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A randomised, open-label, pragmatic pilot comparison of oral and intravenous ketamine in treatment-resistant depression

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ABSTRACT

Background: For depression, ketamine is more conveniently administered by oral than by intravenous (iv) routes. The relative antidepressant efficacy of oral vs iv ketamine is unknown.
Objectives: To assess the acute efficacy and the persistence of improvement with open-label oral versus iv ketamine in outpatients with treatment-resistant depression (TRD).
Methods: Adults with TRD were randomized to oral (N=30) or IV (N=31) ketamine. Oral ketamine was dosed at 150 mg in 50 mL of water, sipped across 15 min. IV ketamine was dosed at 0.5 mg/kg, infused across 40 min. Ketamine sessions (total, 7) were administered on alternate days for 2 weeks. Ongoing antidepressant drugs were continued unchanged. Patients were assessed at baseline, day 14, and day 30. The primary outcome was the endpoint Hamilton Rating Scale for Depression score on day 14. Secondary outcomes were endpoint scores on the Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory, and Clinical Global Impression-Severity of Illness and Improvement.
Results: Overall dropout was lower with oral than with iv ketamine (26.7 % vs 54.8 %; P=0.03). The 2 groups did not differ in depression ratings and in response and remission rates on all instruments on both days 14 and 30. Adverse events such as headache (56.7 % vs 74.2 %) and drowsiness (0.0 % vs 22.6 %) were less common with oral ketamine.
Conclusion: In TRD outpatients treated in general hospitals, oral ketamine maybe better accepted and tolerated than iv ketamine. Conclusions about relative efficacy cannot be drawn because of the high dropout rate with iv ketamine.

1. Introduction

Treatment resistant depressive disorder (TRD) is a disabling and often life-threatening condition affecting millions of people across the globe causing considerable burden on health and socioeconomic status. For depression, treatments targeting monoamine systems usually take >4 weeks to exert their effects (Nierenberg et al., 2000). Recent studies postulate role of glutamate in depression, particularly, N–methyl-D aspartate (NMDA) receptors other than serotonin receptors (Naughton et al., 2014). Ketamine is a non-competitive, voltage-dependent NMDA-receptor channel blocker which has antidepressant action at low doses, and with higher doses, it mimics psychotomimetic drugs and eventually leads to anesthesia (Miller et al., 2016). Evidence suggests that intravenous (iv) ketamine has rapid onset of action on depressive symptoms; even one-time iv ketamine helps in the management of suicidal ideation and relieves depression within two hours and the effect sustains one week post infusion (Andrade, 2023a; Romeo et al., 2015; Vasavada et al., 2016). Simultaneously, repeated ketamine infusions were associated with improved mood symptoms within hours after the first infusion (Zheng et al., 2022) and enhanced neurocognitive performance at the end of the course (Zheng et al., 2019). Evidence suggests that administration of ketamine by oral route reduces depression and suicidality in moderately to severely depressed patients and the benefits sustain with daily dosing (Enarson et al., 1999; Irwin et al., 2013a, 2013b; McNulty and Hahn, 2012; Paslakis et al., 2010).

A few studies have also assessed the efficacy of oral ketamine in patients with TRD and it was found to be effective in all these reports (Al Shirawi et al., 2017; De Gioannis and De Leo, 2014; Domany et al., 2019;

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Hartberg et al., 2018; Swiatek et al., 2016). Few patients had adverse events such as dizziness, drowsiness, and euphoria, but it was mild and transient (Andrade, 2019). However, one of the major limitations in all these studies was that no outcome data were available for the post-treatment weeks. This limitation is important because a course of oral ketamine is more convenient, cheaper, less heroic, and probably more rapid-acting than a course of electroconvulsive therapy (ECT), in the management of depression (Andrade, 2017).

Considering these limitations and since studies are limited with oral ketamine in TRD, the present study was conducted to assess the acute efficacy and the persistence of improvement with oral versus iv ketamine in patients with TRD.

2. Materials and methods

2.1. Setting

This open-label, prospective, outpatient, randomised controlled trial was carried out in the Department of Psychiatry at a multispecialty general hospital in Kerala, India, between September 07, 2020 and December 31, 2020. Written informed consent was obtained from all patients. The study was approved by the Institute Ethics Committee and was registered with the Clinical Trials Registry - India (CTRI/2020/09/027644).

2.2. Sample

Patients of either sex were eligible for participation if they had major depressive disorder (MDD) without psychotic features, based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria (American Psychiatric Association, 2013) and diagnosed by a senior psychiatrist; the same psychiatrist diagnosed all patients. Further inclusion criteria were age 18–65 years, failure to respond to at least 2 previous antidepressants administered in adequate doses for at least 4 weeks (McIntyre et al., 2023), no treatment with ECT during the past 6 months, and a current 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) score of at least 15. Exclusion criteria were major medical or psychiatric comorbidities, current alcohol, smoking, or substance use disorder, ongoing pregnancy or lactation, and detection of abnormalities of concern in the electrocardiogram.

2.3. Treatments

Using a computer-generated random number sequence, patients were assigned to receive either oral or iv ketamine. Oral ketamine, obtained from ketamine vials, was administered in the fixed dose of 150 mg, diluted in 50 mL of water and sipped across 15 min (Andrade, 2019, 2017; Kaur et al., 2023). IV ketamine was administered as an infusion in the dose of 0.5 mg/kg body weight across 40 min (Phillips et al., 2019). The ketamine sessions were conducted on alternate days across 2 weeks (7 sessions in total). Ongoing antidepressants were continued unchanged during the study. Oral clonazepam was allowed for anxiety or agitation.

2.4. Assessments

Patients were rated using the 17-item HAM-D, the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the Beck Depression Inventory (BDI) (Beck et al., 2011), and the Clinical Global Impression scales for Severity and Improvement (CGI-S, CGI-I) (Busner and Targum, 2007; Guy, 1976). Assessments were conducted at baseline and at 2 study endpoints: 1 day after the last ketamine session and approximately 2 weeks later (day 30). Because of the impossibility of blinding patients to the nature of the intervention, and because of the high likelihood of accidental unblinding of the rater during assessments, the study was completely open-label. Adverse effects were assessed through direct enquiry and self-report. The same rater assessed all patients.

2.5. Statistical methods

We planned to recruit approximately 30 patients in each group with a view to detect an effect size (ES) of approximately 0.75 with 80 % power at the 0.05 level of statistical significance (Norman et al., 2012). We powered the study for a large ES of 0.75 as this was intended to be a pilot study. The intent-to-treat sample comprised all patients who consented to participate in the study and who were randomised to oral or iv ketamine groups. Missing ratings were imputed using last-observation-carried forward (LOCF) method.

The primary outcome was a comparison between groups of HAM-D total scores 1 day after the last ketamine session (day 14). Secondary outcomes were a comparison between groups of HAM-D total scores on day 30 and a comparison between groups on other assessments at days 14 and 30. Response was defined as a 50% attenuation of depression ratings on either HAM-D or MADRS. Remission was defined as a HAM-D total $\leq$7 or MADRS total $\leq$10.

Continuous variables were compared between groups using the independent samples t-test or the Mann-Whitney test and categorical variables using the Chi square test or Fisher's exact test. Because, despite randomisation, there were many unexpected differences between groups at baseline, endpoint scores were compared between groups using multivariable linear regression, adjusting analyses for baseline ratings as well as for clinically significant unbalanced variables (number of previous episodes, duration of current episode, and use of clonazepam) (Holmberg and Andersen, 2022). Alpha for statistical significance was set at 0.05 for the primary outcome and 0.01 for the secondary outcomes.

3. Results

3.1. Sample disposition

There were 30 patients randomised to oral ketamine and 31 to iv ketamine; whereas 22 (73.3 %) patients receiving oral ketamine completed the study, only 14 (45.2 %) patients receiving iv ketamine did (χ^2 = 5.00, df=1, P=0.025).

Reasons for drop out in the oral ketamine group were perceived recovery (n=1; 3.3 %), inefficacy (n=4; 13.3 %), adverse effects (n=1; 3.3 %), and loss to follow up (n=2; 6.7 %). Reasons for drop out in the iv ketamine group were perceived recovery (n=1; 3.2 %), inefficacy (n=5; 16.1 %), adverse effects (n=3; 9.7 %), and loss to follow up (n=8; 25.8 %) (Fig. 1).

3.2. Sample characteristics

The sample is described in Table 1. Patients receiving iv ketamine were more likely to be married, had slightly lower years of education, had more previous episodes of depression, had shorter duration of current depressive episode, and were more likely to receive clonazepam during the study.

Most patients were receiving escitalopram (n=57), desvenlafaxine (n=51), or both; a few were receiving fluoxetine (n=3), mirtazapine (n=6), or dothiepin (n=1). Comorbidities in the sample were few and minor. There were 9 patients with diabetes mellitus, 8 with hypertension, and 5 with hypothyroidism. All were stable on treatment.

3.3. Primary outcome

HAM-D scores at baseline and at days 14 are presented in Table 2. In univariate analysis, there was no significant difference between groups at either time point. In multivariable linear regression analysis, there was no significant difference between iv and oral ketamine groups at day

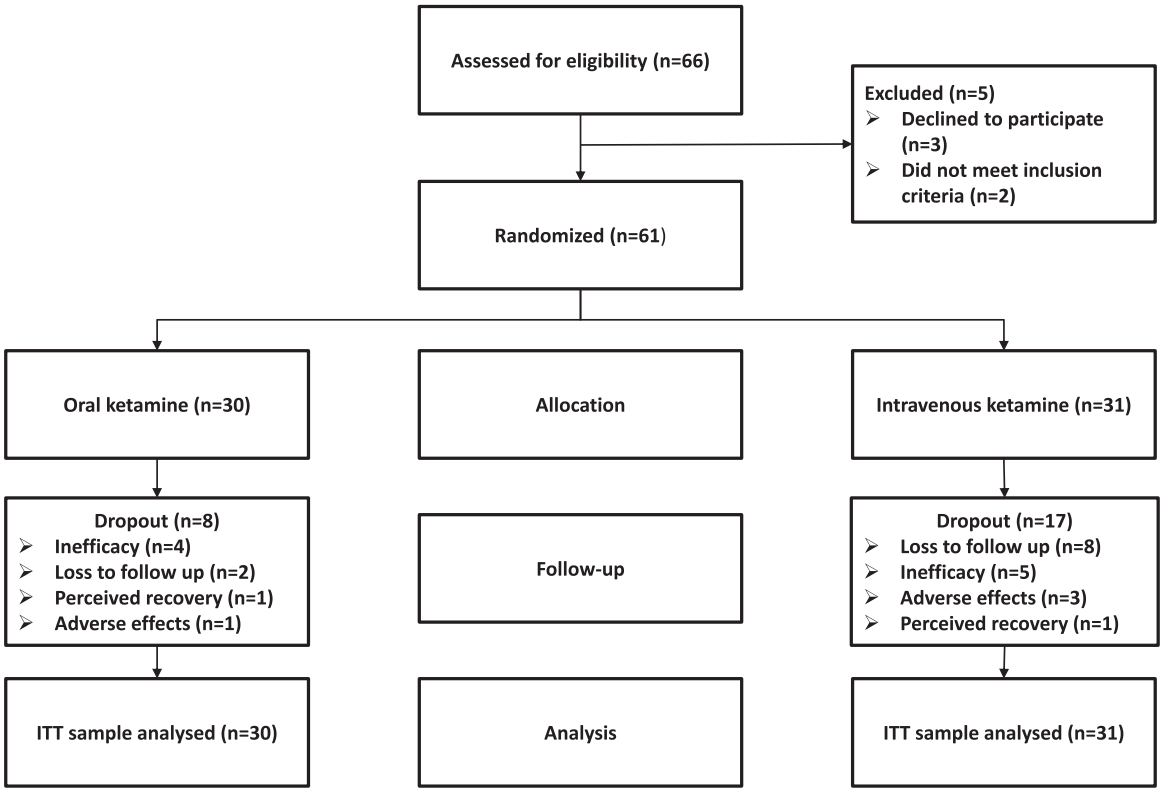

Fig. 1. CONSORT flow diagram for the trial.

14 (P = 0.17).

3.4. Secondary outcomes

HAM-D scores at day 30 and scores on MADRS and BDI at days 14 and 30 are presented in Tables 2–4. In univariate analyses, there was no significant difference between iv and oral ketamine groups on either scale and at any time point. In multivariable linear regression analysis, there was no significant difference between iv and oral ketamine groups on the HAM-D at day 30 (P=0.14), on the MADRS at days 14 (P = 0.09) and 30 (P = 0.10), and on the BDI at days 14 (P = 0.15) and 30 (P = 0.15).

On day 14, response on HAM-D was observed in 14 (46.7 %) vs 14 (45.2 %) patients in oral vs iv ketamine groups respectively; the difference was not statistically significant (P=0.91). These values were 15 (50.0 %) vs 14 (45.2 %) on day 30 (P=0.71).

On day 14, remission on HAM-D was observed in 5 (16.7 %) vs 2 (6.5 %) opatients in oral vs iv ketamine groups respectively; the difference was not statistically significant (Fisher's exact test, P=0.26). These values were the same on day 30.

On day 14, response on MADRS was observed in 15 (50.0 %) vs 12 (38.7 %) patients in oral vs iv ketamine groups respectively; the difference was not statistically significant (P=0.38). These values were the same on day 30.

On day 14, remission on MADRS was observed in 4 (13.3 %) vs 7 (22.6 %) patients in oral vs iv ketamine groups respectively; the difference was not statistically significant (P=0.51). These values were the same on day 30.

The mean (standard deviation) (M[SD]) CGI-S scores were 3.2 (1.2) vs 3.5 (1.5) on day 14 and 3.1 (1.2) vs 3.5 (1.5) on day 30 in oral vs iv ketamine groups, respectively; the groups did not differ significantly at either time point (P = 0.32 and 0.27, respectively).

The mean (standard deviation) (M[SD]) CGI-I scores were 2.7 (0.9) vs 3.3 (1.6) on day 14 and 2.7 (0.9) vs 3.2 (1.6) on day 30 in oral vs iv ketamine groups, respectively; the groups did not differ significantly at either time point (P = 0.13 and 0.15, respectively).

3.5. Adverse events

Adverse events reported by patients are presented in Table 5. Drowsiness and headache were more common with iv ketamine. Miscellaneous adverse events reported included giddiness, unsteadiness, tiredness, and restlessness. Three patients dropped out in the iv ketamine group due to drowsiness (n=2) and headache (n=1); one patient dropped out in the oral group due to vomiting and tiredness. No serious adverse events were encountered.

4. Discussion

We set out to examine differences in acute and sustained efficacy and safety of oral versus iv ketamine, dosed on alternate days for 2 weeks, in TRD. We expected a superiority for iv over oral formulation but found no significant between group differences in depression symptom ratings on days 14 and 30 and no difference in response rates, remission rates, illness severity, or illness improvement over time. Perhaps the most important finding was a higher rate of all-cause dropout with iv ketamine, suggesting that oral ketamine has better acceptability.

The higher dropout in the iv ketamine group and our use of LOCF for imputing missing values may explain why iv ketamine did not outperform oral ketamine (if indeed iv ketamine is a superior treatment) and also why subjects in the oral group experienced a numerically greater drop in depression scores. It is also possible that patients who were retained in the trial may have experienced improvement due to mechanisms involving the placebo effect or Rosenthal effect; a definitive answer to this is not possible as the study did not have a placebo arm. Importantly, because the oral procedure is far less expensive to perform, affordability may add to its acceptability in real life settings (outside a clinical trial environment).

Table 1
Sample characteristics*.

	Oral ketamine (n=30)	Intravenous ketamine (n=31)	Statistical significance
Age (years)	44.6 (12.6)	47.2 (12.0)	t=0.82; df=59; P=0.41
Male	13	12	Chi square = 0.14,
Female	17	19	df=1;
			P=0.71
Single	9	1	Fisher's exact P =
Married	21	30	0.006
Education (years)	11.2 (3.3)	9.3 (4.1)	t=2.07; df=59; P=0.043
Nuclear family	26	25	Fisher's exact P =
Joint family	4	6	0.73
Family history of depression	10	12	Chi square = 0.19;
No	20	19	df=1;
Yes			P=0.66
Previous episodes	21	8	Chi square = 11.21;
0–1	9	23	df=1; P<0.001
2 or more			
Age at first episode (years)	30.8 (14.5)	33.6 (12.6)	t=0.82; df=59; P=0.42
Duration of illness (years)	14.0 (10.7)	13.6 (9.1)	t=0.16; df=59; P=0.88
Duration of current episode (days	167.6 (204.4)	83.4 (78.2)	Mann-Whitney P = 0.036
Previous hospitalisations	18	13	Chi square = 1.99;
No	12	18	df=1;
Yes			P=0.15
Escitalopram dose (mg/d)	16.9 (4.6) (n=27)	15.3 (5.1) (n=30)	t=1.18; df=55; P=0.25
Desvenlafaxine dose (mg/d)	110.4 (29.4) (n=24)	123.2 (46.5) (n=27)	t=1.18; df=44.5; P=0.24)
Receiving clonazepam	15	26	Chi square = 7.94;
Not receiving clonazepam	15	5	df=1; P=0.005
Baseline HAM-D	31.5 (10.3)	32.5 (10.5)	t=0.38; df=59; P=0.70
Baseline MADRS	44.3 (10.7)	41.4 (12.5)	t=1.00; df=59; P=0.32
Baseline BDI	37.9 (10.1)	38.6 (13.3)	t=0.24; df=59; P=0.81
Baseline CGI-S	5.1 (0.7)	5.4 (0.6)	t=1.65; df=59; P=0.10

Abbreviations: BDI = Beck Depression Inventory; CGI-S = Clinical Global Impression-Severity; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale

* Data are mean (standard deviation) or cell frequency counts.

Table 2
HAM-D total scores at baseline and at study endpoints*.

	Oral ketamine (n=30)	Intravenous ketamine (n=31)	Univariate statistical significance
Baseline	31.5 (10.3)	32.5 (10.5)	t=0.38; df=59; P=0.70
Day 14	17.6 (10.1)	20.7 (14.6)	t=0.96; df=53.5; P=0.34
Day 30	17.3 (9.9)	20.8 (14.4)	t=1.11; df=53.3; P=0.27

Abbreviation: HAM-D = Hamilton Rating Scale for Depression

* Data are mean (standard deviation)

We followed consensus iv ketamine dosing guidelines (Sanacora et al., 2017). This meant that individuals with high BMI received higher absolute doses. On the other hand, we did not uptitrate within the 0.5–0.8 mg/kg range. So, some patients receiving iv ketamine may have dropped out due to adverse effects associated with higher doses whereas other may have dropped out due inefficacy associated with inadequate dosing. As a counter-argument, oral ketamine was dosed at a fixed dose of 150 mg; high for those who might have been underweight and low for those of larger build. Nevertheless, drop out due to potential adverse effects or inefficacy were lower with oral ketamine. We agree, however, that the relative efficacy of fixed vs variable dose titration protocols for oral and iv ketamine in MDD merits further examination (Kwaśna et al., 2024).

Table 3
MADRS total scores at baseline and at study endpoints*.

	Oral ketamine (n=30)	Intravenous ketamine (n=31)	Univariate statistical significance
Baseline	44.3 (10.7)	41.4 (12.5)	t=1.00; df=59; P=0.32
Day 14	24.8 (14.7)	26.7 (18.6)	t=0.45; df=56.7; P=0.66
Day 30	24.5 (14.8)	26.6 (18.5)	t=0.48; df=59; P=0.64

Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale

* Data are mean (standard deviation)

Table 4
BDI total scores at baseline and at study endpoints*.

	Oral ketamine (n=30)	Intravenous ketamine (n=31)	Univariate statistical significance
Baseline	37.9 (10.1)	38.6 (13.3)	t=0.24; df=59; P=0.81
Day 14	22.9 (12.9)	24.5 (18.9)	t=0.39; df=53.1; P=0.70
Day 30	22.6 (12.7)	24.5 (18.8)	t=0.47; df=52.9; P=0.64

Abbreviation: BDI = Beck Depression Inventory

* Data are mean (standard deviation)

Table 5
Adverse events.

	Oral ketamine (n=30)	Intravenous (IV) ketamine (n=31)
None	6 (20.0 %)	4 (12.9 %)
Dissociation	13 (43.3 %)	12 (38.7 %)
Drowsiness	17 (56.7 %)	23 (74.2 %)
Headache	0 (0.0 %)	7 (22.6 %)
Nausea	3 (10.0 %)	2 (6.5 %)
Other*	6 (20.0 %)	13 (41.9 %)

* Includes shivering (n=2), tiredness (n=2), giddiness (n=1), and restlessness (n=1) in oral ketamine group; tiredness (n=10), stomach discomfort (n=2), and restlessness (n=1) in IV ketamine group."

There are no prior head-to-head trials of oral versus iv ketamine in TRD. McIntyre and colleagues (McIntyre et al., 2020) meta-analysed and compared the pooled ES of trials involving iv, intranasal, and oral ketamine in TRD. Interestingly, they found that while the iv ketamine had a large ES on days 2–6 after administration, greater than the oral route, which had a small ES, the pattern reversed on days 7–20 and 21–28. At both these time points, oral route of administration improved to a medium ES, whereas the ES of iv administration had attenuated to a range considered small.

At least 3 double-blind RCTs have examined the antidepressant efficacy of repeated dosing with oral ketamine. While two of these were placebo-controlled trials on patients with MDD (Arabzadeh et al., 2018) and TRD (Domany et al., 2019), the third was an active-controlled (oral diclofenac) trial (Jafarinia et al., 2016) involving patients with chronic pain. All three used a fixed dose of ketamine ranging from 50 to 150 mg/day. In all these trials, the ketamine group separated from comparator for the outcome of depression scores; separation was evident as early as week 2 (Arabzadeh et al., 2018). Furthermore, the intervention was well tolerated.

We expected a superiority for iv ketamine over the oral formulation but found none. Better acceptability of oral ketamine may partly explain this finding. Administration of iv ketamine, at most centers, requires a prior anesthetic evaluation, temporary admission to an inpatient unit, and is an invasive procedure involving greater cost (Andrade, 2023b). On the other hand, oral ketamine is a simpler, convenient, inexpensive, and potentially more acceptable treatment (Andrade, 2022) that can be

delivered even at the primary health care level in the absence of specialist personnel. Future research may investigate effects of oral ketamine on different symptom domains in MDD, as shown with iv ketamine (Kwaśny et al., 2024). This may guide personalization of treatment with different ketamine formulations.

At the very least, our findings support consideration of a trial of oral ketamine in outpatient practice, particularly in situations where access to iv ketamine is limited by the availability of anesthetists or lack of time or willingness to get admitted or undergo invasive procedures. Given the lack of a big advantage of ECT over iv ketamine in MDD (Menon et al., 2023; Rhee et al., 2022) and, more specifically, TRD (Huang and Zheng, 2023), and given that the administration of ECT is limited by negative attitudes and cognitive adverse effects (Menon et al., 2024), there may be merit in head-to-head trials examining the efficacy of oral ketamine versus ECT in TRD. The major implication of our findings is that oral ketamine may be a safe, acceptable, and effective alternate to iv ketamine and ECT in treating TRD patients in the community, particularly in low resource settings. Further work must examine the efficacy of oral ketamine against ECT and iv ketamine in larger, randomized studies.

Our study findings must be interpreted carefully, given the many limitations. First, this was a small, pilot, superiority trial (iv > oral), inadequately powered to detect a medium or small ES. Next, the differences between groups at baseline indicate issues with the randomisation process. To address this, we adjusted for important unbalanced variables when comparing groups in the multivariable analysis. No structured instrument was used to assess the diagnosis, adverse effects, antisuicidal effects, psychotomimetic or dissociative symptoms following ketamine therapy. The concurrent use of benzodiazepines may have attenuated the antidepressant effects of ketamine (Andrashko et al., 2020). However, this was a pragmatic trial intended to simulate real-world practice where benzodiazepines are commonly co-prescribed with antidepressants. Nearly all participants were initiated on either escitalopram or venlafaxine; these reflect prescribing practices in our center and align with national antidepressant prescribing trends (Grover et al., 2013). However, this also means that generalization to those receiving other antidepressants as the initial treatment must be done cautiously. Finally, we did not attempt rater blinding for reasons explained earlier.

5. Conclusion

In this pilot, head-to-head comparison of alternate day dosing of oral and iv ketamine for TRD, oral ketamine was associated with lower all-cause treatment dropout. We found no significant between-group difference in depression ratings on days 14 and 30. Further, there were no differences in response rates, remission rates, illness severity, or illness improvement over the study period. The main message is that in community-based outpatient practice, oral ketamine may be a more feasible, acceptable, tolerable, and resource-efficient treatment modality compared to iv ketamine. Further well-powered studies are required to confirm these pilot findings.

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CRediT authorship contribution statement

Pattath Narayanan Suresh Kumar: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Conceptualization. **Chittaranjan Andrade:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Vikas Menon:** Writing – review & editing, Writing – original draft, Formal analysis.

Declaration of Competing Interest

The authors have no conflicts of interest to declare with regard to the contents of this manuscript.

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