patients at this clinic were collaboratively determined between patients and their care teams. The trend of starting patients at a lower median dose of 0.5 mg/kg and increasing their dose throughout treatment allowed clinicians to determine patients' individualized sensitivity to ketamine, to provide the greatest possible symptom alleviation while limiting patient's risk of AEs. The ketamine doses reported in this study are higher than the initial pilot trials reported for psychiatric IM ketamine, for which the highest dose was 0.5 mg/kg [12, 57]. However, the median doses of 0.55 and 0.91 mg/kg at first and sixth ketamine treatments in this cohort are similar to the real-world IM ketamine doses reported by Bonnett et al. for MDD patients [35].

Efficacy

There were significant improvements in depression and anxiety symptoms from baseline to last ketamine treatment in this cohort. The magnitude of improvements in depression and anxiety were similar to the only other study to date to report on a real-world cohort of patients with a variety of mental illnesses receiving IM and SL ketamine-assisted psychotherapy at an outpatient clinic [32]. In that study, patients' average symptom scores decreased from moderate depression (BDI) and anxiety (HAM-A) at baseline to mild depression and anxiety after treatment. Based on a validated conversion of their reported BDI scores to PHQ-9 scores [58], the average estimated 31% reduction in depression symptoms reported from IM and SL ketamine-assisted psychotherapy was similar to this IM ketamine cohort's 34% reduction in depression symptoms. The current study shows that, for patients with a variety of mental illnesses, improvements in average depression and anxiety symptoms occur from before to after outpatient IM ketamine treatment.

Interestingly, while Dore et al. observed on subgroup analysis that patients with PTSD experienced the greatest improvements in depression and anxiety scores, our study did not confirm this finding. In fact, our adequately powered regression analysis did not show any major psychiatric diagnoses to significantly predict the degree of improvement in depression or anxiety symptoms. This suggests that, when covariates such as baseline symptom severity and number of treatments are controlled for, patients with a variety of mental illnesses experience similar improvements in depression and anxiety symptoms

from ketamine treatment. This observation allows us to more appropriately compare depression and anxiety symptom scores between ketamine studies of different diagnostic populations.

A recent case series of real-world data from forty MDD patients receiving six IM ketamine treatments reported large reductions in depression and anxiety symptoms of 55% (PHQ-9) and 51% (GAD-7) [35]. These improvements are greater than the 39% and 42% reductions in PHQ-9 and GAD-7 scores respectively, that were experienced among the patients in this cohort who received either five or six ketamine treatments. This variation could be due to several reasons. Firstly, this difference could be attributed to patients in the current study being more resistant to improvement with ketamine treatment due to their high burden of psychiatric comorbidities relative to the MDD patients in Bonnett et al's study. Secondly, it is also possible that the difference in symptom alleviation between our two studies is due to a variation in dosing schedule. While patients in Bonnett et al's case series received similar IM ketamine injection doses to patients in this cohort (median 0.5 mg/kg at first treatment increased to median 1 mg/kg at sixth treatment), they were administered these doses twice per treatment session, at a 15-minute interval. This resulted in their total session doses being approximately double the total session doses of what was administered to patients in this cohort. Since the therapeutic effects of ketamine have been shown to be dose-dependent [12, 57], this could have resulted in the greater symptom improvements reported by Bonnet et al. Administering multiple subsequent IM ketamine doses during one session as reported by Bonnett et al. could be a useful clinical tool, especially given IM ketamine's shorter peak concentration-times relative to IV ketamine [36]. However, since the adverse effects of ketamine have also been shown to be dose-dependent [12, 57], the safety profile of administering multiple subsequent IM ketamine doses during one session should be evaluated.

Few studies have reported on the efficacy of maintenance ketamine treatments, and the current study provides the first cohort-level analysis on maintenance IM ketamine treatments. Other open-label case series' have reported modest efficacy of twice-weekly maintenance IV ketamine infusions for patients with treatment-resistant depression over 11 months [59, 60], and strong efficacy of weekly maintenance SC ketamine for treatment-refractory GAD or SAD patients over 3 months [24]. For patients in this study who received maintenance IM ketamine treatments, median improvements in depression and anxiety scores of at least 21% and 19% were maintained for 13 months. This provides promising initial evidence that, in a heterogeneous outpatient population, the effects of repeated IM ketamine treatment could be long-lasting with the support of maintenance treatments at a median frequency of 21 days. Importantly, as described by Andrade et al., maintenance ketamine may not be required for all patients, and could depend on what the initial indication for ketamine was [4]. Given the potential clinical benefits of long-term IM ketamine treatment, further research on the long-term efficacy of ketamine treatment with or without maintenance treatments is warranted for a variety of psychiatric patient populations.

Our real-world data suggest that outpatient IM ketamine treatment may also help decrease suicidal ideation, and possibly suicide risk, for this clinically complex patient population. In this cohort, the percent of patients who reported any suicidal ideation decreased from 60% (80/133) at baseline to 47% (63/133) at last ketamine treatment. This could represent a substantial decrease in cohort-level suicide risk, as it

has been shown that outpatients who report any suicidal ideation on the SI item of the PHQ-9 are 3-to-7 times more likely to die by suicide in the next 30 days [46]. While this initial data is promising, future studies on the impact of real-world IM ketamine treatment on not only suicidal ideation, but also suicidal behaviour, is warranted [61].

Safety

This cohort had a good safety profile, and overall rates of AEs as well as rates of specific AEs were comparable to those reported in previous ketamine studies. AEs occurred during 2.3% of the 2,532 treatments in this cohort, which is comparable to the 1.95% of IV ketamine infusions which were discontinued due to AEs as reported in a 2015 systematic review and meta-analysis [62]. The 7.5% and 4.4% of patients who experienced nausea and vomiting respectively in this cohort was comparable to the 13% and 6% reported for patients receiving IM and SL ketamine, who also received preventative administration of antiemetic medication [32]. Also, unstable vital signs were recorded at 0.16% of treatments, which is lower than the 1% (2/205) of IV ketamine infusions where patients experienced elevated blood pressure as reported by Wan et al [62]. While this safety data is promising, it is limited by the retrospective nature of the data collection. Specifically, while we report safety data for over 2,500 treatments, structured follow-up patient data on adverse effects of ketamine after patients had completed their ketamine treatment course were not available. Prospective studies are warranted which evaluate the follow-up safety of IM ketamine months to years after patients have completed their series of ketamine treatments [19], given the potential widespread application of IM ketamine in community psychiatric and primary care clinics.

Limitations

Firstly, the generalizability of the patient characteristics reported here is limited - while this study characterized patients from only one private psychiatric clinic network in the state of Utah, there is likely heterogeneity in the demographics, patient history and clinical characteristics of patients receiving IM ketamine treatment from outpatient clinics across North America.

Secondly, ascertainment bias may be present in this study since many variables, namely social, mental health and substance use history variables, and PHQ-9 and GAD-7 scores only had complete data available for a portion of the cohort. For these variables, the subset of patients for whom data was collected may have been influenced by clinicians' a priori knowledge of each patient's history and clinical issues. For example, baseline anxiety scores may be overestimated in this study. This is because if a patient had high baseline anxiety, alleviating anxiety may have been an objective for their treatment, thus their clinician may have been more likely to collect GAD-7 scores to track improvement in anxiety over time.

Finally, the efficacy results reported here must be interpreted cautiously. This was a naturalistic study: during the study patients continued to receive all their concurrent treatments such as other psychiatric medications and psychotherapy, as in routine clinical care. The fact that this was a naturalistic study with no control group limits the ability to make causal links between IM ketamine treatment and symptom improvement. Furthermore, patients received open-label treatment, thus the possible placebo effect of ketamine treatment was not evaluated. Nonetheless, the clinical data of this analysis describe significant and long-lasting improvements in depression, suicidal ideation and anxiety symptoms upon the initiation of IM ketamine treatment.

Conclusion

IM ketamine is being utilized as an off-label treatment for psychiatric outpatients with a variety of mental illnesses, multiple comorbidities, multiple concomitant medications, and a moderate-to-severe mental health history. On average, patients who receive IM ketamine treatment of varying treatment lengths show improvements in depression, suicidal ideation, and anxiety symptoms from baseline to last treatment. For patients who continue to receive long-term maintenance treatments, median improvements in depression and anxiety do not regress to baseline for over a year. The safety profile of real-world outpatient ketamine treatment is promising, and further prospective analyses of IM ketamine safety should be completed. These findings indicate that IM ketamine treatment could play a key role in outpatient psychiatric treatment for the reduction of depression, suicidal ideation and anxiety symptoms for outpatients with a wide variety of mental illnesses.

Abbreviations

ACEs: Adverse childhood experiences

AE: Adverse event

BDI: Beck Depression Inventory

DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

ECT: Electroconvulsive therapy

EHR: Electronic health records

GAD: Generalized anxiety disorder

GAD-7: Generalized Anxiety Disorder-7

HAM-A: Hamilton Anxiety Rating Scale

IM: Intramuscular

IN: Intranasal

IQR: Interquartile range

IV: Intravenous

MDD: Major depressive disorder

PHQ-9: Patient Health Questionnaire

PTSD: Post-traumatic stress disorder

rTMS: Repetitive transcranial magnetic stimulation

SAD: Social anxiety disorder

SD: Standard deviation

SI: Suicidal ideation

SL: Sublingual

Declarations

Ethics approval and consent to participate

This paper received approval from the University of Utah institutional review board on July 14, 2021 as non-human subject research. The data presented do not contain any information that could identify subjects and requirement for informed consent was waived by the University of Utah institutional review board. This retrospective cohort study was conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author, SA, on reasonable request, but are not publicly available due to patient privacy restrictions.

Competing interests

SA, CM, PT and RR are employed by Novamind Inc., and RR and PT have minority stock ownership in Novamind Inc. MB and LS do not have any competing interests to report.

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Authors' contributions

SA extracted, formatted and analyzed data and completed the manuscript writeup. MB analyzed data and completed the inferential statistics. LS extracted and formatted data. CM, PT and RR reviewed the data analysis and critically reviewed/revised the manuscript writeup. All authors have read and approved the final manuscript.

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Figures

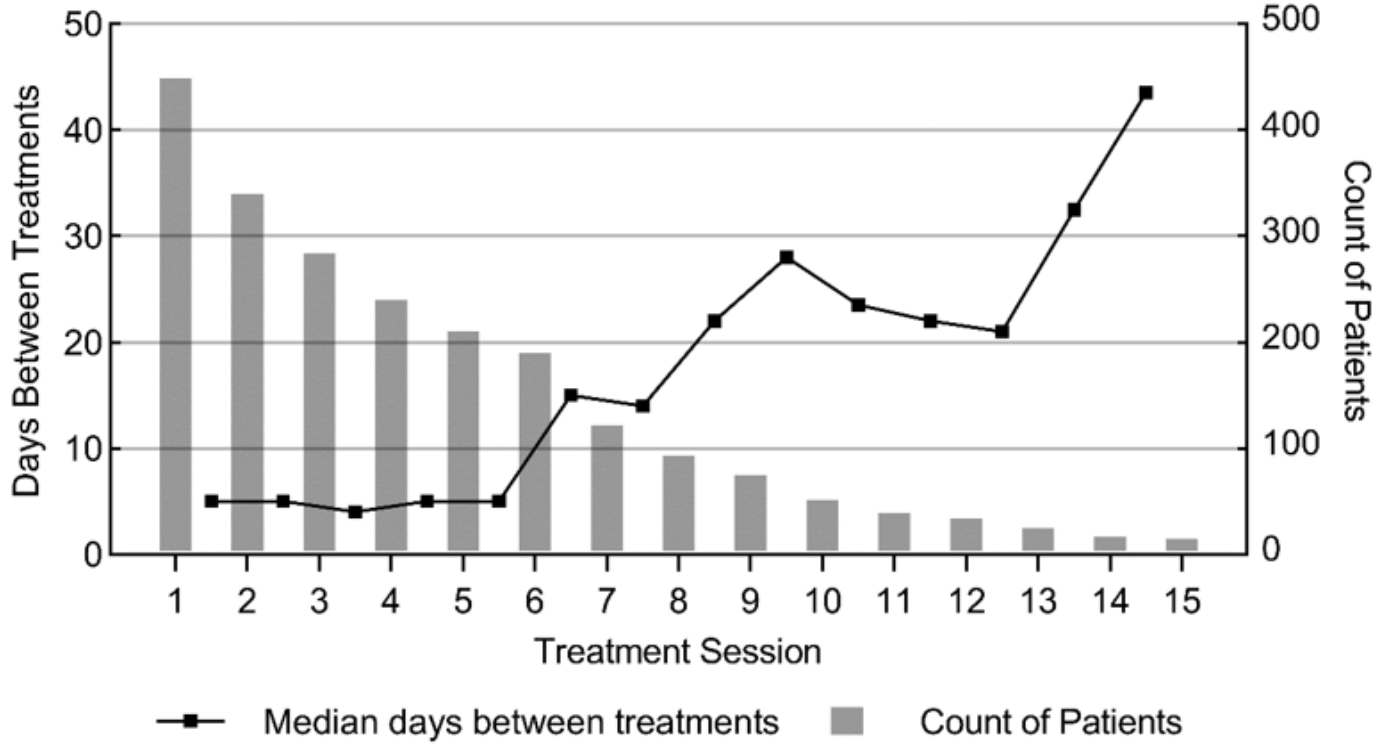

Figure 1

Time between successive IM ketamine treatment sessions 1-15

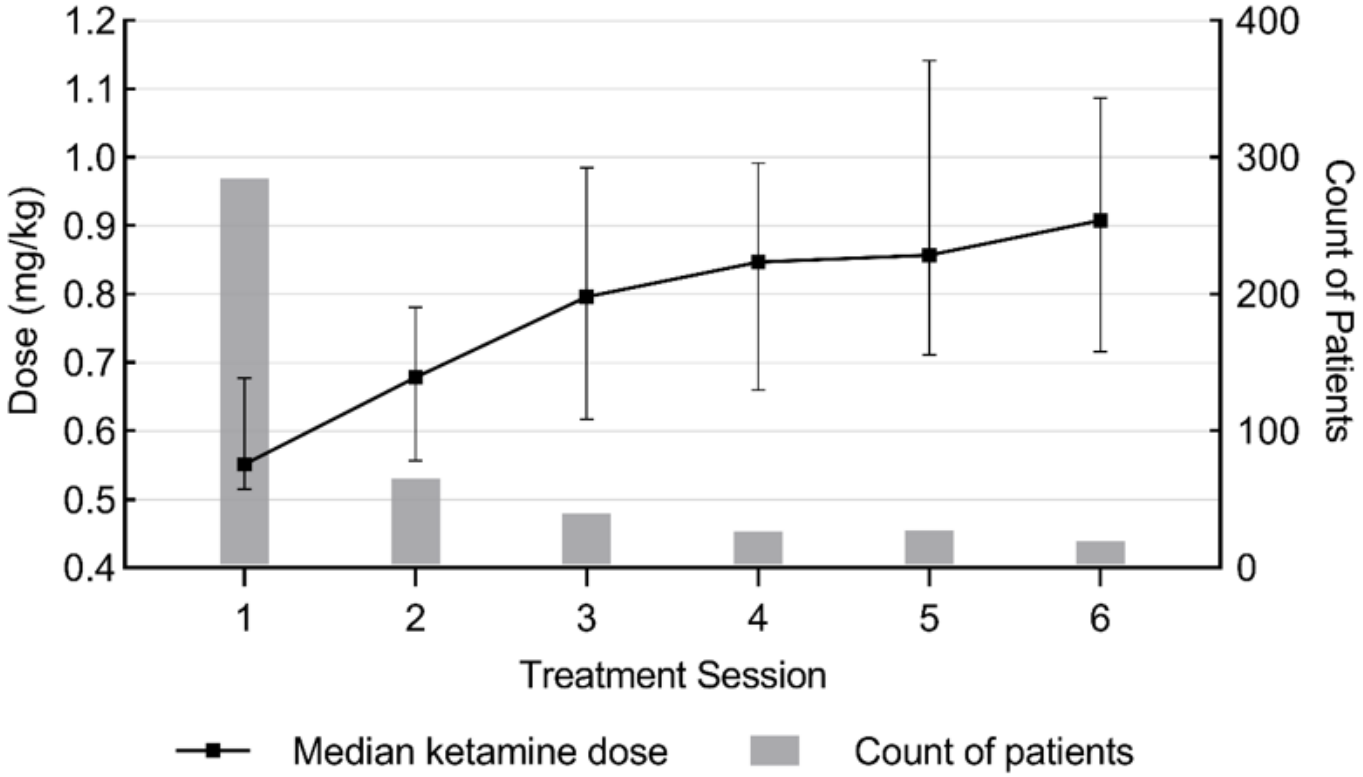

Figure 2

IM Ketamine doses (mg/kg) throughout treatment sessions 1-6

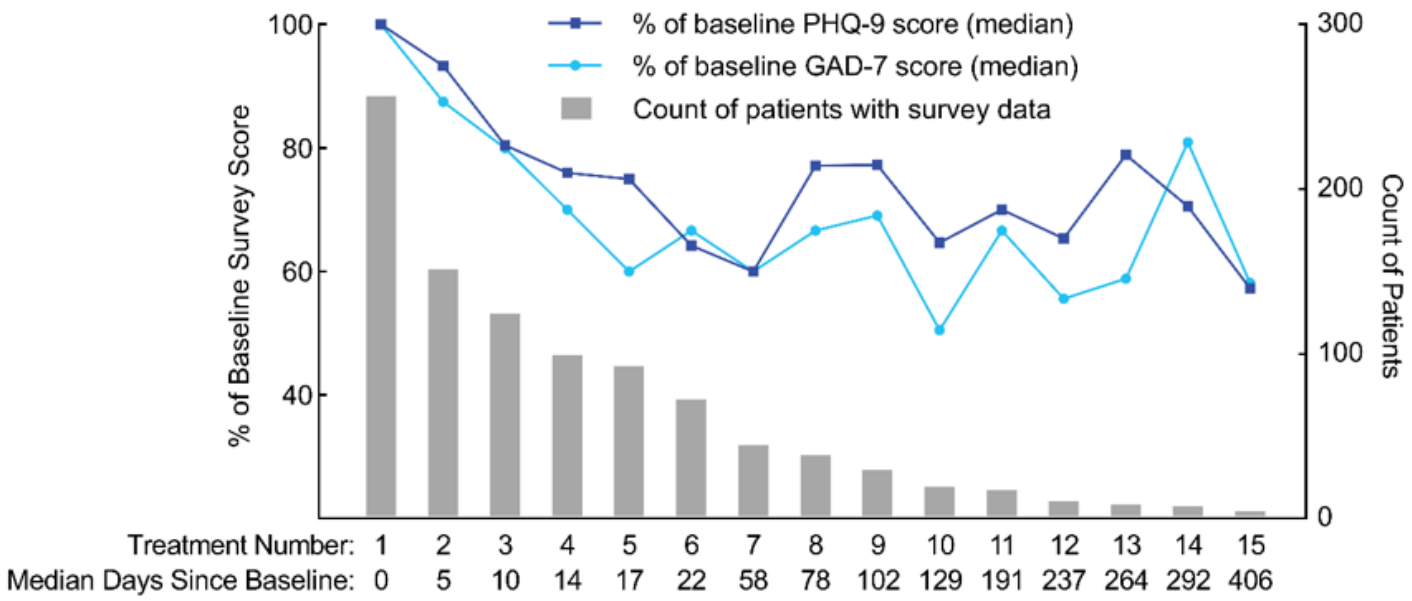

Figure 3

Depression and anxiety scores throughout IM ketamine treatments 1-15 as a percent of each patient's baseline scores

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTable1.pdf
- SupplementalTable2.pdf
- SupplementalTable3.pdf