

Switching to Intranasal Esketamine Maintains the Antidepressant Response to Intravenous Racemic Ketamine Administration: A Case Series of 10 Patients

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Introduction

Major depression is a pervasive neuropsychiatric illness associated with significant morbidity and mortality.^{1,2} Most pharmacological therapies that work on the monoamine system take 4 to 8 weeks to exert clinical benefit and still have high rates of nonresponse.³ Specifically, between 29% and 46% of depressed patients do not fully respond to an adequate dose and duration of traditional antidepressants.⁴ Nearly one third of depressed patients are characterized as having treatment-resistant depression (TRD).⁵ Ketamine, an anesthetic agent, has emerged as an off-label, rapid-acting antidepressant at subanesthetic dosages in patients with major depression who have not responded to multiple antidepressant medication trials. This report is a case series generated from 10 consecutive, severely ill, treatment-resistant adult outpatients with major depression who were administered both IV racemic ketamine and IN esketamine from PsychAtlanta Research Center, a private psychiatric clinic in Marietta, Georgia.⁶ These patients were initially treated with IV racemic ketamine to generate an acute antidepressant response and then transitioned to IN esketamine in efforts to maintain efficacy. Treatment outcomes were retrospectively reviewed to determine whether IN esketamine was safe and effective in maintaining the acute treatment benefits obtained from IV racemic ketamine treatment.

Methods

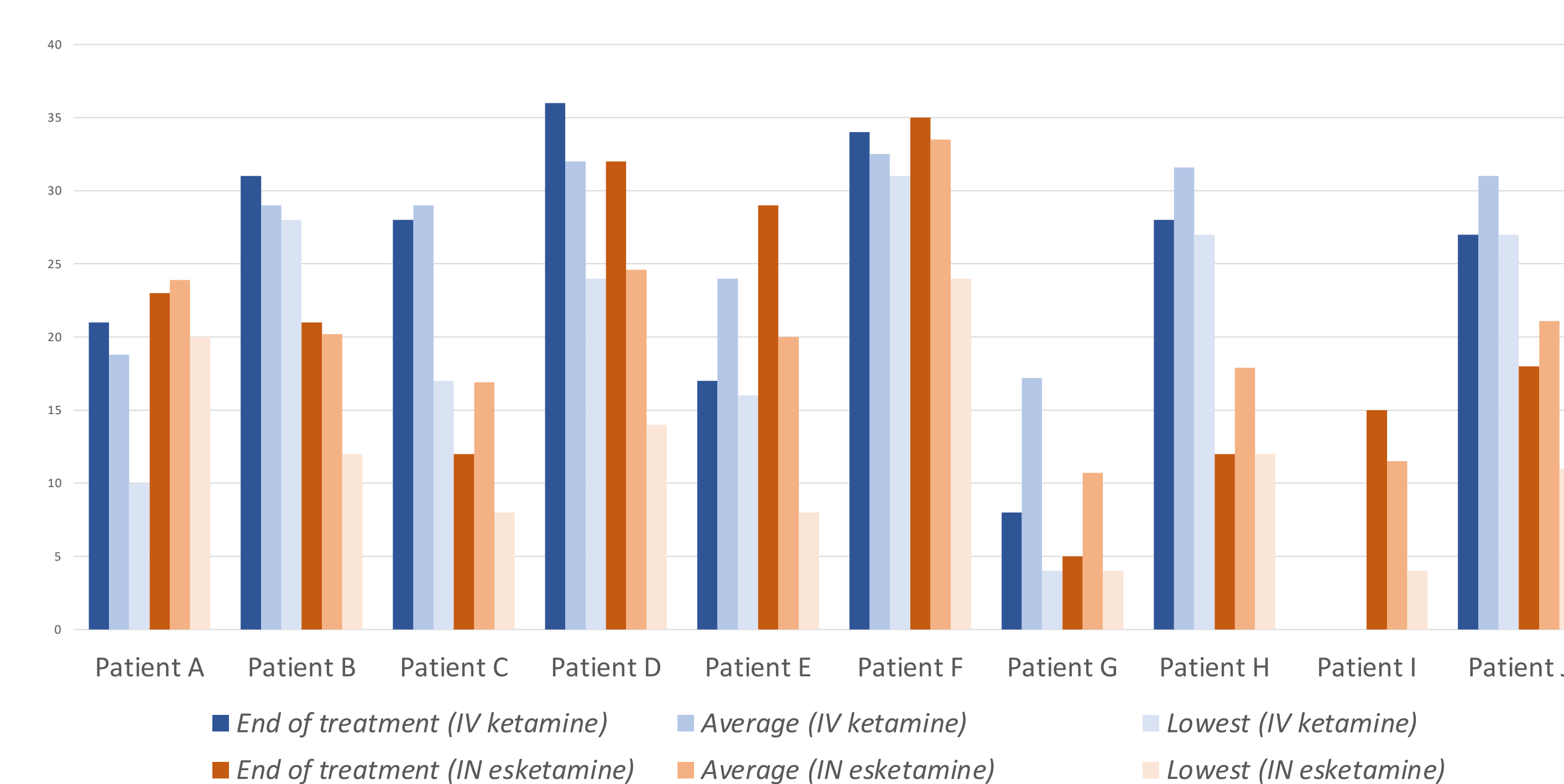
The 10 patients included in this case series received ketamine treatment between September 2018 and December 2020 and had a clinically meaningful response to at least 1 IV infusion of racemic ketamine. Patients were encouraged to undergo a series of 6 ketamine infusions over 14 to 21 days. Once response (>50% improvement) or partial response (25%–50% improvement) occurred as determined by a reduction of Montgomery-Asberg Depression Rating Scale (MADRS), Patient Health Questionnaire 9 (PHQ-9), and/or a Clinical Global Impressions–Improvement (CGI-I) rating of 3 or more and infusions were well tolerated, patients were offered weekly infusions for 4 weeks. Patients then had the option of receiving successive maintenance infusions with variable frequency depending on individual patient response and preference. Vital sign and clinical monitoring, dosing, and frequency of IV ketamine treatment were based on the published available data in this area. Treatment with IV ketamine was initiated at subanesthetic doses of 0.5 mg/kg with flexible dosing based on response and tolerability up to 1.0 mg/kg. The transition to esketamine once treatment response was reached from IV ketamine was primarily due to cost of IV ketamine not covered by health insurance and tolerability of infusions. Patients who transitioned to IN esketamine received an initial dose of 28 mg (n = 1) or 56 mg (n = 9) of IN esketamine, and all patients were eventually titrated up to a target dose of 84 mg for the remainder of treatments. All patients were monitored as required by the REMS protocol for IN esketamine. Before treatment at the beginning of each clinic visit, MADRS and PHQ-9 were completed. CGI ratings were obtained by the treating physician at each treatment.

Table 1. Mood Outcomes

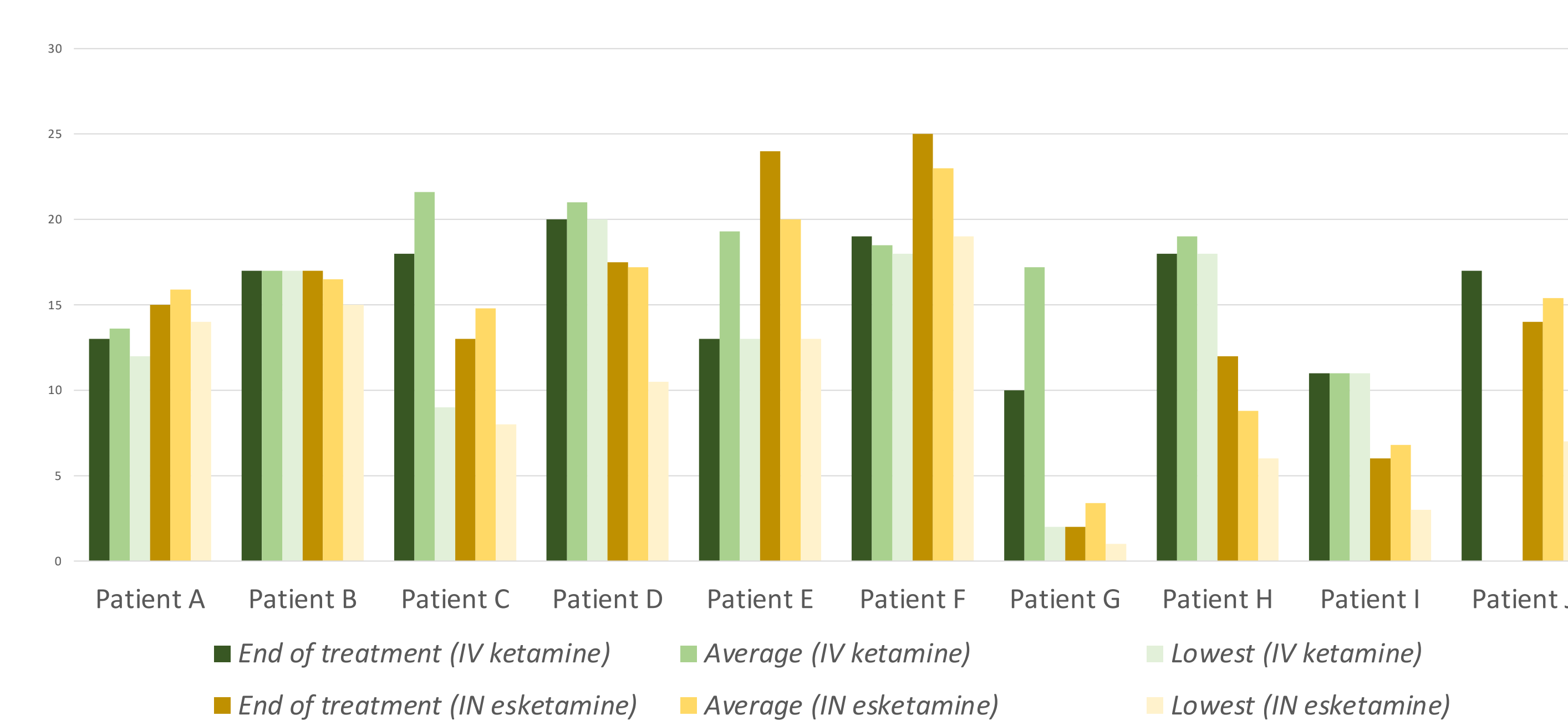
Patient	A	B	C	D	E	F	G	H	I	J
No. of IV ketamine treatments	8	4	14	6	7	3	30	6	1	11
Duration of IV ketamine treatment (weeks)	11	1	10	3	3	13	120	3	na	7
Reason for transition to IN esketamine	Cost	Tolerability	Cost	Cost	Cost	Cost	Cost	Cost	Cost	Cost
No. of IN esketamine treatments	7	13	16	22	28	6	8	10	37	14
Duration of IN esketamine treatment (weeks)	2.1	8	22.1	52.8	43.8	55	3.6	9	36.9	28.4
Continuing treatment (yes or no)	No	No	No	Yes	Yes	No	Yes	No	Yes	Yes
Reason for discontinuation	Time/improvement	Insurance coverage	Time/improvement	na	na	Enrolled in VNS study	na	Insurance coverage	na	na
Employment status (at initiation of IV ketamine treatment)	Unemployed due to depression	Unemployed due to depression	Unemployed due to depression	Homemaker	Unemployed due to depression	Homemaker	Homemaker	Employed	Unemployed due to depression	Unemployed due to depression
Employment status (at last observation point during IN esketamine treatment)	Employed	Employed	Employed	Homemaker	Employed	Started part time work	Homemaker	Employed	Actively looking for work	Actively looking for work
Suicidal ideations (at initiation of IV ketamine treatment)	None	None	Daily suicidal ideation	Daily suicidal ideation	None	Daily suicidal ideation	Daily suicidal ideation	None	Daily suicidal ideation	None
Suicidal ideations (at last observation point during IN esketamine treatment)	None	None	None	None	None	Infrequent suicidal ideation	None	None	None	None
Baseline scores (prior to IV ketamine treatment)										
MADRS	24	32	37	35	16	32	40	38	31	35
CGI	5	5	5	6	5	6	5	5	5	5
PHQ9	17	22	25	23	23	na	18	26	19	na
Scores at initial IN esketamine treatment										
MADRS	21	31	28	36	17	34	8	28	na	27
CGI	4	5	5	5	3	5	2	4	4	4
PHQ9	13	17	18	20	13	19	10	18	11	15
Endpoint scores (final IN esketamine observation point)										
MADRS	23	21	12	32	29	35	5	12	15	18
CGI	4	4	3	4	4	5	1	3	3	3
PHQ9	15	17	13	17.5	24	25	2	12	6	14

Results

Figure 1. MADRS scores



Supplemental Figure 1. PHQ9 scores



Supplemental Table 1. Clinical and Demographic Characteristics

Patient	A	B	C	D	E	F	G	H	I	J
Age	42	43	38	59	45	35	44	47	33	25
Gender	Male	Male	Male	Female	Female	Female	Female	Female	Female	Male
Primary psychiatric diagnosis	TRD	TRD	TRD	TRD	TRD	TRD	TRD	TRD	TRD	TRD
Secondary psychiatric diagnoses	GAD, ADHD	ADHD, GAD	ADHD, GAD	GAD, PTSD	GAD	GAD, PTSD	GAD, PTSD	GAD, Panic	ADHD, GAD, PTSD	GAD
Duration of illness (years)	21	20	20	5	21	25	34	19	14	7
Duration of current episode (years)	15	15	12	5	5	20	6	4	14	7
Concomitant psychiatric medications	Anticonvulsant, antipsychotic, CNS stimulant, mood stabilizer, SSRI	Anticonvulsant, atypical antipsychotic, CNS stimulant, SNRI	Antipsychotic, CNS stimulant, NDRI, SNRI	Benzodiazepine, CNS stimulant, sedative/hypnotic, SSRI	CNS stimulant, SNRI	Mood stabilizer, SSRI	Atypical antipsychotic, mood stabilizer, SNRI	Antipsychotic, atypical antipsychotic, SSRI	Atypical antipsychotic, benzodiazepine, CNS stimulant, NDRI, SSRI	Alpha 2 antagonist, anticonvulsant, atypical antipsychotic, CNS stimulant
ECT	na	Refused	Discontinued due to partial response	Refused	Refused	Discontinued due to side effects	Refused	Refused	Refused	na
TMS	Refused	Refused	na	Unable to afford	Failed	Unable to afford	Refused	Unable to afford	Unable to afford	na

Discussion

In patients with TRD who exhibited an acute response to IV ketamine for depressive symptoms, this case series indicates that switching to IN esketamine can maintain the response. This case series is the first to demonstrate this strategy in real-world patients who are currently taking other antidepressants and psychotropic medications. These results are also in keeping with clinical trials that used single and multiple doses of IV racemic ketamine in reducing depressive symptoms and multidose studies with IN esketamine.

Many patients already receiving IV racemic ketamine for depression may wish to transition to an on-label treatment either for safety and efficacy concerns or because of affordability if their insurance agrees to cover the medication and treatment. Patients in crisis may choose the more affordable IV racemic ketamine treatment initially until IN esketamine is approved by their insurance and they can find a REMS-certified provider and facility. Because isomers can have varying effects from their racemic compounds, clinicians and patients may be concerned over whether IN esketamine will effectively maintain their response without evidence to support this transition.

Our case series has demonstrated that 10 successive patients who have responded to IV ketamine for TRD successfully maintained their antidepressant response when switched to IN esketamine. The MADRS scores, PHQ-9, and CGI scores remained relatively consistent while patients transitioned to IN esketamine, and the majority improved throughout the course of maintenance therapy. IN esketamine was well tolerated, and few adverse effects followed patients' transitions. There was no objective measurement of functional change during treatment; however, it was noteworthy that patients who stopped working due to their depression were able to resume or pursue employment. Another patient who had achieved full remission from her depression was able to go into the workforce after prolonged absence, which she attributed to her improvement with treatment. Four of these patients had pervasive daily suicidal thoughts that abated and remained so with ongoing maintenance therapy. One patient had marked reduction in suicidal ideation throughout treatment. Disassociation, safety profiles, and tolerability were similar to those reported in well-controlled clinical trials with these agents.

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