Efficacy and Safety of Ketamine/Esketamine in Bipolar Depression in a Clinical Setting

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Abstract

Background: Bipolar disorder represents a significant source of morbidity and elevated mortality risk. Ketamine has emerged as a powerful antidepressant; however, there have been few trials of ketamine in bipolar depression and no trials with esketamine in bipolar depression, and few data exist from real-world settings. Here, we report outcomes from a cohort of patients with bipolar depression treated with ketamine/esketamine in a real-world setting.

Methods: Patients with treatment refractory bipolar depression were referred to Yale Psychiatric Hospital Interventional Services for treatment from October 2014 to November 2023. Appropriate patients were treated with intravenous (IV) ketamine (0.5 mg/kg over 40 minutes) or intranasal esketamine (56 or 84 mg). Diagnosis of bipolar depression was done by clinical evaluation by an attending psychiatrist, based on *DSM* criteria. Clinical outcomes were tabulated from medical records.

Results: Overall, 45 patients with bipolar depression were treated with IV ketamine or intranasal (IN) esketamine during the time period specified. Depression severity outcomes were available for 38 patients that completed an acute series, defined as treatment twice weekly for up to 4 weeks. Overall, 15/38 (39%) achieved clinical response (≥50% improvement on the Montgomery-Asberg Depression Rating Scale [MADRS]) and 5/38 (13.2%) achieved remission (≤10 on MADRS) following the acute series. Mean MADRS scores decreased from 31.1 to 19.2 (38.3% mean improvement). Safety data (hypomania/manic symptoms) were available for all 45 patients (518 patient-months of follow-up). No patients experienced any mania/hypomania during the acute series phase (when treatments are given twice weekly). However, 13/45 (28.9%) patients experienced symptoms consistent with a hypomanic or manic episode at some point following the acute phase while continuing to receive ketamine or esketamine during a maintenance phase. There were 16 manic/hypomanic events, indicating 1 event for every 2.7 patient-years. Only 1 event was severe and resulted in hospitalization.

Conclusion: In a small sample of patients with bipolar depression treated with ketamine/esketamine, no evidence of mania/hypomania was seen during the acute phase of treatment. Further research is needed to evaluate whether ketamine or esketamine confers heightened risk of affective switch during maintenance treatment.

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Bipolar disorder, characterized by fluctuating episodes of mania and depression, is a significant source of morbidity and elevated risk of mortality.[1,2] In the natural history of the illness, the ratio of manic to depressive episodes is predominated by the depressive phase, with patients experiencing depressive symptoms for 32%–50% of weeks and manic/hypomanic symptoms for 1%–9% of weeks.[3] Despite the predominance of depressive episodes in the natural course of this disorder, there are limited treatment options available for bipolar depression. While there are concerns about antidepressants leading to affective switch to hypomania/mania,[4] these agents are commonly used in clinical settings.[5] Notably, antidepressants have relatively poor efficacy in the treatment of bipolar depression. Compared to response to antidepressants in individuals with major depressive disorder (MDD), individuals with bipolar depression are 1.6 times less likely to experience response and 3.4 times more likely to experience loss of response during treatment.[6]

Ketamine is a potent *N*-methyl-D-aspartate receptor antagonist.[7] It was first approved for anesthesia in 1970,

Clinical Points

- Few data exist on the efficacy and safety of ketamine/esketamine as potential treatments for bipolar depression.
- In a small sample of patients with bipolar depression treated off-label with ketamine/esketamine, the response and remission rates were 39% and 13%, respectively.
- No cases of mania/hypomania emerged during the initial acute course phase (treatments given twice weekly for 2–4 weeks). Thirteen patients had manic/hypomanic symptoms during continuation/maintenance treatment with ketamine/esketamine; most events (15/16) were mild/moderate and resolved without hospitalization, during a follow-up period of 518 patient-months.

and an increasing amount of evidence since 2000 has shown that it has rapid-acting antidepressant properties at subanesthetic doses.[7,8] Multiple lines of evidence now support that 0.5 mg/kg of intravenous (IV) ketamine has robust and rapid-acting antidepressant effects in treatment-resistant MDD.[9,10]

There is limited evidence of use of ketamine to treat bipolar depression. Two small randomized controlled trials (N = 18 and N = 15) have implemented a single infusion protocol of ketamine in patients with treatment-resistant bipolar depression and found antidepressant effects from 40 minutes to 3 days postinfusion.[11,12] These trials required individuals to remain on either valproate or lithium as a mood stabilizer, while discontinuing any other psychiatric medications. A similarly sized (N = 16) pilot randomized controlled trial allowing for continuation of psychiatric medication examined differences in bipolar depression and suicidal ideation when treated with a single infusion of ketamine versus midazolam.[13] This study was not statistically significant, though this was likely due to very low statistical power.

A larger observational study (N = 53) administered 1 ketamine infusion to individuals concurrently on a mood stabilizer and found a 51% response and 29% remission rate at 7 days postinfusion.[14] Two open-label pilot studies (N = 16 and N = 38, respectively) allowing for continuation of medications and implementing a multiple infusion protocol yielded mixed results. Where one found a 75% response and a 44% remission at week 2 after 6 infusions,[15] the other found an initial decrease in depressive symptoms at 1 week, with depression severity surpassing baseline levels at week 3 despite ongoing ketamine therapy.[16]

Esketamine (the *S*(+) enantiomer of ketamine) was approved by the US Food and Drug Administration (FDA) in March 2019 in the form of a nasal spray under the name Spravato, for use in treatment-resistant depression (TRD).[17] No trials to date have examined esketamine augmentation in bipolar depression.

Yale Interventional Psychiatric Services has been offering ketamine therapy for patients with a major depressive episode since October 2014[18] and esketamine since its FDA approval (2019). In select cases and with careful consideration of risks and benefits, the clinic has also offered both treatments to patients with refractory bipolar depression. Here, we report efficacy and safety outcomes from a cohort of patients with bipolar depression treated with ketamine/esketamine in a real-world setting.

METHODS

Ketamine and esketamine treatments within the Interventional Psychiatry Service at Yale are provided in an interventional suite, which also provides infrastructure for electroconvulsive therapy. After consultation with an attending physician, provision of signed informed consent, and medical clearance (including basic laboratory work, urine toxicology, electrocardiogram, and history and physical examination), patients begin treatment. Using both ketamine and esketamine for the treatment of bipolar disorder is not approved by the FDA. This is emphasized in the written consent form that patients sign prior to treatment. Patients that receive esketamine are also enrolled in the Risk Evaluation and Mitigation Strategy (REMS) program, as required by the FDA. In this context, whether a patient receives esketamine or racemic ketamine is mostly a function of insurance coverage and/or patient preference.

Pretreatment Guidelines/Protocol

Prior to treatment, patients are instructed to fast for 2 hours. As described in our prior paper,[18] in general, we instruct patients to avoid benzodiazepines in the 8–12 hours prior to dosing, based on theoretical concerns and limited prior evidence suggesting an attenuation of antidepressant effects of ketamine when given concomitantly with benzodiazepines.[19] Most other medications are continued as normal on treatment days. As per the REMS rules, both ketamine and esketamine patients are required not to drive on days of treatment.

Upon the patient's arrival to the treatment suite, baseline blood pressure, heart rate, pulse oxygenation, respiratory rate, and temperature are measured. A peripheral IV catheter is inserted for those receiving IV ketamine.

IV ketamine is administered at 0.5 mg/kg over 40 minutes. For those with a body mass index ≥30, the dose was adjusted based on ideal body weight. Esketamine is an intranasal spray, with possible doses of 56 or 84 mg. Generally, the starting dose is 56 mg for treatment-resistant depression or 84 mg for major depression with suicidal ideation. Early in the history

of the clinic, patients receiving IV ketamine were treated with an infusion protocol of 2–4 treatments, given twice weekly. As multiple studies emerged showing the safety of repeated dosing,[20–22] we transitioned to a protocol where patients receive treatments twice weekly for up to 4 weeks, in line with the protocol of esketamine. For both ketamine and esketamine, following a 4-week initial course, it is recommended that those patients who achieve meaningful improvement continue with weekly treatments for an additional 4 weeks and then taper off to less frequent treatments needed to maintain response/remission (generally every 2–4 weeks).

During treatments of racemic ketamine and esketamine, vital signs (blood pressure, heart rate, and oxygen saturation) are monitored intermittently. Patients are observed following treatment initiation to ensure a return to pretreatment mental state. Dissociation is measured by a modified version of the Clinician-Administered Dissociative State Scale (CADSS),[23] based on our prior research,[24] immediately prior to discharge (to ensure discharge readiness criteria) or return to the inpatient unit.

Symptom severity is tracked with the Quick Inventory of Depressive Symptomatology-Self Report[25] scale, as well as the Montgomery-Asberg Depression Rating Scale (MADRS).[26] These assessments are administered at baseline and every fourth treatment thereafter.

During treatment, patients can receive lorazepam or ondansetron as needed for severe anxiety or nausea, respectively.

Regulatory/Analytic Approach

This analysis of existing clinical data was judged exempt of full approval by the Yale School of Medicine IRB (HIC #2000029188). The data were organized from the electronic health record and included any patient that received treatment since 2014. For this analysis, we only include patients with a diagnosis of bipolar depression. Diagnosis of bipolar depression was done by clinical evaluation by an attending psychiatrist, based on *DSM* criteria. Additional chart review was conducted to identify concomitant medications and medical and psychiatric comorbidities, as well as to verify the presence or absence of manic/hypomanic episode that occurred during treatment. For the purposes of this article, we defined mild hypomania to be an event that did not require any intervention; moderate hypomania to be requiring medication change; and severe mania to be requiring hospitalization or emergency department presentation. Keywords used to conduct this search included "mania," "hypoman*," "irritab*," "grandios*," "pressured speech," "YMRS," "racing thoughts," and "agitat*." Descriptive statistics were used to tabulate clinical and demographic data. A linear regression was used to describe symptom trajectory during the initial course of ketamine/esketamine, wherein treatments were provided twice weekly for up to 8 treatments. Given that patients received either esketamine or ketamine, we provided separate tabulations for these treatment groups. However, because of small numbers and the fact that treatment choice was not randomly assigned, formal statistical comparisons between treatment groups were not conducted.

RESULTS

Overall, 45 patients with bipolar disorder were treated with IV ketamine or IN esketamine at the Yale Interventional Psychiatric Service from 2014 to November 2023. The mean age was 37.5 years (SD = 14.5) with a range of 19–78 years (see Table 1). Most (93%) patients identified as white and 7% as black or African American. Most (29/45, 64%) were female, with 16 (36%) males. The median time during which patients received es/ketamine (acute plus maintenance phase) was 3.16 months. Notably, the median time during which patients received esketamine was 4.0 months, while the median time during which patients received ketamine was 1.9 months.

Most patients (40/45, 88.9%) were on an antipsychotic, lithium, or a mood stabilizer/anticonvulsant during the acute series (Supplementary Table 1). Lamotrigine was the most common mood stabilizer being taken during the acute series (19/45, 42%). About half (23/45, 51.1%) of the patients were taking an antidepressant during the acute series. Bupropion was the most common antidepressant being taken during the acute series (9/45, 20%). About half (23/45, 51.1%) of the patients had at least 1 psychiatric comorbid condition, and 24/45 (53.3%) had at least 1 medical comorbid condition (see Supplementary Table 2 for more details).

Efficacy

Outcome data on depression severity were available for 38 patients that completed an acute series. Figure 1 captures the decrease in MADRS and QIDS scores of these patients from first to fourth to final treatment in an acute series. Given that some of these patients had fewer than 8 treatments when our clinic was not yet administering 8 total treatments for the acute course, we used a last-observation-carried-forward approach to calculate response/remission outcomes. Overall, 15/38 (39%) achieved clinical response (≥50% improvement on MADRS) and 5/38 (13.2%) achieved remission (≤10 on MADRS) following the acute series. For the whole group (esketamine and ketamine patients), mean MADRS scores decreased from 31.1 to 19.2 (coefficient = –5.93 per 4 treatments, 95% CI, –7.97 to –3.89, $P < .001$), a mean reduction in symptom

Table 1.

Demographic and Clinical Characteristics (N = 45, Full Safety Sample)[a]

Variable	Esketamine	Ketamine	Total
Sample size (row %)	22 (48.9)	23 (51.1)	45 (100%)
Age, mean (SD), y	38.9 (14.7), range 21–64	36.1 (14.5), range 19–78	37.5 (14.5), range 19–78
Female, n (%)	17 (73.9)	12 (54.5)	29 (64)
Marital status, n (%)			
Single	10 (45.5)	13 (56.5)	23 (51.1)
Married	5 (22.7)	8 (34.8)	13 (28.9)
Divorced/separated	6 (27.3)	2 (8.7)	8 (17.8)
Other	1 (4.5)	0	1 (2.2)
Race, n (%)		**	**
White	20 (90.9)	20 (95.2)	40 (93.0)
African American	2 (9.1)	1 (4.8)	3 (7.0)
Other			NA
History of electroconvulsive therapy, n (%)	6 (27.3)	11 (52.4)**	17 (39.5)**
History of transcranial magnetic stimulation, n (%)	2 (9.1)	2 (8.7)	4 (8.9%)
History of hospitalization, n (%)	18 (81.8)	18 (90.0)***	36 (85.7)***
History of suicide attempt, n (%)	11 (50.0)	8 (38.1)**	19 (44.2)**
Inpatient status at first infusion, n (%)	6 (27.3)	3 (13.0)	9 (20.0)
Baseline QIDS-SR score, mean (SD)	17.5 (4.9)*	17.4 (5.6)*	17.5 (5.2)**
Baseline MADRS score, mean (SD)	32.2 (8.1)*	29.3 (7.9)***	30.8 (8.0)****

[a]This table shows data for full safety sample (N = 45); efficacy data were available for 38 patients. Missing data for 1*, 2**, 3***, and 4**** patients.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depression Symptomatology-Self Report.

severity of 38.3%. Mean QIDS scores decreased from 17.8 to 10.7 (coefficient = −3.59 per treatment, 95% CI, −4.90 to −2.28, $P < .001$), a mean reduction of 40.0% (see Table 2 for data on separate treatment groups).

Safety

Safety data (hypomania/manic symptoms) were available for 518 total patient-months of follow-up (43.1 patient-years) on all 45 patients. Notably, no patients experienced any mania or hypomania during the initial acute series phase (when treatments are given twice weekly); however, 13/45 (28.9%) patients experienced symptoms consistent with a hypomanic or manic episode (16 total episodes) at some point following the acute phase while continuing to receive ketamine or esketamine during a maintenance phase (Table 3), resulting in an observation of 1 event per every 2.7 patient-years. The mean time between the first treatment of ketamine/esketamine and the initial hypomanic/manic event was 297 days (SD 261), and the median time was 266 days (range 51–995 days). Of the manic/hypomanic events, 14 (87.5%) occurred when the patient was on a mood stabilizer, antipsychotic, or lithium.

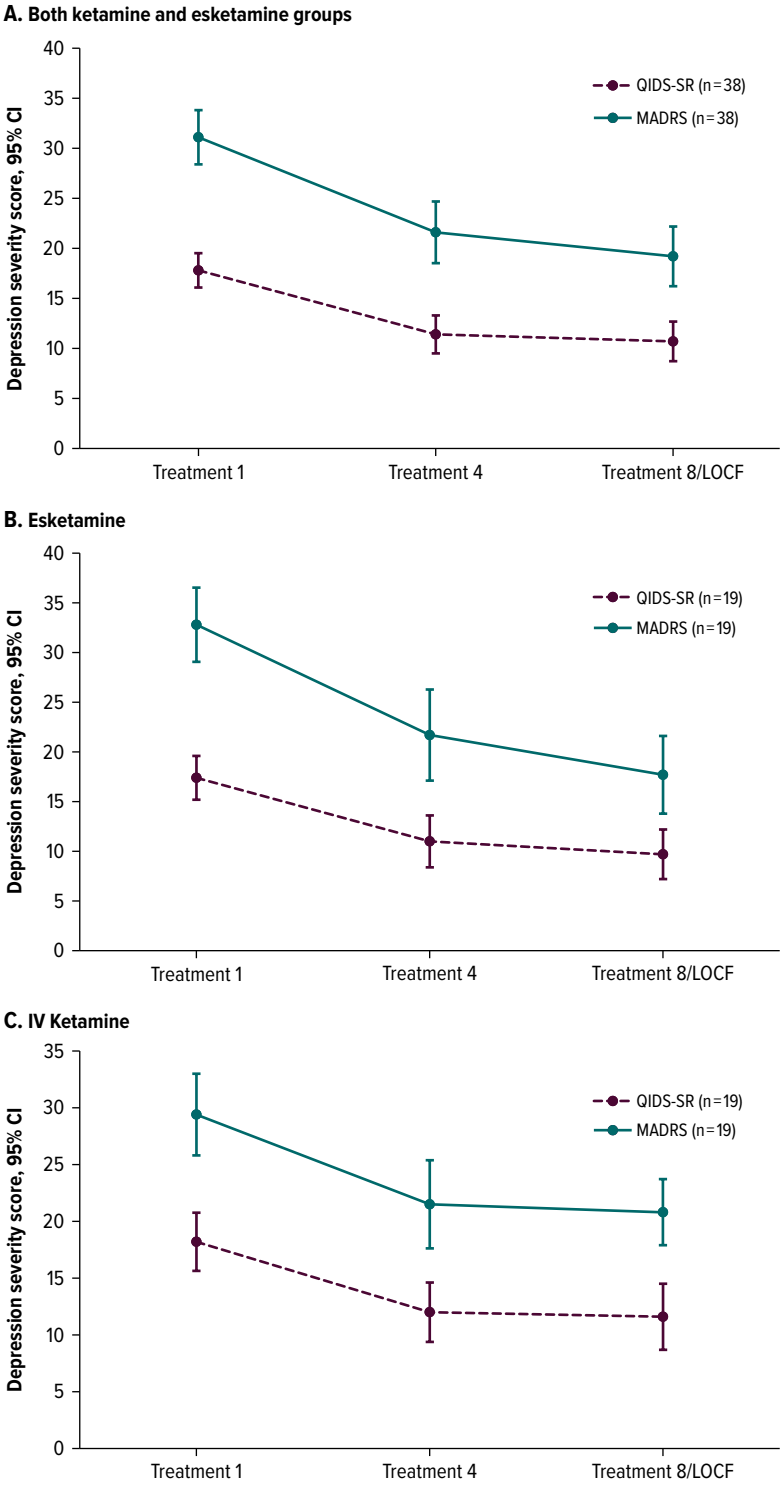
Half (8/16) of these episodes were mild hypomania that resolved without intervention. There were 7 episodes of moderate hypomania that were resolved with medication adjustment (without presentation to emergency department or hospitalization), most often in the form of an atypical antipsychotic.

Six of these 16 events occurred while individuals were receiving IV ketamine over a follow-up period of 270 total patient-months; 10/16 events occurred while individuals were receiving esketamine over a total follow-up period of 247 patient-months.

Two patients who experienced manic/hypomanic symptoms had an initial diagnosis of unipolar depression, such that this was their first hypomanic/manic episode (denoted by an asterisk in Table 3). Both of these patients were getting esketamine treatment, and both patients experienced mild hypomania that resolved without any intervention.

One such patient (patient 47) was a 34-year-old female who had been receiving esketamine treatment for about 5 months. She had reached a maintenance treatment schedule of 84 mg every 2 weeks. She paused treatment due to COVID-19 and for achieving a reasonable level of clinical response from her depressive symptoms. She returned about 7 months later for a repeat acute series. At the second treatment of this second acute series, she reported racing thoughts and feeling like she had a lot of energy, and she was sleeping approximately 5 hours since her last treatment 2 days prior. At the time of this event, she was taking a low/moderate dose of a mood stabilizer (lamotrigine 100 mg bid). Her acute series was

Figure 1.
Depression Severity During Acute Series



Abbreviations: LOCF = last-observation-carried-forward, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report Scale.

Table 2.
Changes in MADRS and QIDS-SR Scores per 4 Treatments[a,b]

	MADRS		QIDS-SR	
Treatment	Coefficient[c]	95% CI	Coefficient	95% CI
Esketamine (n = 19)	−7.55	−9.57 to −5.54	−4.12	−5.20 to −3.03
Ketamine (n = 19)	−4.32	−6.40 to −2.23	−3.25	−4.72 to −1.77
Combined groups (n = 38)	−5.93	−7.97 to −3.89	−3.59	−4.90 to −2.28

[a]Changes in MADRS and QIDS-SR scores are based on a general linear mixed-effects model.
[b]All coefficients were different than zero, $P < .001$.
[c]Coefficients represent change in depression severity per 4 treatments, based on an acute series (twice weekly) for up to 8 total treatments.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report Scale.

continued, and this episode seemed to resolve by her next treatment (5 days later).

Another such patient (patient 48) was a 21-year-old female who had been receiving esketamine treatment for 7 months. She had reached a maintenance treatment schedule of 84 mg every 2 weeks. She stopped due to lack of transportation. She returned 6 weeks later for a repeat mini-acute series (4 treatments in 2 weeks). She started this second acute series at a dosage of 84 mg but lowered to 56 mg at the second treatment of this acute series due to some anxiety during the first treatment. During the fourth treatment of this second acute series, she reported increased goal-directed activity, excessive energy, and a decreased need for sleep. Her Young Mania Rating Scale score at this treatment was 17 (indicating mild hypomania). At the time of this event, she was not on any mood stabilizers. As this was the last treatment of her mini-acute series, she returned a week later for the optimization phase and her symptoms had resolved.

One patient (with a preexisting diagnosis of bipolar disorder) experienced a severe episode of mania that led to psychiatric hospitalization. She experienced improvement during the acute series (42.9% improvement in depression severity by MADRS) and had sustained these gains such that she had been spread out to a maintenance schedule of treatment once every 3 weeks. A week after her 16th treatment (around 5 months after her first treatment), she experienced pressured speech, looseness of association, flight of ideas, disorganization, paranoia, and delusions, leading to hospitalization. Her medication regimen was changed from 20 mg of ziprasidone to 40 mg, and lorazepam 2 mg QHS was added. It was recommended that she stop IV ketamine treatments and switch to electroconvulsive therapy (ECT).

Among the 13 patients that experienced symptoms consistent with at least mild hypomania, most (10/13) are either still receiving ketamine or stopped treatment due to remission; 3 patients switched to ECT following an episode of mania/hypomania.

DISCUSSION

In a sample of 45 patients with treatment-resistant bipolar depression treated with ketamine/esketamine from October 2014 through November 2023, no evidence of mania/hypomania was seen during the acute phase of treatment. Of these patients who did experience a hypomanic/manic episode (13/45 patients, 16 total episodes), the average onset after first treatment was 297 days. The majority (15/16) of episodes were mild or moderate hypomania and did not require hospitalization or presentation to an emergency department. Of the 38 patients for whom efficacy data were available, 39% responded and 13.2% remitted following an acute series.

Efficacy

The response and remission rates of this report are lower than those from randomized clinical trials of ketamine in bipolar depression. The first trial of ketamine in bipolar depression (N = 18) reported a 44% response and 31% remission rate at 24 hours postinfusion.[11] A replication trial (N = 15) reported 43% response and 29% remission rates at 24 hours.[12] In contrast to these controlled trials, our sample was drawn from real-world data and has more heterogeneity and comorbidity. Further, our response and remission rates are reported after completion of an acute series (8 treatments and 28 days), where both aforementioned trials measured response and remission following a single-infusion protocol. Two other trials measuring response and remission after 1 infusion at 24 hours and 7 days, respectively, observed rates of 57% and 43%, and 51% and 29%.[13,14] Trials implementing multi-infusion treatment regimens observed mixed findings. One open-label pilot study measuring improvements at 14 days reported a 75% response and 43.8% remission rate in their subset of bipolar patients (N = 16).[15] A larger sample (N = 38) of patients with bipolar depression reported more modest outcomes, with a worsening over 3 weeks of follow-up (despite ongoing, thrice weekly ketamine therapy) such that mean posttreatment

Table 3.

Details of Hypomanic/Manic Episodes During Longer-Term Follow-Up of 518 Patient-Months

Patient ID	Treatment type	Hypomania severity	Days since 1st treatment	Psychotropics at time of event	Med change required	Hospitalization required
3	Esketamine	Mild hypomania	131	Buspirone 15 mg twice daily, clonazepam 0.5 mg twice daily, gabapentin 900 mg thrice daily, lamotrigine 600 mg daily	No	No
6	Esketamine	Mild hypomania	303	Bupropion 300 mg daily, lamotrigine 200 mg daily	No	No
22	Esketamine	Mild hypomania	51	Aripiprazole 7 mg daily, bupropion 300 mg daily	No	No
36	Esketamine	Mild hypomania	84	Lithium carbonate 600 mg daily, lithium carbonate 900 mg every night at bedtime, lorazepam 2 mg every night at bedtime as needed	No	No
47[a]	Esketamine	Mild hypomania	406	Clonazepam 0.5 mg daily, clonazepam 1 mg every night at bedtime as needed, duloxetine 90 mg daily, lamotrigine 100 mg twice daily	No	No
6	Esketamine	Moderate hypomania	525	Bupropion 300 mg daily, lamotrigine 200 mg daily, quetiapine 25 mg every night at bedtime	Yes	No
18	Esketamine	Moderate hypomania	267	Alprazolam 0.5 mg every night at bedtime as needed, fluvoxamine 25 mg daily	Yes	No
22	Esketamine	Moderate hypomania	574	Aripiprazole 10 mg daily, bupropion 300 mg daily, dextromethamphetamine-amphetamine 20 mg twice daily	Yes	No
40	Esketamine	Moderate hypomania	137	Bupropion 450 mg daily, hydroxyzine 25 mg thrice daily as needed, lamotrigine 200 mg daily, quetiapine 75 mg every night at bedtime every night at bedtime as needed	Yes	No
48[a]	Esketamine	Moderate hypomania	266	Fluoxetine 40 mg daily	Yes	No
14	Intravenous ketamine	Mild hypomania	995	Clonazepam 0.5 mg twice daily as needed, lamotrigine 150 mg daily, lithium carbonate 600 mg twice daily, methylphenidate hcl 10 mg four times a day	No	No
16	Intravenous ketamine	Mild hypomania	630	Gabapentin 900 mg daily, guanfacine ER 1 mg daily, lamotrigine 200 mg every night at bedtime, lurasidone 60 mg daily, lithium carbonate 600 mg twice daily, lorazepam 0.5 mg as needed, trazodone 25 mg as needed, zolpidem 10 mg every night at bedtime	No	No
16	Intravenous ketamine	Mild hypomania	770	Atomoxetine 80 mg daily, gabapentin 900 mg daily, guanfacine ER 1 mg daily, lamotrigine 200 mg every night at bedtime, lurasidone 60 mg daily, lithium carbonate 600 mg twice daily, lorazepam 0.5 mg as needed, trazodone 25 mg as needed, zolpidem 10 mg every night at bedtime	No	No
45	Intravenous ketamine	Moderate hypomania	126	Clonidine 0.2 mg every night at bedtime, gabapentin 300 mg every night at bedtime, lithium carbonate 1500 mg daily, lorazepam 2 mg every night at bedtime	Yes	No
46	Intravenous ketamine	Moderate hypomania	308	Buspirone 10 mg twice daily, clonazepam 1 mg twice daily as needed, divalproex 250 mg twice daily, duloxetine 60 mg daily	Yes	No
31	Intravenous ketamine	Severe (mania with psychotic features)	155	Gabapentin 300 mg every night at bedtime, hydroxyzine 25 mg thrice daily as needed, nortriptyline 25 mg every night at bedtime, ziprasidone 20 mg daily	Yes	Yes

[a]Patient did not have diagnosis of bipolar disorder when treatment began.

depression severity was greater than pretreatment depression severity.[16]

Safety

Our data represent a real-world clinical sample of 518 patient-months, in which 1 hypomanic/manic episode was observed per every 2.7 patient-years (the majority of which did not require hospitalization). Affective switches have not been reported in previous randomized clinical trials of ketamine in bipolar depression with 18[11] and 15[12] patients followed for 2 weeks. A larger observational study (N = 53) also did not observe any hypomanic switching in the 7 days following a single infusion.[14] Our sample provides the longest follow-up period (43 patient-years) to date of patients with bipolar depression treated with ketamine or esketamine. It is difficult to determine whether affective switching is at a rate above the average cycling of bipolar disorder as some affective switching/cycling is expected throughout the natural course of bipolar disorder.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is the largest prospective

evaluation of long-term outcomes for individuals with bipolar disorder.[27] An analysis of STEP-BD examining predictors for recurrence in bipolar disorder (N = 858) followed individuals in a symptomatic episode upon study entry but who recovered within the 2-year follow-up period (median follow-up of 94.5 weeks following study entry and 56.2 weeks following recovery).[28] During this follow-up period, 118 patients (13.8%) experienced recurrent hypomanic/manic symptoms. Comparisons between these rates of mania and those in our report are difficult because of different ways of evaluating mania/hypomania, different definitions of mania/hypomania, and different inclusion/exclusion criteria for the samples. Further research is needed to evaluate whether ketamine or esketamine confers heightened risk of affective switch during maintenance treatment.

There is considerable controversy with respect to whether or not a meaningful clinical difference exists between IV ketamine and intranasal esketamine in the treatment of unipolar depression. One meta-analysis has concluded that ketamine is more efficacious than esketamine[29]; however, this analysis only included 1 single-dose trial that directly compared the 2 treatments. Other reports are limited by the fact that they are reviews of existing data from clinical treatment and are not randomized.[30,31] The current report is the first, to our knowledge, to report clinical outcomes of both ketamine and esketamine conducted in the same setting as a therapy for bipolar depression. Given the very small sample sizes of each treatment group and the nonrandomized nature of our data, we did not conduct comparative analyses between treatment groups.

Several limitations require comment. Although our sample was drawn from a real-world setting, enhancing potential generalizability, its small size and relative lack of racial/ethnic diversity limit generalizability. Another limitation is that the evaluation of manic/hypomanic symptoms was retrospective in nature via manual search of the electronic medical record. It is possible that some events were not detected if they did not require medical intervention, though these events would arguably be less important. Finally, the schedule of ketamine/esketamine treatments was not tightly controlled nor was ancillary treatment (ie, mood stabilizers and antidepressants); thus, manic/hypomanic symptoms could have been related to other changes in treatment management.

In a small sample of patients with bipolar depression treated with ketamine/esketamine, no evidence of mania/hypomania was seen during the acute phase of treatment. Further research with systematic and prospective evaluation of manic/hypomanic symptoms is needed to evaluate whether ketamine or esketamine confers heightened risk in the treatment of bipolar depression.

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Supplementary Material

Article Title: Efficacy and Safety of Ketamine/Esketamine in Bipolar Depression in a Clinical Setting

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Table 1. Concomitant medications during acute course.

Psychotropic Medication Class	N (%)
Any Antidepressant (%)	23 (51.1)
SSRI	8 (17.8)
SNRI	7 (15.6)
TCA	3 (6.7)
MAOI	0
Other (Bupropion, mirtazapine)	11 (24.4)
Antipsychotic	25 (55.6)
Mood stabilizer/anticonvulsant	29 (64.4)
Valproic acid	5 (11.1)
Lamotrigine	19 (42.2)
Gabapentin	10 (22.2)
Other (Topiramate, Oxcarbezapine, carbamazepine)	5 (11.1)
Lithium	15 (33.3)
Sedative/hypnotic	22 (48.9)
Benzodiazepine	19 (42.2)
Zolpidem	3 (6.7)
Zaleplon	1 (2.2)
Stimulant	6 (13.3)
Any psychotropic	43 (95.6)
Other	27 (60.0)
Trazodone	11 (24.4)
Hydroxyzine	7 (15.6)
Buspirone	2 (4.4)
Other	11 (24.4)

Supplementary Table 2. Medical and Psychiatric Comorbidities

Body System	**N (%)**
Eyes, Ears, Nose & Throat	1 (2.2)
Respiratory	4 (8.9)
Cardiovascular	4 (8.9)
Gastrointestinal	4 (8.9)
Genitourinary	1 (2.2)
Musculoskeletal	5 (11.1)
Neurologic	9 (20.0)
Endocrine & Metabolic	9 (20.0)
Hematopoietic/Lymphatic	5 (11.1)
Dermatologic	2 (4.4)
Reproductive/Breast	5 (11.1)
Other	
Vitamin D Deficiency	3 (6.7)
Psychiatric Comorbidity	21 (46.7)
Attention Deficit Hyperactivity Disorder	3 (6.7)
Anxiety (GAD, social phobia)	10 (22.2)
Obsessive Compulsive Disorder	1 (2.2)
Alcohol Use Disorder (in remission)	3 (6.7)
Previous mood episode with psychotic features	3 (6.7)
Post Traumatic Stress Disorder	4 (8.9)
Personality Disorder	2 (4.4)
Eating Disorder	3 (6.7)