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Research paper

Low-dose ketamine for treatment resistant depression in an academic clinical practice setting

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ABSTRACT

Background: Recent studies demonstrating a rapid, robust improvement in treatment resistant depression (TRD) following a single sub-anesthetic infusion of ketamine have generated much excitement. However, these studies are limited in their generalizability to the broader TRD population due to their subject exclusion criteria which typically limit psychiatric comorbidity, concurrent medication, and level of suicide risk. This paper describes the safety and efficacy of sub-anesthetic ketamine infusions in a naturalistic TRD patient sample participating in a real-world TRD treatment program within a major university health system.

Methods: The effects of a sub-anesthetic dose (0.5 mg/kg) of ketamine infused IV over forty minutes on TRD patients participating in a treatment program at the University of California, San Diego was investigated by retrospectively analyzing the medical charts of 41 adult TRD patients with a diagnosis of Major Depressive Disorder (MDD) or Bipolar Disorder (BD).

Results: Subjects were aged 48.6, 78% white, 36.6% female, and 82.9% had MDD. Significant psychiatric comorbidity existed in 73%. Average pre-infusion BDI score was 32.6 ± 8.4 (S.D) and dropped to 16.8 ± 3.1 at 24-h post-infusion ($p < 0.001$). The 24-h response (≥ 50% reduction from pre-infusion) and remission (BDI < 13) rates were 53.7% and 41.5%, respectively. Three quarters of responders maintained responder status at 7-days. Ketamine infusions were well tolerated with occasional nausea or anxiety and mild hemodynamic effects during the infusion.

Limitations: Retrospective nature of this study, lack of control group and use of self-report depression ratings scales.

Conclusions: This is the first published study of sub-anesthetic ketamine infusions in a real-world TRD population. The results suggest that this treatment is effective and well tolerated in this population

1. Introduction

Clinical depression is a prevalent debilitating psychiatric illness involving physical, mood, and cognitive symptoms. It has been reported that approximately 7.6% of the United States (US) population over the age of 12 experience depression over any given two week period (Pratt, 2014) and despite the increasing number of antidepressant medication prescriptions, suicides in the United States increased by 24% between 1999 to 2014, making it the 10th leading cause of death overall in the United States (Curtin et al., 2016).

Approximately one-third of patients with major depression fail to adequately respond to serial trials of currently approved antidepressants, which all share the primary effect of modulating monoamine neurotransmission (Sinyor et al., 2010). While the definition of Treatment Resistant Depression (TRD) is variable, literature has commonly defined the condition as failure of at least two trials of first line antidepressants of both adequate duration and dose (Al-Harbi, 2012). There are limited treatment options for TRD. Electroconvulsive Therapy (ECT) is currently considered the gold standard for TRD, however is limited by cognitive side effects as well as need for anesthesia and seizure induction. Repetitive transcranial magnetic stimulation (rTMS) is a more recent option for TRD which is better tolerated than ECT but may take longer to exhibit efficacy (Xie et al., 2013).

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Several recent studies have demonstrated that a single infusion of low-dose ketamine significantly reduces symptoms of depression within 24-h in TRD patients with Major Depressive Disorder (MDD) or Bipolar Affective Disorder (BD) (Iadarola et al., 2015; Romeo et al., 2015; Xu et al., 2015b). A review of studies investigating low-dose ketamine found that aggregated response rates (≥ 50% reduction from the baseline score on a validated depression rating scale) in randomized controlled trials as well as open label studies were 61% (Kraus et al., 2017).

These findings represent an unprecedented average response rate and speed of efficacy for a depression treatment, let alone a treatment for TRD and they have, understandably, led to great interest in the possibility that ketamine, or another drug designed to mimic ketamine's mechanism of antidepressant action, may represent an effective and rapid treatment for TRD. However, the aforementioned prospective published studies generally selected subjects who met *a priori* determined inclusion and exclusion criteria. For example, most of these studies either only included patients who were willing and able to discontinue their psychotropic medications (Berman et al., 2000; Murrough et al., 2013; Valentine et al., 2011; Zarate et al., 2006) or severely limited allowed medications (Chilukuri et al., 2014; Diazgranados et al., 2010; Ghasemi et al., 2014; Lapidus et al., 2014; Larkin and Beautrais, 2011; Rybakowski et al., 2013; Shiroma et al., 2014; Sos et al., 2013; Zarate et al., 2012). A history of suicidal behavior, active suicidal ideation, and comorbid psychiatric conditions other than anxiety were typically exclusionary in the earlier studies of ketamine for TRD.

It has been shown that subjects recruited for clinical trials in depression are poorly representative of outpatients who seek treatment for depression. Indeed, it has been estimated that 86% of outpatients with clinical depression would not qualify for a typical clinical trial in depression due to exclusion criteria and that candidates who would be excluded are more chronically ill and have greater psychosocial impairment (Zimmerman et al., 2005, 2002).

As evidence accrued demonstrating ketamine's safety and its efficacy in reducing suicidal ideation, the inclusion and exclusion criteria of clinical studies investigating ketamine's antidepressant effects have become less stringent. Nevertheless, even these recent studies have subject eligibility criteria that are not representative of patient selection criteria in real -world clinical practice. (Singh et al., 2016; Vande Voort et al., 2016; Cusin et al., 2017). In some recent studies, suicidal ideation is an inclusion requirement rather than an exclusion criteria as it was in earlier studies. (Vande Voort et al., 2016; Cusin et al., 2017).

Given the strong interest in ketamine's potential as a treatment for TRD based on the highly positive results obtained in published clinical trials, it is important to investigate its efficacy and safety in patients who are more representative of the TRD population.

In this regard, it is notable that at least three open label studies investigated the effects of IV low-dose ketamine in a TRD sample that did not exclude suicidal ideation or concomitant medication. The reported response rates in these studies were 11–25% after a single infusion (Rasmussen et al., 2013; Diamond et al., 2014; Shiroma et al., 2014), a rate much lower than reported in studies that had more restrictive eligibility criteria, and at least one of these reported a significantly higher rate of adverse events as well (Diamond et al., 2014). These findings raise questions about the generalizability of the prospective controlled and open-label studies which showed robust efficacy and tolerability of ketamine in carefully selected TRD subjects.

Based on the published studies suggesting robust and rapid efficacy along with established safety of sub-anesthetic ketamine, an outpatient ketamine treatment program for patients with TRD was developed by one of the authors (DF) at University of California at San Diego (UCSD). In this paper, we report the results of a retrospective analysis of the safety and efficacy of the initial ketamine infusion administered to a cohort of patients in this program.

2. Methods

2.1. Patient selection for ketamine treatment

Patients who received ketamine infusions were generally self-referred or referred by their treating psychiatrist for consideration to receive ketamine treatment for TRD. Candidates were interviewed by the prescribing psychiatrist (author DF) to assess the severity of their depression as well as the extent and outcome of previous treatment trials. As is typical for a clinical practice, the criteria for accepting any patient for ketamine treatment in this clinical program was the determination of a favorable risk vs benefit calculus for that particular patient as determined by the treating clinician. This is a process which is considerably less formal and less restrictive than the *a priori* inclusion and exclusion criteria utilized in prospective research studies because in those studies patient characteristics determined to be unfavorable for a treatment are predetermined for all prospective subjects and applied immutably as exclusionary criteria. However, in real-world clinical treatment, patient characteristics rendering a treatment such as ketamine an unfavorable option may be sufficiently counterbalanced, in the judgement of the treating clinician, by other patient characteristic or circumstances. For example, a clinician may decide to treat a patient with uncontrolled hypertension with ketamine infusions if he has severe debilitating depression associated with concerning loss of appetite and weight loss and suicidal impulses that has not responded to all other reasonable treatments including ECT. However, in a clinical study in which uncontrolled hypertension is an exclusion criteria, this same patient would not be enrolled.

While there were no formal criteria for treatment with ketamine in the clinical practice we are reporting on, candidates were generally deemed to be appropriate if they were experiencing severe depression that significantly reduced their quality of life or placed them at significant risk of suicide and they had failed to respond to several trials of medications in the current episode despite an adequate dose and duration (at least four weeks) or due to intolerance of the medication. Some patients had also failed a course of ECT and/or rTMS. In contrast, factors that significantly reduced, but did not necessarily preclude a patient's candidacy included a history of a psychotic disorder, uncontrolled hypertension, a previous adverse reaction to ketamine, significant active medical conditions, active substance use, pregnancy or breastfeeding.

Patients deemed appropriate for a trial of ketamine treatment were provided with relevant information about the treatment, including the fact that the treatment is not currently FDA approved and not reimbursed by insurance. Patients were provided with a written informed consent document for treatment which described potential risks and limitations in detail as well as reasonable expectations of ketamine treatment for depression. Patients were given an opportunity to ask questions which were addressed by the prescribing physician.

2.2. Ketamine infusions

Ketamine infusions were conducted in a UCSD same-day outpatient procedure center. Patients were permitted to continue their current medication regimen unchanged, but if that regimen included a morning benzodiazepine or opiate, they were asked to hold it on the morning of their ketamine infusion.

Ketamine was dosed at 0.5 mg/kg based on the patient's actual body weight on the day of infusion and infused over 40 min, which is consistent with most previous studies of ketamine for TRD (Iadarola et al., 2015; Romeo et al., 2015; Xu et al., 2015b). The ketamine was prescribed by the treating psychiatrist (DF) and prepared by the procedure center pharmacy staff. The infusion was administered by a nurse on staff at the infusion facility who also conducted the monitoring. Safety monitoring included periodic assessment of vital signs, oxygen saturation, and mental status during the infusion, and for at least 30-min post-

infusion. Beginning 30 min post-infusion, patients were assessed by the nurse and the attending psychiatrist (DF) for the persistence of significant mental status changes, orthostatic hypotension or unsteadiness and any other significant adverse effect (e.g. nausea) that required ongoing monitoring. In the absence of any of these, patients were deemed appropriate for discharge home from the center under the care of a present caregiver.

Patients completed a Beck Depression Inventory (BDI) scale prior to their infusion, and again just before leaving the infusion center (approximately 1 h post-infusion). Patients were provided with a BDI and instructed to complete it 24 h post-infusion and to document in narrative fashion any changes in their mental state since the infusion. The BDI and narrative were reviewed during a follow-up visit which typically occurred 24–72 h after the infusion. An additional BDI survey was solicited from patients who reported having a significant positive response on their BDI at 24 h post-infusion.

2.3. Retrospective analysis

A retrospective chart review of the first 50 patients who received low-dose ketamine infusion in this clinical program was conducted. This retrospective study was approved by UCSD Human Research Protection Program. Charts were included in the analysis if the patient's primary diagnosis was MDD or BD, they were ≥18 years old, and there was a record of the pre-infusion, 1-h and 24-h post-infusion BDI score. The charts were abstracted by one of the authors (BM) using an electronic abstraction sheet. The abstraction sheet was developed before chart reviews began by identifying informational elements from the chart that would be relevant to the analysis. The informational elements were determined by consensus of the authors. The information entered into the abstraction sheet was de-identified.

The dose of ketamine administered was verified by reviewing the patient's weight at the time of infusion and nursing documentation of the milligrams administered. Extracted demographic variables included age, weight, sex, ethnicity, psychiatric history *(e.g. psychiatric diagnoses, past medication trials during current episode, history of ECT, past ketamine),* medical history, past treatments and concurrent psychiatric medications at the time of infusion. Extracted efficacy data included BDI scores pre-infusion, 1-h, 24-h, and, when available, 7-days post-infusion as well as relevant documented comments by attending psychiatrist and nurses. Safety variables extracted included blood pressure, heart rate, and oxygenation status. Adverse effects were assessed by review of the nursing documentation and medication administration record (MAR) records for the administration of medications with antiemetic, anxiolytic, analgesic, or cardiovascular indications during or in the immediate post-infusion period. Any documented verbal reports by patients during or immediately after infusions regarding their subjective experience were also extracted.

2.4. Clinical outcomes and statistical analysis

For most outcome variables, descriptive statistics such as means and standard deviation are reported. Demographic and safety variables, adverse effects, and subjective experience reports were described with mean ± standard deviation for continuous variables and frequencies for categorical variables. The study's primary outcome was percentage of patients classified as responders at 24-h after infusion, with response defined as ≥ 50% reduction in their BDI score from baseline. This was the same primary outcome used in almost all the published randomized and open-label prospective studies of ketamine for depression, although we used a self-reported rather than clinician administered scale. Other outcome measures included response at 1-h and 7-days, remission rate defined as (BDI < 13) (Riedel et al., 2010) at 24-h and 7-days, and mean change in BDI scores from baseline to 1-h, 24-h, and 7-days analyzed using a paired student *t*-test with $\alpha < 0.05$ considered significant.

Table 1
Demographics of included sample and history of depressive treatments (n = 41). Electroconvulsive therapy (ECT), repetitive Transcranial Magnetic Stimulation (rTMS).

Demographics		**N (%)**
Female		15 (36.6)
Male		26 (63.4)
Ethnicity	White	32 (78.0)
	Asian	2 (4.9)
	Black	0 (0)
	Hispanic	0 (0)
	Other	7 (17.1)
Past therapies		**N (%)**
≥ 4 antidepressant trials		41 (100)
Past ketamine		5 (12.2)
Past ECT		11 (26.8)
Past rTMS		10 (24.4)
Primary diagnosis		**N (%)**
Major depressive disorder		34 (82.9)
Bipolar		7 (17.1)

Significant changes in hemodynamic parameters, delineated *a priori* as an increase greater than 20 mmHg in systolic blood pressure (SBP) or 10 mmHg in diastolic blood pressure (DBP) as well as 25 beats per minute (BPM) for heart rate (HR) were described using frequencies.

3. Results

3.1. Sample demographics

Of the first 50 patient charts examined, 41 met inclusion criteria for this analysis. Eight patients were excluded due to missing either a baseline or 24-h BDI score and one patient was excluded due to being < 18 years of age. Excluded charts were reviewed for serious adverse events of which none were identified. Subjects mean age was 48.6 ± 12.73 years. Demographic variables including gender and ethnicity are displayed in Table 1. All patients had failed therapy with at least four antidepressant medications previously; 11 (26.8%) had received past ECT, 10 (24.4%) had past rTMS, and 5 (12.2%) had taken ketamine recreationally at least once by intranasal (n = 1) or oral (n = 4) routes in the remote past.

3.2. Psychiatric and cardiovascular history

Thirty-four (82.9%) patients had a primary diagnosis of MDD while 7 (17.1%) patients had BD. Anxiety was the most common psychiatric comorbidity and was present in 24 (58.5%) patients, while hypertension was the most common pre-existing cardiovascular comorbidity occurring in 10 (24.4%) patients. Other comorbid psychiatric conditions are displayed in Table 2.

3.3. Concurrent psychotropic medication

Table 3 summarizes the concurrent medication(s) of the patient included in this analysis. Patients were taking an average of 2.4 psychotropic medications concurrently when they received ketamine therapy (Table 3). There were 7 patients (17.1%) who were not taking any psychotropic medication at the time of ketamine therapy.

3.4. Efficacy

Fifty-four percent of the sample (n = 22) met the criterion for response 24 h after ketamine and 41.5% (n = 17) achieved remission. Response and remission rates for 1-h post infusion assessments were 51% and 44%, respectively. The mean baseline BDI score was 32.6 ± 8.43 (SD) which improved to 16.8 ± 12.1 (49.5% reduction; $p < 0.001$) and 16.0 ± 11.4 (51% reduction; $p < 0.001$), 1-h and 24-h

Table 2
Psychiatric and cardiovascular comorbidity of included sample (n = 41). Substance Use Disorder (SUD), Borderline Personality Disorder (BPD), Post-Traumatic Stress Disorder (PTSD). Attention Deficit Hyperactivity Disorder (ADHD), Obsessive Compulsive Disorder (OCD). Anxiety disorder included generalized anxiety disorder, panic disorder, social anxiety disorder and anxiety disorder NOS).

Psychiatric comorbidity	N (%)
Anxiety disorder	24 (58.5)
SUD	5 (12.2)
BPD	4 (9.8)
PTSD	2 (4.9)
ADHD	2 (4.9)
Psychotic disorder	0
OCD	1 (2.4)
Traumatic brain injury	1 (2.4)
Autism spectrum disorder	1 (2.4)
Fibromyalgia	1 (2.4)

Table 3
Current pharmacotherapies for depression and comorbid psychiatric conditions. Other augmentation agents included opiates, dronabinol, liothyronine, methylfolate, and sodium oxybate.

Current pharmacotherapies	N (%)
Any Antidepressant	21 (51.2)
> 1 Antidepressant	5 (12.2)
Antipsychotics	12 (29.3)
Mood Stabilizer	8 (19.5)
Anticonvulsant	2 (4.9)
Stimulant	11 (26.8)
Benzodiazepine	17 (41.5)
Sedative/hypnotic	7 (17.1)
Other augmentation agents	5 (12.2)

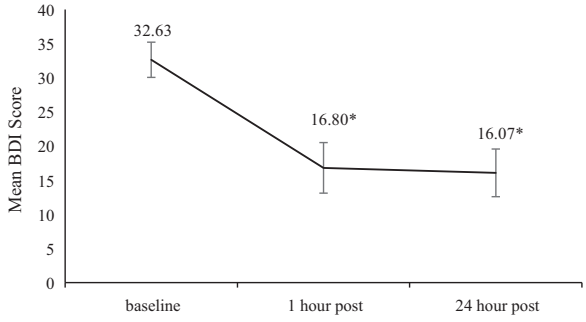

Fig. 1. Baseline (pre-infusion), 1-h post infusion and 24-h post infusion BDI scores in included patients (n = 41). Error bars display 95% confidence intervals. Asterisks denote significantly reduced from baseline ($p < 0.01$)

post-infusion, respectively (Fig. 1). Patients with BD and MDD had comparable reductions in BDI at 24-h (49% and 51%).

Sixteen of the 22 patients who were responders at 24-h had record of a 7-day post-infusion BDI. Among that subset of patients, 12 (75%) continued to meet the responder criterion. The mean BDI scores for this subset of patients across the 7 days is illustrated in Fig. 2.

3.5. Hemodynamic effects

Effects on heart rate and blood pressure differed from patient to patient although ketamine tended to produce a modest and transient increase in blood pressure and heart rate. Seven patients (17.1%) experienced a rise in SBP > 20 mmHg and 12 (29.3%) had a rise in DBP > 10 mmHg, while one patient had a rise in HR > 25 BPM. No patient's blood pressure required intervention with antihypertensive medication and no oxygen desaturation (SaO2 < 93%) events occurred.

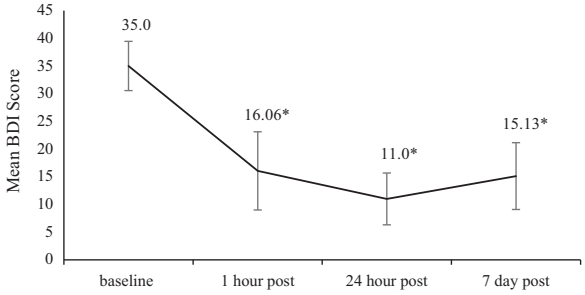

Fig. 2. Baseline (pre-infusion), 1-h post, 24-h post, and 7-day post BDI scores in the subset of patients with a completed 7 day post-infusion BDI (n = 16). Error bars display 95% confidence intervals. Asterisks denote significantly reduced from baseline ($p < 0.01$)

3.6. Adverse effects

Three patients required the use of an antiemetic (7.3%) due to post-infusion nausea while they were still in the infusion center, and one patient experienced vomiting. One patient with significant pre-existing anxiety at baseline required stopping the infusion within 10 min and the administration of 1 mg of oral lorazepam. After approximately 15 min of receiving the lorazepam, the patient requested the infusion be re-started and was able to finish the infusion without further problems or excessive anxiety. Notably this patient met the criteria for remission at 24 h. Five of the patients had a mild (< 20%) increase in their BDI from baseline to 24 h. However, the score increases were small and not identified as clinically significant by patients or treating psychiatrist.

3.7. Subjective effects and patient experience

Every patient reported experiencing a 'psychedelic' phenomenon although the quality and intensity varied. The subjective phenomenon they reported including one or more of the following: perceptual disorders, a sense of detachment from their bodies (dissociation), enhancement of insight into reality, a sense of relaxation or well-being. Among the charts that included patient descriptions of the emotional quality of the psychedelic experience (n = 18), all but one reported that it was pleasant. Comments made by patients right after the infusion included: "It was like I was in a biological membrane…very pleasurable"; "it was like it melted my armor (of depression)"; "Ketamine filled in my missing piece. I feel whole for the first time since the accident 33 years ago."

Select comments from patients that felt a therapeutic benefit at 24-h included: "the world was brighter"; "a Christmas miracle"; and "I was finally standing up straight and experiencing the world".

4. Discussion

In this retrospective study, we evaluated the efficacy and safety of an initial 0.5 mg/kg, 40-min intravenous ketamine infusion in a sample of TRD patients treated as part of an outpatient academic clinical practice. We believe this to be the first report of ketamine infusion treatment for TRD patients participating in a clinical practice (rather than prospective research), although a retrospective report of oral ketamine treatment in a depressed hospice population has been reported (Irwin et al., 2013).

Our results generally show that a single infusion of low-dose ketamine is efficacious and generally well tolerated in the sample population treated in a 'naturalistic' clinical context.

The response rate in this sample at 24-h after the index infusion (53.7% responders) is slightly lower than the average response rate of 61% reported at 24-h post infusion in prospective studies evaluating ketamine in TRD patients, although those studies tended to use an interviewer-based rating scale (MADRS, HAM-D) as the primary measure rather than BDI. Excluding the 6 patients whose charts were missing 7-

day BDI scores, the 7-day response rate was 46% (16/35). This is comparable to the 7-day response rates from prospective studies (35–52%) (Rybakowski et al., 2013; Sos et al., 2013; Zarate et al., 2006). Of note, the presence of concomitant medication(s) in these patients makes interpretation of ketamine's efficacy somewhat more complicated.

A previous meta-analysis found ketamine to have a larger effect size in open-label trials compared to randomized trials, which the authors attributed to an expectancy bias (Coyle and Laws, 2015). This may suggest that ketamine was slightly less efficacious in our sample given patients were aware they were receiving ketamine. However, the authors also remark on the disparity of response rates in published literature and call for larger sample sizes to ensure more precise estimates of response rates (Coyle and Laws, 2015).

The prospective study in the extant literature that most closely resembles the naturalistic features of the clinical practice we analyzed was the open-label case series by Diamond et al. which also utilized the BDI self-rating as the primary measure. In that study, concomitant medications were not required to be discontinued and suicidal ideation did not exclude patients. Surprisingly, that study found a much lower response rate (11%) and much worse tolerability within the first 24-h after ketamine infusion. The administration of ketamine in an ECT suite in the Diamond et al. study may have contributed to the lower tolerability and efficacy of those treatments. In fact, despite patients in this study rating the ECT suite as 'suitable' for ketamine administration, many patients complained it was too noisy, chaotic, or distressing (Diamond et al., 2014). Notably, prior to relocating to the current outpatient setting, the UCSD ketamine treatment program administered ketamine in a Post-Anesthesia Care Unit (PACU) which is similar to an ECT setting. Three TRD patients received ketamine in that location and none of them experienced any notable benefit, prompting a location change to the outpatient procedure center. Differences in patient populations, methodological differences between the prospective open-label design used in their study versus retrospective evaluation in ours, or small sample size may also explain differing results between our sample and that reported by Diamond et al.

The use of various psychotropic medications, baseline demographics, and comorbid conditions may play a role in augmenting or diminishing the response to utilization of ketamine in TRD (Coyle and Laws, 2015; Ionescu et al., 2014; Niciu et al., 2013, 2015; Xu et al., 2015a). However, post-hoc exploratory analyses using contingency tables in our study did not reveal apparent differences in response or remission rates by gender, comorbid anxiety, or medication use, although this study was not powered to show differences in these areas.

Ketamine is known to transiently increase hemodynamic parameters, and about 50% of our sample population experienced a transient increase in blood pressure and/or heart rate, but none of them required medication treatment or infusion interruption for these changes (Iadarola et al., 2015; Romeo et al., 2015; Xu et al., 2015b).

There are several limitations to our study. First, the retrospective nature of the studies design may introduce various forms of bias including selection or information bias. Charts that were excluded due to missing data which if included may have resulting in different efficacy rates. In addition, the ability to fully capture adverse effects may be limited when reviewing paper chart or electronic medical record data as analysis relies heavily on nursing and/or physician documentation. Second, lack of a control group may introduce a placebo effect, although large effect size and available randomized data published elsewhere may help to alleviate concerns that results found are due to a placebo effect alone. Third, ketamine for TRD is not covered by private or public sector insurance plans, which required patients pay for their treatment out of pocket. Additionally, some patients in our sample traveled from out of state to receive ketamine therapy, both of which suggest a more financially secure sample population than the average patient with TRD. Lastly, the sample described is from a single academic site and all patients were interviewed by a single psychiatrist (DF) who also prescribed the ketamine treatments. Therefore, although our sample is more generalizable to patients with TRD than those enrolled in clinical trials due to less restrictive exclusion criteria it may not be truly representative of all patients with TRD in the United States.

In conclusion, ketamine appears to produce a rapid antidepressant effect and is well tolerated in a naturalistic outpatient community TRD sample with prevalent comorbidities and concurrent psychiatric medications.

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