Rapid effectiveness of intravenous ketamine for ultraresistant depression in a clinical setting and evidence for baseline anhedonia and bipolarity as clinical predictors of effectiveness

by

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Abstract

Background

Intravenous ketamine has been established as an efficacious and safe treatment, with transient effect, for treatment-resistant depression. However, the effectiveness of intravenous ketamine in non-research settings and with ultraresistant depression patients remains understudied.

Aims:

This study aimed to measure the response and remission rates in ultraresistant depression patients in a clinical setting by means of a retrospective, open label, database study. Secondarily, the study investigated previous findings of clinical predictors of effectiveness with intravenous ketamine treatment in an ultraresistant depression population.

Methods:

Fifty patients with ultraresistant depression were treated between May 2015 and December 2016, inclusive, in two community hospitals in Edmonton using six ketamine infusions of 0.5mg/kg over forty minutes over two to three weeks. Data were collected retrospectively from inpatient and outpatient charts. Statistical analysis to investigate clinical predictors of effectiveness included logistic regression analysis using a dependent variable of a 50% reduction in rating scale score at any point during treatment.

Results:

The average treatment resistance was severe at baseline, with a Maudsley Staging Method for treatment-resistant depression score of 12.1/15, and an average Beck Depression Inventory score of 34.2. Ninety percent of patients were resistant to electroconvulsive therapy. The response rate to intravenous ketamine was 44% and remission rate was 16%. As a single predictor, moderate or severe anhedonia at baseline predicted a 55% increased likelihood of response. As a combined predictor, moderate or severe anhedonia at baseline with a diagnosis of bipolar depression predicted a 73% increased likelihood of response.

Conclusion:

In a clinical setting, intravenous ketamine showed effectiveness in a complex, severely treatment-resistant, depressed population on multiple medication profiles concurrently. This study gave support to anhedonia and bipolar depression as clinical predictors of effectiveness.

Declaration of Conflicts of Interest:

None.

Preface

This thesis is original work by Rejish Thomas. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Rapid antidepressant and antisuicidal actions of ketamine: A retrospective chart review of results from the Covenant Health- and Alberta Health Services-approved Grey Nuns Community Hospital Ketamine for Ultraresistant Depression Clinic," Study Number Pro00065341 on June 10, 2016 and Covenant Health Research Operational/Administrative Approval, Project Name "Rapid antidepressant and antisuicidal actions of ketamine: A retrospective chart review of results from the Covenant Health- and Alberta Health Services-approved Grey Nuns Community Hospital Ketamine for Ultraresistant Depression Clinic," Study Number 1795, on June 14, 2016.

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List of abbreviations

(2R,6R)-HNK	(2R-6R)-hydroxynorketamine
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDI-I	Beck Depression Inventory - I
BDI-II	Beck Depression Inventory - II
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BPRS	Brief psychiatric rating scale
CANMAT	Canadian Network for Mood and Anxiety Treatments
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECT	Electroconvulsive therapy
eEF2	Eukaryotic elongation factor 2
FHA	First degree family history of alcoholism
GABA	*gamma*-Aminobutyric acid
GSK-3	Glycogen synthase kinase 3
HRSD-17	Hamilton Rating Scale for Depression 17
HRSD-21	Hamilton Rating Scale for Depression 21

IV	Intravenous
MADRS	Montgomery Asberg Depression Rating Scale
MDD	Major depressive disorder
MSM	Maudsley Staging Method for Treatment Resistant Depression
mTOR	Mammalian target of rapamycin
mTORC1	Mammalian target of rapamycin complex 1
NMDA	N-methyl-D-aspartate
PFC	Prefrontal cortex
RCT	Randomized controlled trial
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TRD	Treatment-resistant Depression
URD	Ultraresistant depression

Chapter 1

1.1 Introduction

An underserved and suboptimally treated population exists in depressed patients who have failed a comprehensive treatment regimen of antidepressants, augmentation strategies, psychotherapy and electroconvulsive therapy (ECT) and can be described as suffering from ultraresistant depression (URD). There is a paucity of treatments available with the effect size necessary to achieve remission for these patients. Intravenous (IV) ketamine is an agent with a novel mechanism of action that has been demonstrated to have a large effect size and response rate in treatment-resistant depression (TRD) (Coyles and Laws, 2015). However, there is no current evidence in URD in a clinical setting.

There are challenges to be considered when studying this population and IV ketamine:

What is the prevalence of TRD and URD? How can URD be defined? What is the mechanism of action of ketamine in URD? What is the evidence base behind IV ketamine for the treatment of URD? Is there a way to better prognosticate a response to ketamine for an individual patient?

To answer these questions, I conducted a literature review.

1.2 Review of the literature

1.2.1 Estimating prevalence of URD

When using the colloquial definition of an inadequate response to adequate trials of two or more antidepressants, it can be extrapolated from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial that over 35% of major depressive disorder (MDD) patients develop treatment-resistant depression (TRD), and of that population, 40% remain depressed after ECT which is considered the gold standard treatment for TRD (Kennedy et al., 2016; Prudic et al., 1996; Trivedi et al., 2006). URD patients carry a large burden of illness (Kessler, 2012; Vos et al., 2015). Considering MDD is one of the most common presentations in psychiatry, with a lifetime prevalence of 16.6% according to the National Comorbidities Study and is the second highest disabling disease using daily adjusted life years lost in the WHO study, this leaves an unfortunately large population with enduring suffering and very few treatments available (Kessler et al., 2005; Global burden of disease study 2013 collaborators, 2013).

1.2.2 Attempts to define TRD

There is currently no consensus on an accepted definition for TRD. The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines define it as a "failure [lack of a 20% improvement] following adequate trials of two or more antidepressants" (Kennedy et al., 2009). Ideally, an accurate definition of TRD would give predictive validity and guide clinical decisions. The CANMAT definition is inadequate in these realms, mostly because it aims for an inadequate

goal, it contains many assumptions and it ignores confounders of depression. The CANMAT definition of treatment resistance aims for a 20% response instead of remission, likely because a 20% response is when clinicians will augment or persist with treatment instead of switch. However, the treatment goal in depression is remission because not achieving full remission is associated with an increased risk of relapse (Paykel et al., 2008). The evidence available may be inadequate to accurately define treatment resistance due to the heterogeneity and unclear etiology of depression. The CANMAT definition also carries assumptions. First, it assumes the antidepressant was tolerated and side effects did not drive the treatment failure. Second, it assumes the failed trial was under conditions of reasonable adherence and of adequate dose. Further, it assumes the depression is one syndrome despite its heterogeneity and that it is not better explained by a mimic of depression. The medical and psychiatric mimics of depression are extensive and often very difficult to parse from MDD. The use or withdrawal of many substances such as alcohol, cigarettes, steroids, stimulants and some antihypertensives have also been shown to mimic depression. Finally, it does not include comorbidities that make MDD harder to treat. Personality disorders or traits are common in this population but are excluded from most TRD clinical trials (Newton-Howes et al., 2006). Further, comorbid anxiety, psychosis and cognitive disorders that are suboptimally treated negatively impact treatment. The best available scale to measure TRD is the Maudsley Staging Method for Treatment Resistant Depression (MSM), as it does have some evidence in predicting treatment resistance. A patient can have a score from 3 to

15, gaining points for duration, severity with or without psychosis, electroconvulsive therapy, failed antidepressants and use of augmentation strategies (Fekadu et al., 2009a,b). Of note, like the other staging methods, there is no mention of failed psychotherapy modalities. Further study of this staging method is in progress, to provide clinicians with a more accurate estimate of patient response rates. Without accurate biomarkers to diagnose URD, the task is very difficult and can only be done by expert opinion. It is important to attempt a definition, because TRD should be treated with more evidence-based treatments such as ECT and psychotherapy before considering an experimental treatment (Kennedy et al., 2016). For purposes of this study, we defined URD with flexible inclusion criteria to account for urgency and compassion in a clinical setting in that suicidality was considered, as well as accounting for failing five antidepressant trials and an adequate or intolerable ECT trial. Though the variability in these factors makes it difficult to study TRD as a homogenous population and expect efficacy, trials involving NMDA receptor antagonists attempted this challenging task.

1.2.3 History of NMDA antagonists as treatments for TRD

Clinically, the interest in the N-methyl-D-aspartate (NMDA) glutamate receptor and the glutamate pathway in depression may have started in 1971 with evidence that amantadine (a weak NMDA receptor antagonist) had clinical efficacy in depression (Vale et al., 1971). This was followed by evidence of efficacy of several NMDA receptor antagonists in rodent models of depression such as the forced swim test and the chronic mild stress model in the 1990s (Trulls and

Skolnick, 1990; Papp and Moryl, 1994; Layer et al., 1995). In 2000, Berman et al. administered the first randomized controlled clinical trial of ketamine on nine depressed patients after a two-week medication washout period. Patients were randomized to receive two infusions over a week of an IV saline solution or an IV 0.5mg/kg ketamine HCl solution over forty minutes. It was demonstrated that ketamine produced a significant decrease in depressive symptoms based on the 25-item Hamilton Rating Scale for Depression compared to placebo after three days of 14 +/- 10 points vs. 0 +/- 12. The effects were transient, with relapse over one to two weeks. This study demonstrated an impressive and rapid antidepressant efficacy with a new mechanism of action, although the exact mechanism of action remained unclear.

1.2.4 Potential mechanism of action of IV ketamine for TRD

Ketamine is a glutamate NMDA receptor competitive antagonist, which is a different mechanism of action than of other antidepressants whose action is based on the monoamine hypothesis of depression. NMDA receptor antagonism is believed to be the most important mechanism of action by which ketamine has an antidepressant effect, but the exact mechanism of action remains unknown. Other NMDA receptor antagonists, such as memantine and lanicemine, have been studied in depression and they were unable to produce the robust antidepressant effects beyond their half-lives as ketamine has, inferring there is more to ketamine's mechanism of action than NMDA receptor antagonism (Iadarola et al., 2015). In one theory, at subanaesthetic doses ketamine has a preferential affinity for *gamma*-aminobutyric acid (GABA)-secreting interneurons whose firing is

driven by NMDA receptors. This in turn results in pyramidal cell disinhibition and glutamate release with subsequent activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors along with the release of brain-derived neurotrophic factor (BDNF) and activation of downstream signaling pathways such as mammalian target of rapamycin (mTOR) (Duman, 2014). Therefore, the BDNF release results in synaptogenesis to drive an antidepressant effect. Li et al. (2010) demonstrated this rapid synaptogenesis effect in rat brain dialysis twenty-four hours post IV ketamine treatment in rat models of depression. The most consistent structural changes associated with MDD involve neuronal atrophy and brain volume loss in the prefrontal cortex (PFC) and hippocampus (Arnone et al., 2012). In fact, chronic stress is known to induce reductions in spine density and in the length and number of dendritic branches in the rat hippocampus and PFC (Radley et al., 2008; Radley and Morrison, 2005) It has been demonstrated that these synaptic and structural plasticity dysfunctions may be reversed by ketamine (Li et al., 2011). In knock-out mice, the antidepressant effect was reduced or eliminated by knocking out the following targets: AMPA, BDNF, eukaryotic elongation factor 2 (eEF2), glycogen synthase kinase 3 (GSK-3) and mammalian target of rapamycin complex 1 (mTORC1). Sigma 1 receptors have also been implicated in the antidepressant effect (Strasburger et al., 2017). The best evidence to narrow ketamine's robust antidepressant effects has been a recent paper in *Nature* that found that a metabolite of ketamine, (2R,6R)-hydroxynorketamine **(**(2R, 6R)-HNK) was sufficient for similar antidepressant effects without psychomimetic side effects (Zanos et al., 2016). However, there

has also been evidence to refute (2R, 6R)-HNK as the responsible metabolite (Shirayama and Hashimoto, 2018). In summary, the unique mechanism of ketamine's robust antidepressant effect could very well be the product of a complex interaction of multiple mechanisms of action or through metabolites.

1.2.5 Review of evidence for IV ketamine for TRD

There have been consistent positive findings regarding ketamine's antidepressant effect since the Berman et al. (2000) study. For context, clinicians are used to agents that have effect through monoamines that have an effect size of approximating 0.3 over the course of weeks for unipolar depression (Kirsch et al., 2008). In 2006, Zarate et al. demonstrated IV ketamine to have efficacy in unipolar TRD with a very large effect size of 1.46 after 24 h compared to placebo. Ketamine's efficacy has been demonstrated in treatment-resistant bipolar depression as well. Diazgranados et al. (2010b) had subjects with diagnoses of bipolar I or II depression, refractory to at least one adequate antidepressant trial and a mood stabilizer trial, on therapeutic levels of lithium or valproate receive a single infusion of IV ketamine HCl (0.5mg/kg over 40 minutes) or placebo. Efficacy was seen from 40 minutes post infusion to 3 days post infusion (largest Cohen's *d* at day 2 of 0.80). The response rates were 71% and 6% for the ketamine group and the placebo group respectively. Later, Murrough et al. (2013a) conducted a study with midazolam as an active control, which was important as ketamine treatment leads to an immediate sensation that a saline placebo does not give, which could be a confounder that contributes to the large antidepressant effect demonstrated. Murrough et al. (2013a) conducted a two-site,

parallel arm, RCT of single infusion IV ketamine HCl (0.5mg/kg over 40 minutes) compared to midazolam. The study population was unipolar TRD defined as an inadequate response to three antidepressant trials. Twenty-four hours post infusion, the ketamine group had a mean Montgomery Asberg Depression Rating Scale (MADRS) score of 7.95 points lower than the midazolam group, with a Cohen's *d* of 0.81. The response rate for the ketamine group was 64% and the response rate for the midazolam group was 28%. In 2014, ketamine also demonstrated efficacy as an antisuicidal agent in a TRD population, with a Cohen's *d* of 0.82 after 24 hours compared to midazolam as the active placebo (Price et al., 2014). As of January 2015, according to a meta-analysis by Coyle and Laws (2015) there had been 21 studies on ketamine, 8 of which were randomized controlled trials (RCTs), with a total number of patients of 437. Seventeen of these studies were testing the effects of one dose of ketamine and few had an active control. The meta-analysis showed an overall effect that took place within hours and an effect size of approximately 1.3 for MDD and bipolar depression, which was sustained for 3-32 days. With multiple infusions, the time to relapse of depression has been seen to be stretched to an average of 18 days after the last infusion. The overall response rate at 72 hours is 40-90%. IV ketamine's antisuicidal effects have been studied in three RCTs and three open label trials as of January 2015. It was not possible to have long term followup for suicide attempts or deaths, so suicidal ideation was used as the dependent variable. Overall, 169 patients were studied with the largest RCT being 57 patients. The effect sizes were large, ranging from 0.82–1.37. The earliest effect

seen was, remarkably, after 40 minutes and the longest sustained effect was 10 days (Reinstaller and Youseff, 2015). The effect has been seen to be independent of anxiolytic and antidepressant effect, with improvement of depression only accounting for 19% of the antisuicidal effect (Ballard et al., 2014).

Ketamine is considered safe in the short term at the subanaesthetic dose used for TRD. Wan et al. (2015) studied 204 infusions of ketamine and found the attrition rate to be 1.95%. The most common immediate side effects were drowsiness, dizziness, dyscoordination, blurred vision and minor psychotomimetic or dissociative symptoms. One-third also had transient hemodynamic changes. These effects all remitted spontaneously within hours. There were no cases found to have persistent psychomimetic changes. Extrapolations from ketamine abuse literature are not accurate since the patient populations are very different and users are often on high and inconsistent doses of other substances as well. Potential risks identified in ketamine abuse data are ulcerative cystitis, cognitive issues and cardiovascular events that are mostly transient elevations in blood pressure (Zhu et al., 2016).

1.2.6 Potential clinical predictors of effectiveness for IV ketamine

The literature around the MSM for TRD demonstrates that a higher level of treatment resistance predicts poorer outcomes (Fekadu et al., 2009a,b). Therefore, this is a population in which clinicians may consider the use of experimental treatments like IV ketamine. However, given the current experimental nature of ketamine treatment, it would be ideal to collect biomarkers of response that would give knowledge about which particular patients are more likely to respond. Until

now, most of the biomarker research has been done in single infusion ketamine treatments. In search of symptoms of depression to stratify the depression phenotype that may respond to IV ketamine, evidence exists for anhedonia, anxiety/somatization, fatigue and suicidal ideation (DiazGranados et al., 2010a; Ionescu et al., 2014; Lally et al., 2014; Reinstatler and Youssef, 2015; Saligan et al., 2016). As for baseline sociodemographic variables, family history of an alcohol use disorder in a first degree relative (FHA) has been reported to be a clinical predictor of effectiveness, and this finding has been replicated (Luckenbaugh et al., 2012). In addition, a higher body mass index (BMI) and early response have been linked to initial and sustained response (Murrough et al., 2013b; Niciu et al., 2014). Alcoholism and higher BMI have been implicated in inflammation, which gives further support to ketamine's theorized mechanism of action being anti-inflammatory and affecting synaptogenesis (Abdallah et al., 2016; Shelton and Miller, 2011; Wang et al., 2010). The current literature requires further replication, and combining this information with other modalities, like neuroimaging, genetics and/or electroencephalography, may increase the predictive accuracy.

1.3 Study aims

This study aimed to measure the response and remission rates of a six-infusion course of IV ketamine in a clinical setting of ultraresistant depressed patients, to add applicability to the literature. We hypothesized that the response and remission rates with IV ketamine in this URD sample will be less than with the TRD data. Additionally, the study aimed to add to the previous literature on previous findings of clinical predictors of effectiveness to IV ketamine in a clinical setting of URD patients.

Chapter 2: Methods

2.1 Database collection

Data were collected from all patients who received ketamine at the Grey Nuns Community Hospital or Misericordia Community Hospital for depression from the inaugural patient on May 13, 2015 to December 31, 2016, retrospectively through pharmacy records. It was deemed *a priori* that fifty subjects were sufficient for the proposed statistical analysis. One patient had a significant response by clinician notes but did not complete rating scales, so was not included. Four patients had no response based on clinical notes and did not complete end rating scales, and were included in the study as non-responders. An electronic database was created and information from electronic outpatient charts, paper inpatient charts and paper outpatient charts were inputted. All admission and discharge summaries in Edmonton have a standardized format, which allowed for extraction of past and present medical diagnoses, family history of addiction and mental illness, and history of substance use. Demographics, BMI, rating scales and side effects from tracking sheets were extracted from nursing protocols before and during the infusions. Laboratory results, MSM scores and past and present psychopharmacologic drug use were extracted from a combination of all sources available. Personality and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic information were collected only if the words “disorder” or “traits” were ever documented in the “diagnoses” section of any of the sources. Some patients underwent more than 6 treatments of ketamine, but no data were collected beyond the sixth post ketamine rating scale.

2.2 Inclusion criteria

Inpatients or outpatients who satisfied three out of four criteria were permitted to be given IV ketamine and all were included in this study. The criteria used were: 1) a diagnosis of a major depressive episode (unipolar or bipolar) determined by usual standard of care clinical opinion based on years of observation, 2) refractory (defined by clinician) to pharmacological treatment with at least five psychotropic medications for treating a mood disorder, 3) refractory (underwent at least six ECT treatments without adequate response, defined by clinician) to or not suitable for ECT (not including refusal due to preference) and 4) acutely suicidal.

2.3 Exclusion criteria

Patients meeting inclusion criteria were excluded if presenting with active psychosis, drug or alcohol abuse/dependence, dementia/delirium, a significant personality disorder believed to be the primary issue, a significant unstable medical condition, pregnancy, dissociative identity disorder, a history of allergic reaction to ketamine or a history of any severe adverse reaction to ketamine. There were no suggestions to discontinue any medications through the study period and no specific medication classes were excluded. Additionally, substance use disorders that were in remission and past use of ketamine or phencyclidine were not excluded.

2.4 Administration of IV ketamine

A baseline assessment by a physician included a physical examination, blood work (complete blood count, electrolytes, aspartate transaminase, alanine transaminase, gamma-glutamyltransferase, thyroid-stimulating hormone), an

electrocardiogram, a urine drug screen 24 hours before if deemed appropriate and a medical consult when necessary. After informed written consent was received, IV ketamine was administered in the inpatient unit or in the recovery room of the hospital by a nurse at a dose of 0.5mg/kg over forty minutes (Berman et al., 2000). A physician was on site during the procedure. Monitoring included measurement of oxygen saturation, blood pressure and heart rate, with vital signs taken pre-, mid- and immediately post-infusion, as well as pre-discharge. Infusions were repeated 2-3 times per week with a recommended maximum of 6 infusions. If side effects occurred during the infusion, the clinician had options to slow down the rate of the infusion, intervene with medications (low dose quetiapine and/or lorazepam), stop the infusion, or continue with close observation.

2.5 Rating scales

At baseline, one or more of the following scales were used: the MADRS, the Beck Depression Inventory-I or –II (BDI-I or BDI-II), the Hamilton Rating Scale for Depression 17 or 21 (HRSD-17 or HRSD-21) and the Brief Psychiatric Rating Scale (BPRS). The MADRS and HRSD-17 were used as a self-rated scale so were only used for baseline symptomatology information. All other scales were used as recommended (Beck et al., 1961, 1996; Hamilton, 1960; Overall and . Gorham, 1962; Montgomery and Asberg, 1979).

The frequency and type of rating scale administered was left to the clinician's discretion, with a suggestion to administer rating scales at least at baseline, post-

treatment 1, post-treatment 3 and on completion. When rating scales were given post treatment, though the timing of administration of post-treatment rating scales was not standardized, they were typically given at least four hours after the infusion was complete, which extends past the half-life of IV ketamine.

A side effect tracking scale was uniquely created for this patient population based on known short term side effects at the initiation of the treatment (see Appendix 1) (Serafini et al., 2014). Nursing staff were instructed to fill out the tracking sheet at least 3 times between initiation and the end of the recovery period. Notes were made if the patient experienced any side effects (categorized as "mild"), side effects requiring decreasing the rate of infusion or requiring intervention (categorized as "moderate") or side effects requiring premature stoppage of the infusion (categorized as "severe").

2.6 Statistical analysis

Clinical and demographic characteristics at baseline were compared between responder and non-responder groups using independent t-tests. Response was defined as a 50% reduction in BDI-I, BDI-II or HRSD-21 scores between baseline and any time point during treatment. Remission was defined by accepted criteria for each scale (Beck et al., 1961, 1996; Hamilton, 1960).

Logistic regression analyses all involved a dependent variable of response. Three separate logistic regression calculations were done to provide further power.

1) Categorical independent variables of age (>50 and ≤50), gender, FHA, suicidality (0 on any scale or other), anxiety (0 or 1 versus 2 or higher on any scale), unipolar versus bipolar depression and anhedonia (0 or 1 versus 2 or 3 on any scale).

2) Continuous independent variables of BMI, age and MSM.

3) Categorical independent variables of patients on lamotrigine (glutamate release inhibitor and voltage-gated sodium channel blocker), benzodiazepines and antipsychotics (first, second or third generation) during ketamine treatments.

Missing data were dealt with by excluding the patient from that analysis rather than using the mean.

Chapter 3: Results

Baseline characteristics of the population demonstrated an average MSM TRD level of severe with low variance at 12.1 out of 15, in addition to being 90% ECT-resistant and 86% psychotherapy-resistant. All the patients except one were concomitantly on other medication while receiving the treatment course. Diagnoses of Cluster B and C personality traits were given to one patient by previous clinician documentation in 44% and 48% of the population, respectively, and 64% of the population had a documented DSM-5 diagnosis of an anxiety disorder at least once in their lifetime.

Baseline characteristics of responders and non-responders were compared. In the case of continuous variables, a test of equal means was performed using an independent sample *t*-test. In the case of categorical variables, tests of equal proportions were conducted using standard normal *z*-statistic. Only "concurrent use of lamotrigine" ($p=0.015$) was found to be statistically different between responders and non-responders at $p<0.05$, and bipolarity ($p=0.080$) was the only factor that was statistically different at $p<0.1$ (Table 1).

	Total	**Responders**	**Non-responders**
N=	50	22	28
Mean Age (Years)	51.6 (13.8)	52.5 (12.5)	50.9 (14.9)
Mean Level of Education (Years)	14.0 (2.4)	14.4 (2.2)	13.7 (2.6)
Mean BMI (kg/m^2)	30.9 (7.0)	31.2 (6.6)	30.6 (7.4)
Females to Males Ratio	1.8	2.1	1.5
ECT failed percentage	90.0% (45/50)	86.4%(19/22)	92.9% (26/28)

Psychotherapy failed percentage	86.0% (43/50)	81.8%(18/22)	89.3% (25/28)
Number of previous antidepressant trials	8.1 (4.5)	8.1 (3.9)	8.1 (5.0)
Number of previous augmentation trials	9.4 (4.2)	10.1 (3.2)	8.9 (4.8)
Maudsley Treatment Resistance (/ 15)	12.0 (1.6)	12.0 (1.3)	12.0 (1.8)
Percentage of Cluster A Personality Traits	6.0% (3/50)	4.5% (1/22)	7.1% (2/28)
Percentage of Cluster A Personality Disorder	0.0% (0/50)	0.0% (0/22)	0.0% (0/28)
Percentage of Cluster B Personality Traits	44.0% (22/50)	45.5%(10/22)	42.9% (12/28)
Percentage of Cluster B Personality Disorder	16.0% (8/50)	9.1% (2/22)	21.4% (6/28)
Percentage of Cluster C Personality Traits	48.0% (24/50)	45.5%(10/22)	50.0% (14/28)
Percentage of Cluster C Personality Disorder	8.0% (4/50)	4.5% (1/22)	10.7% (3/28)
Percentage of Mild Side Effects	80.0% (40/50)	72.7%(16/22)	85.7% (24/28)
Percentage of Moderate Side Effects	10.0% (5/50)	13.6% (3/22)	7.1% (2/28)
Percentage of Severe Side Effects	8.0% (4/50)	9.1% (2/22)	7.1% (2/28)
Unipolar Depression	46.7% (21/45)	31.6% (6/19) *	57.7% (15/26) *
Bipolar Depression	53.3% (24/45)	68.4%(13/19) *	42.3% (11/26) *
FHA	22.0% (11/50)	27.3% (6/22)	17.9% (5/28)
Concurrent use of lamotrigine	10.0% (5/50)	22.7% (5/22) **	0.0% (0/28) **
Concurrent use of an antipsychotic	66.0% (33/50)	72.7%(16/22)	60.7% (17/28)
Concurrent use of a benzodiazepine	34.0% (17/50)	31.8% (7/22)	35.7% (10/28)
Number of medication free patients	2.0% (1/50)	4.5% (1/22)	0.0% (0/28)
Lifetime history of:			
A suicide attempt	20.0% (10/50)	13.6% (3/22)	25.0% (7/28)
DSM 5 Anxiety Disorder	64.0% (32/50)	63.6% (14/22)	64.3% (18/28)

DSM 5 Obsessive Compulsive and Related Disorders	12.0% (6/50)	13.6% (3/22)	10.7% (3/28)
DSM 5 Trauma and Stressor Related disorders	8.0% (4/50)	4.5% (1/22)	10.7% (3/28)
Alcohol use disorder	44.0% (22/50)	45.5% (10/22)	42.9% (12/28)
Tobacco use disorder	72.0% (36/50)	81.8% (18/22)	64.3% (18/28)

Table 1. Baseline demographic and clinical data of patients receiving IV ketamine, separated by total, responders and non-responders. Numbers in parenthesis represent standard deviation or proportions. **Proportions are significantly different at $p<0.05$. * Proportions are significantly different at $p<0.1$.

Total number of patients on concurrent medications and past trials of medications were collected and listed in Table 2. This study was underpowered to investigate the effect of medications on treatment response.

	Concurrently on treatment	**Previous trials of treatment**
Selective Serotonin Reuptake Inhibitor	17 (34%)	50 (100%)
Serotonin and norepinephrine reuptake inhibitor	12 (24%)	46 (92%)
Trazodone	10 (20%)	19 (38%)
Mirtazapine	11 (22%)	24 (48%)
Buproprion	6 (12%)	29 (58%)

Vortioxetine	8 (16%)	24 (48%)
Tricyclic antidepressants	7 (14%)	32 (64%)
Monoamine oxidase inhibitors (irreversible)	1 (2%)	14 (28%)
Monoamine oxidase inhibitors (reversible)	0 (0%)	7 (14%)
Benzodiazepine	17 (34%)	47 (94%)
Lithium	8 (16%)	24 (48%)
Non-lithium mood stabilizer (valproic acid, lamotrigine, carbamazepine, topiramate)	18 (36%)	41 (82%)
First generation antipsychotic	3 (6%)	11 (22%)
Second generation antipsychotic	28 (56%)	47 (94%)
Aripiprazole	6 (12%)	34 (68%)
Thyroid supplement augmentation	12 (24%)	18 (36%)
Stimulant (methylphenidate or amphetamine derivatives)	12 (24%)	25 (50%)
Memantine	0 (0%)	Unknown
Buprenorphine	0 (0%)	Unknown
Opiates	2 (50%)	Unknown

Riluzole	0 (0%)	Unknown
No current medications	1 (2%)	N/A

Table 2. Total number of patients concurrently and previously on medication. Numbers in parenthesis represent percentage of total study population.

The response rate in this population was 44% and the remittance rate was 16%. There were no instances where a patient responded during the treatment and did not sustain response when followed to the end of treatment, which was substantiated by clinical notes throughout the study period. Specific subscales followed for remission over the course of treatment found that 54.0% and 68.9% of patients who were at least mildly depressed or suicidal at baseline scored a zero on depressed mood and suicidality subscales, respectively, during treatment. Complete symptom remission percentages in other subscales are listed in Table 3.

	Symptom Captured with Baseline Rating Scale	Percentage of Symptom Remission at any point during Treatment
Depressed Mood	50	54.0%
Suicidal	45	68.9%
Anhedonia	49	34.7%
Greater than Mild Anhedonia	31	41.9%
Low energy	50	8.0%
Concentration	37	18.9%
Appetite change related best to mood	34	47.1%
Psychomotor retardation related best to mood	13	38.5%
Early Insomnia	14	42.9%
Middle Insomnia	15	53.3%
Late Insomnia	14	35.7%
Agitation	44	59.1%
Anxiety	24	29.2%

Table 3. Symptom subscales of depression from combined HDRS-21, BDI-I and BDI-II data and percentage with complete symptom remission at any point during treatment with IV ketamine.

For the full database of factors analyzed by logistic regression, refer to Supplemental 2. All logistic regression calculations for remission as the dependent variable were not found to be statistically significant (Supplemental 3). Logistic regression was done to investigate clinical predictors of effectiveness for BMI, age and MSM as well as with presence or absence of lamotrigine, benzodiazepines and antipsychotics during treatment to a dependent variable or presence or absence of response, and no statistical significance was found (Supplemental 4).

Logistic regression was performed predicting the presence or absence of response from categorical data of independent variables of age, gender, anxiety, anhedonia, bipolarity, FHA and suicidality. At least moderate anhedonia at baseline and bipolar depression were seen as predictors in this regression model. The finding was more significant when the two factors were combined. When investigated alone, patients with at least moderate anhedonia at baseline were found to be 55% more likely to respond to IV ketamine ($p=0.072$, $OR=1.21$) and patients with bipolar depression were found to be 54% more likely to respond ($p=0.087$, $OR=1.18$). Together, patients with a diagnosis of bipolar depression and at least moderate anhedonia at baseline were 73% more likely to respond to IV ketamine

(p=0.035 for bipolar and p=0.011 for anhedonia, OR= 3.03). (Table 4) The 2-predictor model is most appropriate, as it demonstrates significant improvement in prediction.

A

Response	**Estimate**	**Standard Error**	**z value**	**p value**
Intercept	-0.930	1.088	-0.855	0.393
Gender	-0.068	0.921	-0.073	0.941
Age	-0.442	0.774	-0.571	0.568
FHA	0.707	0.949	0.744	0.457
Anhedonia	2.488	1.296	1.920	0.055 *
Suicidality	-0.648	1.332	-0.486	0.627
Anxiety	0.510	0.769	0.662	0.508
Bipolar	1.413	0.815	1.734	0.083 *

B

	Estimate	**Standard Error**	**z value**	**p value**
Intercept	-0.956	0.526	-1.816	0.069
Anhedonia	1.150	0.638	1.802	0.072 *

C

	Estimate	**Standard Error**	**z value**	**p value**

Intercept	0.167	0.410	0.408	0.683
Bipolar	1.089	0.633	1.710	0.087 *

D

	Estimate	**Standard Error**	**z value**	**p value**
Intercept	-0.968	0.681	-1.422	0.155
Anhedonia	2.075	0.820	2.530	0.0114 **
Bipolar	1.549	0.736	2.105	0.0353 **

Table 4. Results of logistic regression calculations versus the dependent variable of presence or absence of response to IV ketamine treatment. A) Categorical independent variable calculations; B) Single predictor logistic regression for anhedonia; C) Single predictor logistic regression for polarity of depression; D) Two predictor logistic regression for polarity of depression and anhedonia. Gender = male versus females; Age = ≥50 years old versus <50 years old; FHA = positive versus negative family history of a first degree relative with past or present alcohol use disorder; Anhedonia = zero or mild anhedonia versus moderate or severe anhedonia on baseline rating scales; Suicidality = zero versus presence of suicidality on baseline rating scales; Anxiety = zero or mild anxiety versus moderate or severe anxiety on baseline rating scales; Bipolar = presence of bipolar depression. *= $p<0.1$; **= $p<0.05$.

Chapter 4: Conclusion and discussions

4.1 Relevance of the study

This retrospective, database study in a clinical setting with 50 patients represents the highest level of TRD that has been studied for IV ketamine. In this population, 90% have failed ECT, which is one of the most effective treatments for TRD (UK ECT Review Group, 2003). Basic science and research trials have thus far confirmed that IV ketamine has a novel mechanism of action with a large effect size in bipolar and unipolar TRD similar to ECT and a rapid, although short term effect that is safe in the short term (Coyle and Laws, 2015; ann het Rot et al., 2010; Berman et al., 2000; Wan et al., 2015). This study adds applicability and information on predictive factors in a heterogeneous population. When considering the growing number of IV ketamine clinics for TRD in North America, this applicability contributes to the literature to inform existing practices (Yan, 2016). The heterogeneity and complexity of these patients make them difficult to study in research settings, as was seen in our population with a high proportion of comorbid personality traits, comorbid anxiety disorders and a mixture of unipolar and bipolar depressed patients.

4.2 Primary outcome

The response and remittance rates that were achieved are very encouraging for an underserved population, given that a higher level of treatment resistance infers a poor prognosis (Fekadu et al., 2009a,b; Trivedi et al., 2006). As expected with a higher level of treatment resistance, the remission rate of 16% was lower than the

Serafini et al. (2014) systemic review findings of 26%-67%. The response rate of 44% is also consistent with the lower end of the Coyle and Laws (2015) meta-analysis results of a 40-90% response rate. In terms of suicidality, this population responded to ketamine at a rate superior to that of the Price et al. (2014) study. When measuring the percentage of the population that scored a zero on a suicidality rating subscale, Price et al. (2014) reported 53%, whereas this study yielded a 68% remission at any point in treatment. Further, 55% of the population remitted in the depressed mood subscale of a rating scale at some point in the study, and this correlates with the positive clinical opinion of ketamine effectiveness. Also, this rate is much higher than the remission rate. This brings up the possibility that IV ketamine has a differential effect on different subscales of depression.

4.3 Secondary outcome

Given the heterogeneity in the study population and the lack of biomarkers, it could be hypothesized that the sensitivity of the study to find clinical predictors of effectiveness to ketamine would be low. Due to the sample size, the percentage of some of the predictors present were of low frequency, and this limits the ability to assess many of the predictors with sufficient power. Nevertheless, there was evidence for at least moderate anhedonia as a single clinical predictor of effectiveness. This is especially encouraging as treatment for anhedonia is an unmet need in psychiatry. It is known that anhedonia is a negative prognostic factor for depression, as standard antidepressants do little to treat anhedonia and anhedonia is a major risk factor for suicide (Fawcett et al., 1990; McMakin et al.,

2012; Nutt et al., 2007; Spijker et al., 2001; Uher et al., 2012). Growing evidence is supporting the role of anhedonia as a potential clinical predictor of effectiveness to ketamine. Lally et al. (2014) demonstrated, in a randomized, placebo-controlled, double blind trial of single infusion ketamine to 36 patients with bipolar depression, that ketamine had anti-anhedonic effects and that these effects were related to action at the anterior cingulate cortex. Anhedonia has been localized to the anterior cingulate cortex in resting state functional magnetic resonance imaging (fMRI), electroencephalography and deep brain stimulation studies as well (Mayberg et al., 1997; McInerney et al., 2017; Wacker et al., 2009). Among other roles, the anterior cingulate cortex functions in error detection, task shifting, conflict monitoring and reward based learning (Bush et al., 2000, 2002). In terms of clinical predictors of effectiveness, this was also seen in fMRI studies showing that fearful face stimuli elicit responses in the anterior cingulate cortex. Dysfunction in the anterior cingulate cortex at baseline significantly predicted patient response to single infusions of ketamine 4 hours post-treatment (Salvadore et al., 2009).

The exact mechanism of action of ketamine's anti-anhedonic effects remains unknown. The current hypothesis of ketamine's antidepressive mechanism of action is that of synaptogenesis through the glutamate pathway (Duman, 2014; Li et al., 2010). Anhedonia is in part related to pathology in the reward system, motivation, rumination and distraction, leading to a difficulty in managing negative thoughts and feelings (Cohen et al., 2012; Lally et al., 2014; Lehmann et

al., 2016; Wacker et al., 2009). The negative, self-referential, ruminative aspect of MDD has been related to an increased resting state functional activity and a decreased reactivity in the default mode network (Hamilton et al., 2011). Lehmann et al. (2016) demonstrated with fMRI responsive to negative face stimuli and treatment with single infusion ketamine that ketamine had action in the anterior cingulate cortex, perhaps normalizing neuronal connection. Further, they found patients with less ability to distract from negative experiences at baseline had more pronounced findings in the anterior cingulate cortex.

My study gave evidence for bipolarity as a predictive factor to response, which has not been previously described (Pennybaker et al., 2017; Rong et al., 2018). However, it is in keeping with consistent evidence that IV ketamine has a robust effect on bipolar depression, which is encouraging, as this is a patient population with few available treatment options and often a large burden of illness (Coyle and Laws, 2015; Kennedy et al., 2016). A meta-analysis by Coyle and Laws (2015) investigated polarity and treatment effect and found that effect sizes were not significantly different four hours post-treatment, but IV ketamine effect sizes on bipolar depression were larger after seven days. This extended effect may have been captured and may have been seen as an additive effect in the multiple doses given over 2-3 weeks in this study. A limitation to this finding is that the diagnosis was based on a standard of care diagnosis by a clinician and not by a standardized diagnostic tool. However, the standard of care diagnosis in this real-world population has increased accuracy due to lengthy longitudinal relationships

with clinicians through many previous treatment failures. Further, given the sample size, a specific study of polarity of depression as a clinical predictor of response is warranted to confirm these findings.

An interesting yet underpowered finding of this study was that of the five patients on lamotrigine throughout treatment, all responded to IV ketamine. Theoretically, lamotrigine functions to inhibit the release of glutamate which is opposed to the proposed mechanism of action of ketamine (Duman, 2014; Doyle et al., 2013). Anand et al. (2000) found that lamotrigine attenuated dissociation and increased immediate mood-elevating properties. However, Mathew et al. (2010) administered lamotrigine 300mg versus a placebo 2 hours prior to IV ketamine (0.5mg/kg over forty minutes) and discovered no significant difference in side effects or antidepressant effect. Our study did not quantify dissociation, but the effect seen gives support to lamotrigine as a possible adjunct to IV ketamine.

This study has also added to the majority of evidence that ketamine is a well-tolerated treatment in the short term. Patients often described an abnormal but pleasant sensation (82% with mild side effects) that did not require treatment. Only 4 out of 50 patients suffered side effects that resulted in aborted treatment. This is comparable to the Wan et al. (2015) reported dropout rate of 3.1%.

4.4 Limitations

Despite this study's strength in its applicability, there are limitations due to its design. Confounders are an issue for *post hoc* analysis without controls. Although the response rate and effect size previously achieved in the literature are robust, a large active placebo effect still exists, with one study documenting a 28% response rate with midazolam (Murrough, et al., 2013a). The clinical setting allowed for different medication combinations and for many different concomitant psychosocial interventions that may have confounded the study. The placebo effect is mitigated in this sample to some extent as most of the other interventions were continuations of previous interventions that the patient had responded to minimally, if at all, over many years. Further, the measurements were self-rated, which have been shown to have less reliability than clinician-rated scales, especially in patients with personality disorders (Snyder and Pitts, 1986). Additionally, diagnosis would have ideally been achieved by a standardized instrument, but it was done in this study by usual care, which was a longitudinal relationship with a psychiatrist. This limitation was mitigated by a lengthy relationship with a psychiatrist, however; diagnostic criteria of depression allows heterogeneity that clinicians do not agree on, as the interrater reliability in depression as a diagnosis in the DSM-5 field trials was found to be questionable with a pooled intraclass kappa of 0.28 (Regier et al., 2013).

All retrospective studies can encounter an information bias, which could have led to missing, misinterpreted information that played a role in the results and how

certain variables have been found to influence the two groups. In this study, we could not control the outcome assessment, but instead needed to rely on others for accurate record-keeping under the instructions they were given at the time.

4.5 Future Directions

The findings reported here should be replicated with larger clinical sample sizes, and this could be accomplished with similar logistic regression techniques through national and international data registries to strengthen the data (Malhi et al., 2016). With enough information, the patient can be given a more accurate indication of their probability to response to treatments. As biomarker research continues to progress, clinical indicators could be combined with biomarkers to make composite clinical decision making tools (Kessler, 2018). The pathology of DSM-5 diagnoses seems heterogeneous and subtyping prognosticating factors to treatments may be more helpful (Insel and Cuthbert, 2015). For example, the advancements of fMRI techniques have produced exciting findings that may be able to stratify depression phenotypes with the goal of giving more appropriate treatments sooner. Drysdale et al. (2017) studied over 1000 depressed patients with fMRI and were able to subdivide patients into four "biotypes" of depression. They also found that one biotype was more responsive to repetitive transcranial magnetic stimulation (rTMS) than the others. Further, Abdallah et al. (2017) demonstrated that MDD patients had a distinctly dysfunctional global brain connectivity with global signal regression parameters shown through fMRI techniques in the prefrontal cortex, posterior cingulate, precuneus, lingual gyrus and cerebellum. This pattern normalized with ketamine treatment. McMahon and

Insel (2012) suggest the next step in psychiatry is to have treatments for subgroups of patients within diagnostic categories that share common etiology and therefore would maximize the likelihood of response. This is the concept of personalized medicine or precision medicine. With a connection to more feasible clinical measures, lessons learned from research pertaining to ketamine could be making a step towards personalized medicine and could prevent the many years of functionally disabling depression we see in the TRD population (Kessler, 2012).

In this study, due to the heterogeneity and relative small sample size, hypothesis-driven statistics were chosen. With larger samples, machine learning may be able to find unique clinical predictors of effectiveness. Where psychiatric research often has to make many assumptions, control difficult confounders, and have treatments that are not fully understood, machine learning is able to find prognosticating factors in large datasets while making few formal assumptions and perhaps thriving with large amounts of observational data instead of a small amount of RCT data (Bzdok and Meyer-Lindenberg, 2017). IV ketamine also works quickly, giving less time for confounders to interfere with the response and more promise to find subgroups that may respond better.

Unfortunately, we were unable to collect followup data in this study. As the literature strongly shows, the antidepressant effect of ketamine seen in responders is transient (Coyles and Laws, 2015). Prediction of response is the question

analyzed in this study, but prediction of long lasting effect is another useful clinical problem. Pennybaker et al. (2017) found that 12.9% of depressed patients in a cohort of 93 who were retrospectively studied from 4 previous RCTs still met criteria for response (a 50% reduction in MADRS score) two weeks after a single infusion. This population requires more study to understand if particular subgroup factors could predict this long-lasting response. By comparing factors between two-week responders and non-responders, Pennybaker et al. (2017) found that FHA and a higher dissociation severity score on the Clinical Administered Dissociation States Scale during the infusion, as well as day 1 improvement in sadness, anhedonia and concentration measures on the MADRS correlated strongly to antidepressant effects at 2 weeks (Bremner et al., 1998). A similar study could be done after a set of 6 infusions in the clinical setting. Given that a possible mechanism of action of IV ketamine is neuroplasticity, which may have long lasting effects, it would be interesting to follow a cohort of responders versus non-responders over years to see if the severity or frequency of mood episodes improves (Li et al., 2011).

Finally, given that IV ketamine at the dose of 0.5mg/kg works in bipolar and unipolar depression with no documented switch to mania, it would be plausible for ketamine to be effective in the new DSM-5 defined mixed mood state. This study's baseline scales were not adequate to detect mixed mood states.

4.6 Conclusion

In a clinical setting, a course of 6 infusions of ketamine showed effectiveness in a complex, severely treatment-resistant, depressed population on multiple concurrent medications. Given the large unmet need of this patient population, the response rate seen with ketamine is encouraging. An international registry of all patients undergoing IV ketamine has been advocated for by the American Psychiatric Association Council Research Task Force on Novel Biomarkers and Treatments. Such a registry would certainly build on this study and further the applicability and effectiveness of data on IV ketamine for the treatment of URD (Sanacora et al., 2017). This study gives support to previous findings that depression with at least moderate anhedonia is a clinical predictor of effectiveness for IV ketamine. Continued study is warranted regarding clinical predictors of effectiveness to ketamine treatment and feasible clinical decision-making tools to avoid years of disability and failed antidepressant trials, and enhance the quality of life for these patients.

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Appendix

Side Effects	**Times Checked**							
Dizziness, feeling faint, unsteadiness								

Blurred vision								
Headache								
Dry mouth								
Nausea								
Restlessness								
Abnormal body sensations and/or feeling strange or unreal								
Changes in perception of stimuli (hearing voices, seeing things)								
Feeling drowsy or sleepy								
Difficulty concentrating								
Increased blood pressure and/or heart rate								

Supplemental 1. Side effects tracking sheet used by nursing staff during ketamine administration.

A

Substitution Number for Patient Name	Response[2]	Age > 50	Gender	Baseline Suicidal	Baseline Anxiety	FHA	Baseline Anhedonia	Bipolar	Age (years)	BMI	MSM
4510	1	1	F	0	0	0	0	1	60	26.573	14
6580	1	0	M	0	1	0	0	0	50	28.198	12
1710	1	0	F	0	1	0	2	1	33	36.577	10
5010	1	0	F	1	1	0	3	1	43	34.607	12
95900	1	1	M	1	1	0	2	0	69	NA	13
9511	1	0	M	0	0	0	0	NA	35	25.328	10
67030	1	1	F	1	1	0	2	1	74	23.128	13
62600	1	1	F	1	0	1	3	1	63	27.084	13
69510	1	1	F	1	0	1	2	1	71	28.720	12
11610	1	0	F	1	0	0	1	1	38	32.253	11
65010	1	1	F	1	0	1	3	0	57	39.542	12
48420	1	0	F	0	0	1	2	1	50	19.141	12
09100	1	0	F	1	1	0	2	1	41	24.463	13
42720	1	0	F	1	0	1	2	0	50	29.532	14
82710	1	1	F	1	0	0	2	0	56	36.245	14
53700	1	0	M	1	0	0	2	NA	45	NA	11
13620	1	0	M	1	0	0	2	1	48	28.571	11
58100	1	0	F	1	1	0	3	1	34	30.487	11
19100	1	1	M	1	1	1	1	NA	68	40.930	11
17410	1	0	F	1	1	0	2	1	46	29.239	12
66631	1	1	M	1	1	0	3	0	62	44.006	12
2237210	1	1	F	1	0	0	3	1	61	39.520	10
5520	0	1	F	0	0	1	0	1	52	21.423	NA
110	0	1	M	1	1	0	2	0	64	47.469	12
2910	0	1	M	0	1	0	0	1	65	28.669	13
6330	0	0	F	NA	NA	0	NA	1	30	27.510	5
6810	0	1	F	0	1	0	1	0	59	42.225	11
9910	0	1	M	0	1	0	0	0	52	25.280	12
2410	0	0	F	0	0	0	0	1	29	40.824	9
9920	0	1	F	0	1	1	1	0	51	39.958	12
9510	0	1	M	0	1	0	0	0	59	29.174	14
0920	0	1	F	0	0	0	0	0	54	22.959	14
5230	0	0	M	1	1	0	3	NA	34	26.698	12
17710	0	0	F	1	1	0	2	NA	38	32.124	NA
95510	0	0	F	1	1	1	1	1	40	35.818	11
0651	0	1	M	0	1	0	1	0	78	31.808	12
68100	0	1	M	0	0	0	0	1	77	25.003	12
75620	0	0	M	1	1	0	2	0	46	34.351	12
73910	0	1	F	1	1	0	3	0	55	35.209	13
36780	0	1	F	1	0	0	2	0	55	28.304	13
68520	0	1	F	1	0	1	3	0	53	19.467	12
05451	0	0	F	1	0	0	2	0	37	27.548	13
00720	0	1	F	1	0	0	2	1	57	23.858	12
11510	0	0	F	1	1	0	2	1	31	31.093	13
05180	0	1	M	0	0	0	1	1	69	30.817	11
13710	0	1	M	1	0	0	2	0	66	21.985	13
49810	0	0	M	1	0	0	3	0	24	33.391	14
60410	0	1	F	1	0	1	1	1	60	NA	11
70810	0	0	F	1	0	0	2	1	29	20.540	12
4237210	0	1	F	1	0	0	2	0	60	42.531	14

Currently on an 1st Gen AP	Currently on an 2nd Gen AP	Currently on an 3rd Gen AP	Currently on lamictal	Currently on BZD
0	1	0	0	0
0	0	0	1	0
0	0	0	0	0
0	0	0	0	0
0	1	0	0	0
1	0	1	0	0
0	1	0	1	1
0	1	0	1	1
0	1	0	0	0
0	1	0	1	0
0	1	0	0	0
0	1	0	0	0
0	0	0	0	1
0	0	0	0	0
0	1	0	0	0
0	1	0	0	1
0	0	0	0	0
0	1	0	1	0
0	1	1	0	0
0	1	0	0	1
0	1	0	0	1
0	0	1	0	1
0	1	0	0	1
0	1	0	0	0
0	1	0	0	0
0	1	0	0	0
0	1	0	0	1
1	1	0	0	0
0	0	0	0	1
0	0	0	0	0
0	0	0	0	1
0	1	0	0	1
0	0	0	0	0
0	0	0	0	1
0	1	0	0	0
0	0	0	0	0
0	1	0	0	0
0	0	0	0	0
0	0	1	0	0
0	0	1	0	0
0	1	0	0	1
1	1	0	0	1
0	1	0	0	0
0	0	0	0	1
0	0	1	0	0
0	1	0	0	0
0	0	0	0	0
0	0	0	0	0
0	1	0	0	0
0	0	0	0	1

B

Legend	
Substitution Number for Patient Name	Number allocated to patient based on last digits of identifying number
Response?	A decrease of over 50% of baseline total rating scale score at any point during treatment course = 1
Age > 50	Age > 50 =1
Gender	Male =M, Female =F
Baseline Suicidal	Presence of baseline suicidality = 1
Baseline Anxiety	Presence of scale defined moderate or higher anxiety = 1
FHA	First degree family history of alcoholism = 1
Baseline Anhedonia	Presence of scale defined moderate or higher anhedonia = 1
Bipolar	Presence of being declared bipolar 1 or 2 in any admission or discharge summaries
Age (years)	Chronological age of patient in years
BMI	Body mass index measured in kilograms per meters squared at baseline
MSM	Maudsley Staging Method for treatment resistant depression out of 15
Currently on an 1st Gen AP	Concomitantly on a first generation antipsychotic during ketamine treatments
Currently on an 2nd Gen AP	Concomitantly on a second generation antipsychotic during ketamine treatments
Currently on an 3rd Gen AP	Concomitantly on a third generation antipsychotic during ketamine treatments
Currently on lamictal	Concomitantly on a lamictal during ketamine treatments
Currently on BZD	Concomitantly on a benzodiazepine during ketamine treatments

Supplemental 2. A) Database of individual patient factors used in the logistic regression models. NA = not applicable due to missing data; B) Legend for the database.

A

	Estimate	Standard Error	z value	p value
Intercept	-3.325	2.156	1.543	0.123
Gender	2.176	1.573	1.383	0.167
Age Over 50	0.243	1.139	0.213	0.831
FHA	1.903	1.557	1.222	0.222
Anhedonia	0.796	1.544	0.515	0.606
Suicidality	-0.186	1.456	-0.128	0.899
Anxiety	0.302	1.217	0.248	0.804
Bipolar	1.217	1.322	0.920	0.357

B

	Estimate	Standard Error	z value	p value
Intercept	-1.696	0.788	-2.153	0.031
Antipsychotics	0.497	0.895	0.556	0.579
Lamotrigine	0.373	1.230	0.303	0.762
Benzodiazepines	-1.479	1.122	-1.319	0.187

C

	Estimate	Standard Error	z value	p value
Intercept	-2.712	4.348	-0.624	0.533
BMI	-0.011	0.060	-0.181	0.856

MSM	0.0004	0.306	0.001	0.999
Age	0.025	0.032	0.796	0.426

Supplemental 3. Results of logistic regression calculations versus the dependent variable of remission to IV ketamine treatment. A) Categorical independent variable calculations. B) Categorical independent variable calculations of drugs received concurrently during treatment. C) Continuous independent variable calculations. Gender = male versus females; Age Over 50 = ≥50 years old versus <50 years old; FHA = positive versus negative family history of a first degree relative with past or present alcohol use disorder; Anhedonia = zero or mild anhedonia versus moderate or severe anhedonia on baseline rating scales; Suicidality = zero versus presence of suicidality on baseline rating scales; Anxiety = zero or mild anxiety versus moderate or severe anxiety on baseline rating scales; Bipolar = presence of bipolar depression; Antipsychotics = any antipsychotic used during treatment; Benzodiazepines = any benzodiazepine used during treatment; BMI = body mass index; MSM = Maudsley Staging Method for treatment resistant depression score from 3-15.

A

	Estimate	Standard Error	z value	p value
Intercept	-0.548	0.549	-0.999	0.318
Antipsychotics	0.543	0.616	0.882	0.378
Benzodiazepines	-0.167	0.609	-0.273	0.785

B

	Estimate	Standard Error	z value	p value
Intercept	-0.081	2.844	-0.029	0.977
BMI	0.004	0.044	0.086	0.931
MSM	-0.051	0.201	-0.258	0.796
Age	0.007	0.023	0.309	0.757

Supplemental 4. Results of logistic regression calculations versus the dependent variable of response to IV ketamine treatment. A) Categorical independent variable calculations of drugs received concurrently during treatment. B) Continuous independent variable calculations. Antipsychotics = any antipsychotic used during treatment; Benzodiazepines = any benzodiazepine used during treatment; BMI = body mass index; MSM = Maudsley Staging Method for treatment resistant depression score from 3-15.