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ORIGINAL ARTICLE

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Treating bipolar depression with esketamine: Safety and effectiveness data from a naturalistic multicentric study on esketamine in bipolar versus unipolar treatment-resistant depression

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Abstract

Background: Bipolar depression accounts for most of the disease duration in type I and type II bipolar disorder (BD), with few treatment options, often poorly tolerated. Many individuals do not respond to first-line therapeutic options, resulting in treatment-resistant bipolar depression (B-TRD). Esketamine, the S-enantiomer of ketamine, has recently been approved for treatment-resistant depression (TRD), but no data are available on its use in B-TRD.

Objectives: To compare the efficacy of esketamine in two samples of unipolar and bipolar TRD, providing preliminary indications of its effectiveness in B-TRD. Secondary outcomes included the evaluation of the safety and tolerability of esketamine in B-TRD, focusing on the average risk of an affective switch.

Methods: Thirty-five B-TRD subjects treated with esketamine nasal spray were enrolled and compared with 35 TRD patients. Anamnestic data and psychometric assessments (Montgomery-Asberg Depression Rating Scale/MADRS, Hamilton-depression scale/HAM-D, Hamilton-anxiety scale/HAM-A) were collected at baseline (T0), at one month (T1), and three months (T2) follow up.

Results: A significant reduction in depressive symptoms was found at T1 and T2 compared to T0, with no significant differences in response or remission rates between subjects with B-TRD and TRD. Esketamine showed a greater anxiolytic action in subjects with B-TRD than in those with TRD. Improvement in depressive symptoms was not associated with treatment-emergent affective switch.

Conclusions: Our results supported the effectiveness and tolerability of esketamine in a real-world population of subjects with B-TRD. The low risk of manic switch in B-TRD patients confirmed the safety of this treatment.

KEYWORDS
bipolar depression, esketamine, glutamate, mood disorders, pharmacological treatment, rapid-acting antidepressant, real-world study, TRD, treatment-resistant depression

1 | INTRODUCTION

1.1 | Current treatments available for bipolar depression

Bipolar depression accounts for the majority of symptomatic periods in both type I and type II bipolar disorder (BD) and is associated with an elevated risk of suicide and high morbidity and mortality rates.[1] In this context, depressive symptoms and major depressive episodes dominate the clinical course of BD, although manic/hypomanic episodes are required for the diagnosis of BD.[2] However, while several treatments are available for the manic phase of BD, particularly antiepileptic agents, few are effective for bipolar depression.[2] Indeed, a large 26-week study found that the use of antidepressants was not effective in the treatment of patients with type I or II BD.[3] Moreover, currently available antidepressant medications are often poorly tolerated, associated with a delayed onset of action of several weeks, and, above all, capable of inducing an affective switch or rapid cycling in subjects with BD.[4] Furthermore, brain stimulation techniques represent relevant therapeutic tools in this condition, with electroconvulsive therapy (ECT), historically recognized as a rapid antidepressant agent, able to significantly improve severe forms of bipolar depression.[5] Nowadays, other brain stimulation techniques, for instance, repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS), both targeting the dorsolateral prefrontal cortex (DLPFC), are employed as possible augmentation strategies for bipolar depressed patients.[6,7] Indeed, these techniques act specifically on peculiar symptomatologic dominion, such as anhedonia.[8] Furthermore, some studies have reported their ability to increase cortical excitability, positively modulating mood[9] with an extremely low risk of an affective switch, as reported by a recent meta-analysis on this matter.[10] However, the role of rTMS and tDCS in treating bipolar depression may not have been explored enough, and further research in this area is still needed.

1.2 | Partial response and treatment resistance

Although several treatment options for bipolar depression are emerging, many patients achieve only partial remission, not adequately responding to treatment, with residual symptoms persisting despite the use of several medications, even if there is good compliance, and the treatment has been taken long enough with an adequate dosage.[1] Depression may be considered resistant to treatment when at least two trials with antidepressants from different pharmacological classes (adequate in dose, duration, and compliance) fail to produce significant clinical improvement.[11] Treatment-resistant depression (TRD) is a condition historically considered peculiar to Major Depressive Disorder (MDD). Nevertheless, treatment-resistant depression in BD (B-TRD) represents a common and rapidly growing phenomenon in everyday practice and can occur even with evidence-based first-line treatments.[12] Indeed, as no specific therapies have been approved for this condition, in clinical practice, the re-evaluation of the initial diagnosis and optimization of the initial regimen using switching to other antidepressants, augmentation strategies (e.g., combination therapy, lithium, and other mood stabilizers, thyroid hormones, atypical antipsychotics, etc.) or even monotherapy with second-generation antipsychotics have been considered within the psychopharmacologic options.[12] For instance, several lines of evidence indicate that, among unipolar subjects with TRD, approximately 50% are misdiagnosed with BD when evaluated one year after the first diagnosis of TRD.[13] In addition, BD in TRD appears to be twice as prevalent as in MDD.[12] Finally, non-response in bipolar depression occurs in 40% of patients after eight weeks of treatment with quetiapine.[14] Other first-line medications, such as lithium, lamotrigine, olanzapine, or the olanzapine-fluoxetine combination, may have similar or even less favorable outcomes.[12]

1.3 | New treatment options available for depressive symptoms

Historically, available treatments for depressive disorders were based on the monoaminergic hypothesis, which linked MDD to a significant depletion of the neurotransmitters dopamine, noradrenaline, and serotonin.[15] This hypothesis, over the years, has proven to be insufficient, given the failure of a significant proportion of patients to monoaminergic agents. Thus, by engaging other targets together with them, physicians can help patients with residual symptoms and TRD cases.[15] In this context, the interest of the scientific community in the role of glutamate in unipolar and bipolar depression has increased in recent years, with the aim of developing potential new therapeutic agents for these disorders.[16] The glutamatergic hypothesis for depressive disorders has been supported by the antidepressant efficacy of ketamine, an antagonist of the ionotropic N-methyl-D-aspartate (NMDA) receptor.[16] Ketamine has shown good efficacy in both bipolar[17,18] and unipolar[19] TRD, with response rates ranging from 50–70%.[20] Furthermore, in the various studies conducted,[18,21–23] no cases of manic switch after ketamine use in B-TRD have been shown, with preliminary data supporting effectiveness and safety among those patients.[23,24] However, its clinical use is severely limited by the numerous side effects and the intravenous administration.[25] Besides, the use of Ketamine and derivates in bipolar depression represents a promising field, with a recent international expert consensus pointing to the urgency of further investigation in this area.[25]

Esketamine, the S-enantiomer of ketamine, has recently emerged as a potential treatment for TRD. Its rapid antidepressant action and good efficacy (approximately 40%–50% in the maintenance phase, as demonstrated in several randomized controlled trials, RCTs)[26] have led to its approval by several medical agencies as a new therapeutic tool for unipolar TRD. Furthermore, esketamine-nasal spray (ESK-NS) exhibits a more favorable safety profile than ketamine, thus confirming its potential use in outpatient settings.[26] The excellent safety profile was confirmed by the

SUSTAIN-2 study, in which no manic symptoms were reported among adverse events[27]; furthermore, no other ESK-NS RCT reported manic symptoms or affective switches.[26] Currently, the approval of ESK-NS for B-TRD is limited by two main factors: firstly, the absence of studies focused on bipolar depression, apart from a single case report that indicated the potential effectiveness of ESK-NS in combination with mood stabilizer therapy in a patient with BD[28]; secondly, the considerable concerns raised regarding possible affective switches induced by ESK-NS, although studies in unipolar TRD have not reported this evidence. Indeed, the European Medicines Agency (EMA) ESK-NS Summary of Product Characteristics (SPCs) does not contraindicate ESK-NS use among subjects with BD, suggesting a careful evaluation between the risk and benefits of its application in this condition.

1.4 | Aim of the study

Considering the previous findings and the growing need for antidepressant agents for BD, the main objective of our research is to compare ESK-NS antidepressant action in two samples of unipolar and bipolar TRD, providing preliminary insights on its effectiveness among subjects with B-TRD. Secondarily, this study will address the safety and tolerability of ESK-NS in bipolar subjects, focusing on the average risk of an affective switch.

2 | MATERIALS AND METHODS

2.1 | Participants and study design

Data presented in this manuscript are part of the REAL-ESK study, an observational, retrospective, and multicentric study of subjects with TRD treated with ESK-NS.[29] Treatment was carried out as part of an early access program that supplied ESK-NS to the main mental health centers in Italy.

Thirty-five subjects affected by B-TRD and treated with ESK-NS were included in the B-TRD group. Subsequently, to create a control group composed of TRD subjects, B-TRD subjects were matched one to one for age to extract from the REAL-ESK study,[29] thus generating a TRD sample ($n = 35$). Furthermore, TRD and B-TRD groups were compared and did not statistically differ for sociodemographic data and baseline severity symptoms.

Subjects enrolled in the B-TRD group were carefully evaluated by qualified psychiatrists, investigating the previously documented history of manic or hypomanic episodes (all B-TRD had at least one hypomanic or manic episode in their clinical history, according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders /DSM-5).[30]

Several Italian mental health facilities were involved in this study, the coordination centers being both the 'G. d'Annunzio' University of Chieti and the University of Brescia. Other centers involved were: Fondazione Policlinico Universitario Agostino Gemelli IRCCS of Rome, 'A. Moro' University of Bari, University of Rome Tor Vergata, Sapienza University of Rome, 'Milano Statale' University, 'Milano Bicocca' University, 'Magna Graecia' University of Catanzaro, University of Pavia, University of Torino, University of Foggia, 'Villa Maria Pia' Clinic of Rome, 'Von Siebenthal' Clinic of Rome, ASL Frosinone, ASL Napoli 1, ASL Sud Tirol, ASP Messina, ASL Umbria 2, ASL Roma 5, Department of Mental Health and Addiction Services, ASST Grande Ospedale Metropolitano 'Niguarda' of Milan, Villa S. Giuseppe Hospital, Ascoli Piceno and the Mood Disorder Unit, IRCCS San Raffaele Scientific Institute of Milan, Italy.

The inclusion criteria for patients were the following: (a) age over 18 years; (b) experiencing a depressive episode; (c) being treated with a selective serotonin reuptake inhibitor (SSRI) or a serotonin noradrenaline reuptake inhibitor (SNRI); (d) for the B-TRD group, subjects were included following the operational definition of B-TRD proposed by Murphy and colleagues "Tried and failed at least two adequate trials (in dosage achieved and duration) from 2 classes of antidepressants and two classes of mood stabilizers (including atypical antipsychotic agents)"[31]; (e) for the TRD group, TRD was defined as the absence of an adequate clinical response after two conventional antidepressant treatments.[11]

Patients with comorbid organic pathologies that represent an absolute contraindication to ESK-NS according to the EMA (i.e., untreated arterial hypertension or previous cerebrovascular disorders) were excluded from the study.

2.2 | Study procedures and measurements

Anamnestic data were retrospectively collected and included information on sociodemographic factors, the history of the disease, the treatment history for the current depressive episode, antidepressant trials experienced during the current episode, augmentation strategies (combined use of mood stabilizers / antipsychotic medications or not) and other therapeutic tools applied to treat TRD. Data were also collected in cases of premature study withdrawal or the occurrence of clinically relevant events, such as admission to or discharge from inpatient care, symptom relapse, or remission of major depressive episodes. Anamnestic data were collected from patients' medical records at baseline (T0), while psychometric assessments were collected at T0, after one month (T1), and three months (T2) from the start of treatment. The Montgomery–Asberg Depression Rating Scale (MADRS) and the Hamilton Depression Scale (HAM-D-21 items) were used by clinicians to characterize depressive symptoms. The Hamilton Anxiety Rating Scale (HAM-A-21 items) was used to assess the severity of anxiety symptoms.

Patients were defined as *responders* with an overall 50% reduction in the MADRS or HAM-D-21 score compared to the baseline assessment,[32] while *remission* was defined as a MADRS score <10 or a HAM-D-21 score <7.[33]

A qualified psychiatrist carefully evaluated adverse events related to ESK-NS administration and reported in the patient medical records.

The study was approved by the local ethics committee of the Università degli Studi di Brescia (Protocol Number: NP5331). All patient data were treated confidentially and anonymously, and the study was conducted following the Declaration of Helsinki.[34]

2.3 | Statistical analyses

Statistical analyses were performed using SPSS 20.0 software (SPSS Inc.) and JASP for Mac (JASP version: 0.16.4; JASP Team, 2022). All tests were two-tailed, with a statistical significance level set at $p < 0.05$. Continuous variables are expressed as mean ± standard deviation (SD), while categorical variables are reported as average numbers and percentages. The Kolmogorov–Smirnov normality test was used to verify the normality distribution of our data in both groups (B-TRD and TRD). Subsequently, parametric tests were used since the data distribution was found to be normal. The student *t*-test was conducted to assess changes in continuous variables, whereas the Pearson χ^2 test was performed for categorical variables.

Furthermore, a general linear model approach was used to analyze the "between factor" × "within factor" interaction effect (between factor: TRD vs. B-TRD; within factor, treatment time: baseline/pre-treatment/T0 vs. at the end of the 1st month of treatment/T1 vs. at the end of the 3rd month of treatment/T2) on MADRS and HAM-A total scores. Two separate models of repeated measures analysis of variance (rm-ANOVA) were employed with MADRS and HAM-A as dependent variables to investigate the interaction effect. The sphericity of the covariance matrix was tested with Mauchly's test of sphericity; in the case of violation of the sphericity assumption, Greenhouse–Geisser epsilon (ε) adjustment was used. For strict control of the type I error, post-hoc pairwise comparison tests were performed using Scheffé's method for multiple comparisons. Measures of effect size were partial eta2 (η_p^2) in rm-ANOVA and Cohen's *d* or Hedges' *g* in pairwise comparisons, respectively, if groups had the same sample size or different sample sizes.

3 | RESULTS

3.1 | Baseline characteristics and differences between the two groups

The final set of patients consisted of 70 subjects, 35 from the TRD group (mean age: 52.57 ± 12.77) and 35 from the B-TRD group (mean age: 52.57 ± 12.77) B-TRD group consisted of 17 subjects with a BD type 1 and 18 Subjects with a BD type 2.

As mentioned above, B-TRD and TRD groups did not differ statistically in age, gender, occupancy level, years of education, or duration of the disease. Subjects with B-TRD subjects showed higher lifetime suicide attempt rates than subjects with TRD, consistent with previous evidence indicating higher suicidality in those affected by BD.[35] Concerning pharmacotherapy, both groups had a history of different antidepressant trials experienced in their lifetime (TRD group: 3.00 ± 0.98; B-TRD group: 3.28 ± 0.85); TRD group had significantly higher levels of SNRI as actual therapy versus the B-TRD group (42.8% vs. 20%; $\chi^2 = 4.619$ df = 1 $p = 0.032$), while more B-TRD than TRD subjects were treated with mood stabilizers (100% vs. 57.14%; $\chi^2 = 14.885$ df = 1 $p < 0.0001$). No significant differences in the psychometric baseline scores were found between the TRD and B-TRD groups. However, the B-TRD group showed higher baseline suicidality levels than the TRD group (MADRS ITEM-10: 2.75 ± 1.54 vs. 1.73 ± 1.48, $t = -2.766$, df = 65 $p = 0.007$). All sociodemographic and clinical data are extensively reported in Table 1, while current pharmacotherapies and ESK-NS dosages are reported in Table 2. Furthermore, ESK-NS dosing patterns followed EMA SPCs indications in both groups, with two doses administered per week in the induction phase (first month) and one dose per week in the following two months.

TABLE 1 Sociodemographic and clinical data of the sample

	B-TRD group $n = 35$	TRD group $n = 35$
BDI/BDII	17/18	
Sex ratio (M/F)	17/18	15/20
Age (years)	52.77 ± 10.9	52.77 ± 10.9
Education (years)	13.4 ± 4.82	13.88 ± 3.59
Depression episodes duration (months)	15.94 ± 11.81	13.68 ± 11.12
Age at onset of depression (years)	33.31 ± 11.65	34.35 ± 14.2
Number of previous depression episodes (*n*)	3.97 ± 2.79	3.79 ± 3.05
Duration of depression (years)	19.45 ± 9.84	17.12 ± 10.33
Number of adequate antidepressant trials (*n*)	3.28 ± 0.85	3.00 ± 0.98
Baseline clinical measures		
MADRS	37.07 ± 8.11	34 ± 9.54
HAM-D	27.79 ± 8	23.4 ± 10.8
HAM-A	29.88 ± 9.39	30.9 ± 11.81
Suicidality (MADRS item 10)	2.75 ± 1.54	1.73 ± 1.48
Status		
Single	9	13
Married	22	18
Divorced /widowed	4	4
Occupation		
Unemployed	15	15
Employed	20	20
Previous suicidal attempts		
No	23	31
Yes	11	4

Abbreviations: BDI, bipolar disorder, Type I; BDII, bipolar disorder, Type II; B-TRD, bipolar treatment-resistant depression; F, female; HAM-A, Hamilton-Anxiety scale; HAM-D, Hamilton Depression scale; M, male; MADRS, Montgomery-Asberg Depression Rating Scale; TRD, treatment-resistant depression.

3.2 | Drop-out rates in both groups

Of the total number of 35 subjects in the TRD group, seven patients had to discontinue ESK-NS treatment during the follow-up period: at T1, three subjects dropped out, two of them due to inefficacy and one patient due to serious side effects (severe sedation and dissociative symptoms), while at T2 3 subjects discontinued for inefficacy and one due to an affective switch. In contrast, four of the 35 subjects in the B-TRD group dropped out, one after two weeks for psychomotor agitation after treatment with ESK-NS and the appearance of manic symptoms after ESK-NS administration, one at T1 and one at T2 for inefficacy, and, finally, one subject before T2 for medical problems unrelated to the administration of ESK-NS.

In total, 33 subjects in the B-TRD group and 32 subjects in the TRD group were included in the data analysis at T1, while 31 subjects with B-TRD and 28 with TRD were included at T2.

TABLE 2 Current pharmacotherapies

Current pharmacotherapies (*n*)	B-TRD group *n* = 35	TRD group *n* = 35
Serotonin-norepinephrine reuptake inhibitors	7 (20%)	15 (42.8%)
Selective serotonin reuptake inhibitors	16 (45.71%)	16 (45.71%)
Other antidepressants	18 (51.43%)	19 (54.28%)
Mood stabilizers	35 (100%)	20 (57.14%)
Lithium	16 (45.87%)	6 (17.14%)
Lamotrigine	3 (8.57%)	6 (17.14%)
Valproate	3 (8.57%)	1 (2.85%)
Oxcarbazepine	1 (2.85%)	0
Gabapentin	2 (5.70%)	2 (5.70%)
Pregabalin	1 (2.85%)	4 (11.42%)
Lithium-Valproate combination	2 (5.70%)	1 (2.85%)
Lithium-Lamotrigine combination	5 (14.28%)	0
Valproate-Lamotrigine combination	1 (2.85%)	0
Lithium-Carbamazepine-Valproate combination	1 2.85%)	0
Antipsychotics	24 (68.57%)	16 (45.7%)
Quetiapine XR	10 (28.57%)	5 (14.28%)
Lurasidone	5 (14.28%)	0
Olanzapine	5 (14.28%)	2 (5.70%)
Aripiprazole	3 (8.57%)	5 (5.70%)
Brexpiprazole	0	2 (5.70%)
Paliperidone	1 (2.85%)	0
Asenapine	0	1 (2.85%)
Clozapine	0	1 (2.85%)
Esketamine dosage: 28 mg	5 (14.3%)	2 (5.7%)
Esketamine dosage: 56 mg	20 (57.1%)	12 (34.3%)
Esketamine dosage: 84 mg	10 (28.6%)	21 (60%)

Abbreviations: B-TRD, bipolar treatment-resistant depression; TRD, treatment-resistant depression.

3.3 | ESK-NS effectiveness in TRD and B-TRD groups

In the rm-ANOVA, the multivariate test showed a not significant effect of the "TRD vs. B-TRD"×"T0 vs. T1 vs. T2" interaction factor (Wilks' Lambda = 0.938, $F_{2,52} = 1.728$, $p = 0.188$, $\eta_p^2 = 0.062$) on MADRS. Mauchly's test of sphericity was significant: $W = 0.839$, $\chi_2^2 = 9.102$, $p = 0.011$. The univariate rm-ANOVAs for MADRS confirmed this not significant interaction factor effect ($F_{1.723,91.334} = 2.445$, $\varepsilon = 0.862$, $p = 0.100$, $\eta_p^2 = 0.044$). As shown in Table 3 and Figure 1, MADRS values: (a) did not differ between TRD and B-TRD at T0 ($p = 0.940$, $g = 0.347$); (b) showed a significant decrease separately in TRD and B-TRD at T1 (TRD: T0 vs. T1, $p < 0.0001$, $d = 1.155$; B-TRD: T0 vs. T1, $p < 0.0001$, $d = 1.305$) and T2 (TRD: T0 vs. T2, $p < 0.0001$, $d = 1.949$; T1 vs. T2, $p = 0.017$, $d = 0.633$; B-TRD: T0 vs. T2, $p < 0.0001$, $d = 2.642$; T1 vs. T2, $p < 0.0001$, $d = 1.033$); (c) did not differ between TRD and B-TRD at T1 ($p = 0.984$, $g = 0.195$) and T2 ($p = 0.986$, $g = 0.217$).

In general, in the B-TRD group, nine subjects (25.7%) responded in T1 and 24 subjects (68.57%) in T2, while six patients (17.14%) were remitters in T1 and 17 (48.57%) in T2. Furthermore, in the TRD group, nine subjects (25.7%) responded in T1, 20 subjects (57.14%) in T2, while 3 (8.57%) were remitters in T1 and 10 (28.57%) were remitters in T2.

3.4 | ESK-NS anxiolytic effectiveness

Regarding the anxiolytic effect of ESK-NS, the rm-ANOVA showed a not significant effect of the "TRD *vs.* B-TRD"×"T0 *vs.* T1 *vs.* T2" interaction factor (Wilks' Lambda = 0.953, $F_{2,42} = 1.027$, $p = 0.367$,

TABLE 3 Mean (standard deviation) values of MADRS and HAM-A in TRD and B-TRD groups at baseline / pre-treatment (T0), at the end of the 1st month of treatment (T1), and the end of the 3rd month of treatment (T2)

	MADRS			HAM-A		
	T0	T1	T2	T0	T1	T2
TRD	34 (9.54)	21.79 (11.51)	14.97 (9.99)	30.9 (11.81)	21.4 (10.09)	16.2 (11.17)
B-TRD	37.07 (8.11)	24.04 (11.58)	12.78 (10.17)	29.88 (9.39)	19.8 (12.19)	11.2 (10.12)

Abbreviations: B-TRD, bipolar treatment-resistant depression; TRD, treatment-resistant depression.

η_p^2 = 0.047) on HAM-A. Mauchly's test of sphericity was not significant: W = 0.869, χ_2^2 = 5.902, p = 0.052. The univariate rm-ANOVAs for HAM-A confirmed this not significant interaction factor effect ($F_{2,86}$ = 1.112, p = 0.334, η_p^2 = 0.025). As shown in Table 3 and Figure 2, HAM-A values: (a) did not differ between TRD and B-TRD at T0 (p = 1.000, g = 0.097); (b) showed a significant decrease separately in TRD and B-TRD at T1 (TRD: T0 vs. T1, p = 0.003, d = 0.865; B-TRD: T0 vs. T1, p = 0.0002, d = 0.927) and T2, particularly in B-TRD group (TRD: T0 vs. T2, p < 0.0001, d = 1.279; T1 vs. T2, p = 0.330, d = 0.489; B-TRD: T0 vs. T2, p < 0.0001, d = 1.914; T1 vs. T2, p = 0.003, d = 0.768); (c) did not differ between TRD and B-TRD at T1 (p = 0.999, g = 0.142), and at T2 (p = 0.794, g = 0.472). In addition, remitters from anxiety symptoms (HAM-A <7)[36] in T2 were significantly higher in the B-TRD group than in the TRD one (35% vs. 2.86%; χ^2 = 9.443 df = 1 p = 0.002). Differences in the anxiolytic effects of ESK-NS among the two groups are represented in Table 3 and Figure 2.

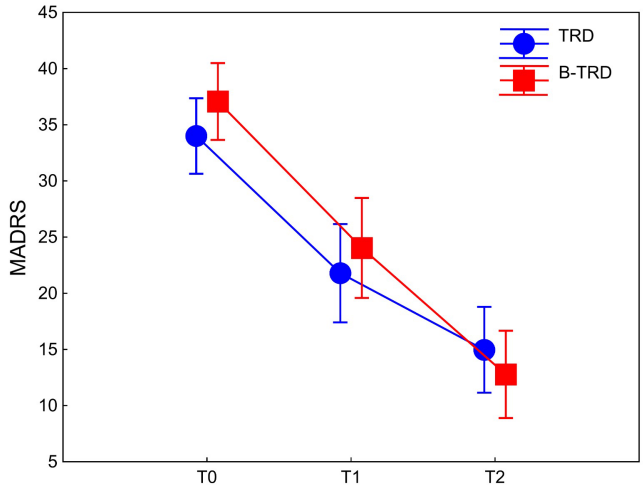

FIGURE 1 Means (blue circles and red squares, respectively, TRD and B-TRD) and 95% confidence intervals (vertical bars) of the MADRS total score at baseline/pre-treatment (T0), at the end of the first month of treatment (T1), and the end of the third month of treatment (T2). B-TRD, bipolar treatment-resistant depression; MADRS, Montgomery-Asberg Depression Rating Scale; TRD, treatment-resistant depression.

3.5 | Safety of ESK-NS in BD

TRD and B-TRD groups did not differ in terms of the percentage of subjects reporting side effects (57.14% of B-TRD vs. 77.15% of TRD; χ^2 = 3.014 df = 1 p = 0.075).

The type and percentage of side effects in both groups are extensively reported in Table 4.

Only one case of the affective switch was reported in the B-TRD group, and there was no significant difference with the TRD group in terms of affective switch risk or maniacal symptom development (2.86% in B-TRD vs. 2.86% in TRD; χ^2 = 0.0001 df = 1 p = 1.000). Furthermore, there was only one case of reported psychomotor agitation in the B-TRD group after ESK-NS treatment, which was forced to discontinue after two weeks of treatment.

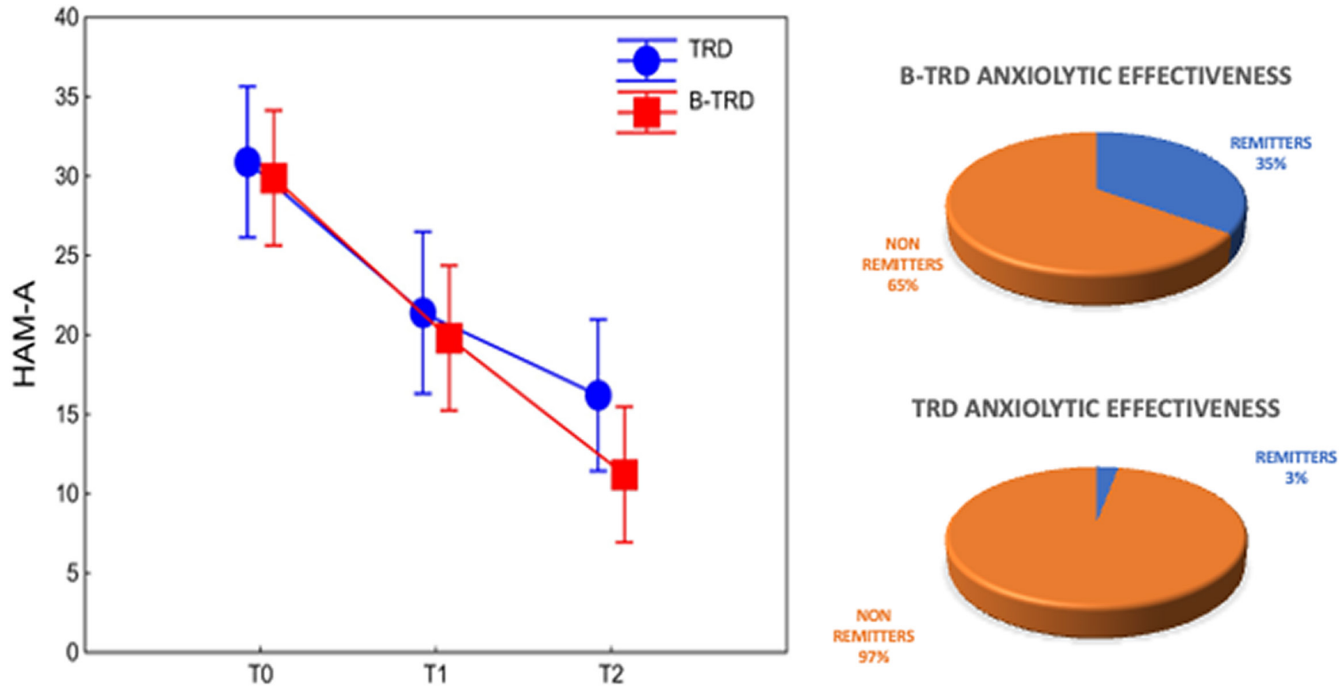

FIGURE 2 Means (blue circles and red squares, respectively, TRD and B-TRD) and 95% confidence intervals (vertical bars) of the HAM-A total score at baseline/pre-treatment (T0), at the end of the first month of treatment (T1), and the end of the third month of treatment (T2). Percentage of remitters from anxious symptoms at T2 in B-TRD and TRD groups. B-TRD, bipolar treatment-resistant depression; TRD, treatment-resistant depression.

TABLE 4 Reported adverse events in the TRD and B-TRD groups

	B-TRD group		TRD group	
Adverse event	***n***	**%**	***n***	**%**
Increased blood pressure	0	0	3	8.57
Dissociation	11	31.4	14	40
Sedation	10	28.57	16	45.71
Manic symptoms	1	2.85	1	2.85
Anxiety	1	2.85	0	0
Dizziness, headache	1	2.85	1	2.85
Subjects with any side effect	20	57.14	27	77.14

Abbreviations: B-TRD, bipolar treatment-resistant depression; TRD, treatment-resistant depression.

4 | DISCUSSION

4.1 | ESK-NS effectiveness in both TRD and B-TRD groups

To our knowledge, this is the first multicentric, real-world study to evaluate the effectiveness, safety, and tolerability of ESK-NS in a B-TRD sample. ESK-NS showed good effectiveness in terms of response and remission rates in both TRD and B-TRD groups. Our findings are consistent with previous studies on both intravenous ketamine[24] and esketamine[37]; the latter, in particular, highlighted the effectiveness of intravenous esketamine in anhedonic features in both MDD and BD patients,[37] thus suggesting a potential comparable effectiveness in the two conditions. Besides, our results confirmed the rapid antidepressant action of ESK-NS (MADRS mean score reduction from T0 to T1, B-TRD group:−13.03, TRD group:−12.21; see Table 3), in line with results of previous RCT studies[26] indicating a rapid antidepressant action of ESK-NS, with a reduction in MADRS scores within the first day of treatment and significant response rate in the first month, when the clinical response to ESK-NS is expected.[32] Furthermore, we found a dramatic increase in ESK-NS effectiveness from T1 to T2 (responders increased in the B-TRD group from 25.7% to 68.57%, in the TRD group from 25.7% to 57.14%), suggesting the presence of later responders. Practically, although the induction phase is often considered a critical point for evaluating ESK-NS effectiveness, our study indicates that continuing ESK-NS beyond this phase could result in a later successful response. Secondarily, ESK-NS appeared to be effective in subjects affected by bipolar depression. Indeed, although our primary endpoint was set to demonstrate similar effectiveness of ESK-NS in B-TRD patients compared to TRD, our results went far beyond this goal. Although without statistical significance, the number of B-TRD remitters was higher than TRD subjects at T2 (48.57% and 28.57%, respectively). Interestingly, the general linear model showed a higher effect size in B-TRD subjects compared to TRD ones: in particular, comparing MADRS variations between T1 and T2, the effect size was medium in the TRD group (Cohen's $d = 0.633$) and large in the B-TRD group (Cohen's $d = 1.033$) thus suggesting a more powerful action of ESK-NS among B-TRD subjects. These findings are particularly intriguing since the absence of previous studies on ESK-NS effectiveness in BD should be the starting point for further studies on this matter.

4.2 | ESK-NS as a glutamatergic option for the treatment of bipolar depression

Two lines of evidence support the critical role of glutamatergic dysfunction in BD. Firstly, different neuroimaging studies indicate the impairment of glutamate neurotransmission in the different stages of BD,[38] specifically involving the DLPFC and the anterior cingulate cortex (ACC), two areas of the brain with a critical role in mood disorders.[39] Secondly, ketamine, another glutamatergic agent, showed a good clinical efficacy and tolerability as antidepressant in BD.[18,21–23] Furthermore, as already mentioned, one of the main factors contributing to treatment resistance in depression is represented by BD, which is often misdiagnosed as MDD.[13] Considering these last pieces of evidence and our main findings, we can speculate that glutamatergic dysfunction may be a 'trait' feature of BD. Thus, ESK-NS and other glutamatergic agents may be primary options for treating mood swings in BD. Nevertheless, to validate our hypothesis, these findings should be confirmed by RCT with larger samples of patients and placebo control.

4.3 | Safety and tolerability of ESK-NS

Regarding the safety and tolerability of ESK-NS in subjects with BD, the B-TRD and TRD groups did not differ statistically in terms of the percentage of reported side effects. However, BD subjects showed lower levels of reported side effects (57.14% of B-TRD subjects vs. 77.15% of TRD subjects). Furthermore, ESK-NS-related adverse effects were reduced after the treatment without leading to any significant sequelae. Moreover, no differences were found in affective switches between the TRD and B-TRD groups, with only one case in the B-TRD group of discontinuation related to manic symptoms and psychomotor agitation. In addition to the very low risk of manic switch, the safety of ESK-NS in bipolar patients is

confirmed by the absence of the increase in suicidality or need for acute hospitalization.

Overall, there was no increased risk of treatment-emergent hypomania or psychosis or dissociation in subjects with B-TRD compared to those with TRD, in line with previous evidence reported in studies on ketamine in BD,[23,24] a finding which is very relevant, considering the previous concerns about possible risks of ESK-NS use in BD. However, B-TRD subjects in our study were all treated with mood stabilizers when starting ESK-NS. While the use of mood stabilizers is expected in real-world settings, it could be an essential study bias for assessing the overall risk of ESK-NS-induced affective switch.

4.4 | The anxiolytic effect of ESK-NS

Along with the antidepressant effectiveness, the anxiolytic effect of ESK-NS recorded here deserves to be considered. As well described in the literature, anxiety symptoms or comorbidity with a general anxiety disorder (GAD) are common in both unipolar and bipolar depression.[40] The close relationship between MDD and GAD is due, on the one hand, to common symptoms and, on the other hand, to common genetic risk factors.[40] Anxiety symptoms also have high comorbidity in BD: epidemiological studies have shown that patients with BD and co-occurring anxiety symptoms or anxiety disorders are susceptible to higher rates of depressive episodes and increased suicidal behavior.[41] Furthermore, in the phenomenology of MDD, anxiety symptoms have often been included as part of so-called 'agitated depression,' which has been questioned about being a 'mixed-features' depression and part of the bipolar spectrum rather than the unipolar depression itself.[42] In this regard, the more significant decrease of anxious symptoms in the B-TRD group compared to TRD appear noteworthy, with a stronger effect size in the former (T1 vs. T2, $p = 0.003$, Cohen's $d = 0.768$) and a lower in the latter (T1 vs. T2, $p = 0.330$, Cohen's $d = 0.489$), in addition to a considerable higher remission rate at T2 in B-TRD subjects (35% against 3%, respectively). As detected by the HAM-A psychometric scale, anxiety symptoms could be related, from a phenomenological point of view, to different psychopathological domains. Several items of the HAM-A, in fact, refer to a wide range of symptoms (e.g., general anxiety, insomnia, pronounced psychomotricity, emotional tension, etc.) that could, on the one hand, be interpreted as characteristics of an anxiety disorder, but, on the other, could be symptoms of a manic/hypomanic affective state. Speculating on this, the anxious symptoms in both TRD and B-TRD groups could express different clinical conditions, which explained the differences in anxiolytic effectiveness.

On the one hand, anxious symptoms in the TRD group could be interpreted as genuine symptoms of GAD in the context of a depressive episode. On the other hand, the more severe anxious symptoms in the B-TRD group could be the clinical manifestation of 'agitated depression' or 'depression with mixed-features,' in which anxiety symptoms refer to symptoms such as psychic akathisia, hyperactivity, or tension that are part of a hypomanic/manic clinical presentation. Furthermore, mixed features have been described as frequent in the context of both (BD) type I and type II, affecting approximately 30% of the subjects during a depressive episode.[43] Therefore, the anxiolytic effect of ESK-NS in subjects with BD could be consistent with its specific action on the 'mixed-features' domain of bipolar depression. In line with our findings, a recent study revealed the efficacy of intravenous ketamine in the rapid treatment of mixed features in subjects with TRD, hypothesizing glutamatergic agents as possible therapeutic alternatives in these states.[44] Consistently, the role of ketamine/esketamine in treating mixed features/anxiety symptoms could be related to brain dysfunction in glutamate/gamma-aminobutyric acid (GABA) homeostasis, which has been often implicated in the pathophysiology of both mood and anxiety disorders.[45] Furthermore, several preclinical and clinical studies indicate the ability of glutamatergic drugs to 'stabilize' this homeostatic system,[46,47] probably acting on brain networks that are often impaired in subjects with BD, independently of the affective episode.[48,49] Clearly, this possible explanation is speculative and should be considered as a starting point for further studies on this topic, perhaps using specific scales to assess mixed features in the context of TRD.

4.5 | Limitations and strengths of the study

As previously mentioned, further studies are needed to substantiate the efficacy of ESK-NS in B-TRD, as our work has some limitations. Firstly, our sample size is small; RCT studies on this topic with a larger number of participants are needed. Secondly, the use of psychometric scales to assess manic switches in patients with BD (such as the Young Mania Rating Scale / YMRS) would be worth considering. In our study, a careful clinical assessment was performed by expert psychiatrists who, however, could have benefited from the use of structured scales to assess manic symptoms. Thirdly, the short follow-up period (3 months) represents a limitation of the study, as a long-term evaluation could provide more insight into sustained affective stabilization induced by ESK-NS.

However, our work has important strengths. The most relevant is the innovativeness of the study: before now, as far as we know, ESK-NS had not been considered a treatment for resistant depression in bipolar patients. Another aspect of being underlined is the multicentricity of our study, conducted in several hospitals in various Italian regions. Finally, the non-randomized nature of the study leads to a narrowing of the gap with clinical reality, representing a real-word situation.

5 | CONCLUSIONS

Our findings support the effectiveness and tolerability of ESK-NS in a real-world population of subjects affected by B-TRD. The prolonged effectiveness to threemonths and the possible action

on mixed features in patients with BD represent intriguing results. Furthermore, the low risk of manic switch in patients with B-TRD, superimposed on the TRD group, confirms the safety of this treatment. Undoubtedly, ESK-NS represents a challenge for the future of resistant depression treatment in BD.

AUTHOR CONTRIBUTIONS

All persons who meet the authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. MdG, AVi, GMar, GMai, ABer, SB, and MP conceptualized the hypothesis and the design of the study. GMar, SB, BDO, AS, ABell, MC, MdN, RDC, GDL, PDF, SDF, GN, GRo, AValc, DN, SDM, RB, VM, AC, IA, MO, and SBel were responsible for the patient recruitment and the collection of clinical data. The REAL-ESK Study Group contributed to the collection of clinical data. GdA, GMar, GDL, CCav, SC, and MP performed the statistical analysis, carried out data interpretation, and wrote the first draft of the manuscript. MdG, AVi, GDL, ABer, BDO, and RSMcI revised the manuscript and provided substantial comments. All authors contributed and approved the final manuscript.

CONFLICT OF INTEREST

Giovanni Martinotti has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier, and Recordati. Alessandro Bertolino and Ileana Andriola were both speakers at the Janssen-sponsored conference. Bernardo Dell'Osso has received lecture honoraria from Angelini, Lundbeck, Janssen, Pfizer, Neuraxpharm, Arcapharma, and Livanova. Massimo di Giannantonio has been a consultant and/or a speaker and/or has received research grants from Angelini, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier, and Recordati. Giorgio Di Lorenzo has been a speaker and/or a consultant for Angelini, FB-Health, Janssen-Cilag, Livanova, Lundbeck, Neuraxpharm, Otsuka, and Recordati. Antonio Vita received grant/research support and speaker/consultant fees from Angelini, Boehringer Ingelheim, Innovapharma, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Recordati, Roche, Rovi Pharma, and Takeda. Giuseppe Maina has been a consultant/speaker for Angelini, Boheringer, Fb Health, Innovapharma, Italfarmaco, Janssen, Otsuka, Lundbeck, and Sanofi. Raffaella Zanardi has been a consultant/speaker for Baldacci and Italfarmaco. Dr. Roger McIntyre has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie, Atai Life Sciences. Dr. Roger McIntyre is the CEO of Braxia Scientific Corp. The remaining authors declare that the research was conducted without any commercial or financial relationship that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, GdA, upon reasonable request

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REFERENCES

1. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *Lancet (London, England)*. 2020;396(10265):1841-1856. doi:10.1016/S0140-6736(20)31544-0
2. McIntyre RS, Calabrese JR. Bipolar depression: the clinical characteristics and unmet needs of a complex disorder. *Curr Med Res Opin*. 2019;35(11):1993-2005. doi:10.1080/03007995.2019.1636017
3. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007;356(17):1711-1722. doi:10.1056/NEJMoa064135
4. Levenberg K, Cordner ZA. Bipolar depression: a review of treatment options. *Gen Psychiatry*. 2022;35(4):e100760. doi:10.1136/gpsych-2022-100760
5. Bahji A, Hawken ER, Sepehry AA, Cabrera CA, Vazquez G. ECT beyond unipolar major depression: systematic review and meta-analysis of electroconvulsive therapy in bipolar depression. *Acta Psychiatr Scand*. 2019;139(3):214-226. doi:10.1111/acps.12994
6. Gama-Chonlon L, Scanlan JM, Allen RM. Could bipolar depressed patients respond better to rTMS than unipolar depressed patients? A naturalistic, observational study. *Psychiatry Res*. 2022;312:114545. doi:10.1016/j.psychres.2022.114545
7. D'Urso G, Toscano E, Barone A, et al. Transcranial direct current stimulation for bipolar depression: systematic reviews of clinical evidence and biological underpinnings. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2023;121:110672. doi:10.1016/j.pnpbp.2022.110672
8. Spano MC, Lorusso M, Pettorruso M, et al. Anhedonia across borders: Transdiagnostic relevance of reward dysfunction for non-invasive brain stimulation endophenotypes. *CNS Neurosci Ther*. 2019;25(11):1229-1236. doi:10.1111/cns.13230
9. Martinotti G, Montemitro C, Pettorruso M, et al. Augmenting pharmacotherapy with neuromodulation techniques for the treatment of bipolar disorder: a focus on the effects of mood stabilizers on cortical excitability. *Expert Opin Pharmacother*. 2019;20(13):1575-1588. doi:10.1080/14656566.2019.1622092
10. Miuli A, Sepede G, Stigliano G, et al. Hypomanic/manic switch after transcranial magnetic stimulation in mood disorders: a systematic review and meta-analysis. *World J Psychiatry*. 2021;11(8):477-490. doi:10.5498/wjp.v11.i8.477
11. Conway CR, George MS, Sackeim HA. Toward an evidence-based, operational definition of treatment-resistant depression: when enough is enough. *JAMA Psychiat*. 2017;74(1):9-10. doi:10.1001/jamapsychiatry.2016.2586
12. Fornaro M, Carvalho AF, Fusco A, et al. The concept and management of acute episodes of treatment-resistant bipolar disorder: a systematic review and exploratory meta-analysis of randomized controlled trials. *J Affect Disord*. 2020;276(May):970-983. doi:10.1016/j.jad.2020.07.109
13. Sharma V, Khan M, Smith A. A closer look at treatment resistant depression: is it due to a bipolar diathesis? *J Affect Disord*. 2005;84(2–3):251-257. doi:10.1016/j.jad.2004.01.015
14. Sienaert P, Lambrichts L, Dols A, De Fruyt J. Evidence-based treatment strategies for treatment-resistant bipolar depression: a

systematic review. *Bipolar Disord*. 2013;15(1):61-69. doi:10.1111/bdi.12026
15. Blier P. Neurobiology of depression and mechanism of action of depression treatments. *J Clin Psychiatry*. 2016;77(3):e319. doi:10.4088/JCP.13097tx3c
16. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology*. 2012;62(1):63-77. doi:10.1016/j.neuropharm.2011.07.036
17. Zhuo C, Ji F, Tian H, et al. Transient effects of multi-infusion ketamine augmentation on treatment-resistant depressive symptoms in patients with treatment-resistant bipolar depression—an open-label three-week pilot study. *Brain Behav*. 2020;10(8):e01674. doi:10.1002/brb3.1674
18. Wilkowska A, Włodarczyk A, Gałuszko-Węgielnik M, Wiglusz MS, Cubała WJ. Intravenous ketamine infusions in treatment-resistant bipolar depression: an open-label naturalistic observational study. *Neuropsychiatr Dis Treat*. 2021;17:2637-2646. doi:10.2147/NDT.S325000
19. Memon RI, Naveed S, Faquih AE, et al. Effectiveness and safety of ketamine for unipolar depression: a systematic review. *Psychiatry Q*. 2020;91(4):1147-1192. doi:10.1007/s11126-020-09830-6
20. Shin C, Kim YK. Ketamine in major depressive disorder: mechanisms and future perspectives. *Psychiatry Investig*. 2020;17(3):181-192. doi:10.30773/pi.2019.0236
21. Zheng W, Zhou YL, Liu WJ, et al. A preliminary study of adjunctive ketamine for treatment-resistant bipolar depression. *J Affect Disord*. 2020;275:38-43. doi:10.1016/j.jad.2020.06.020
22. Zheng W, Zhou YL, Liu WJ, et al. Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression. *J Psychiatr Res*. 2018;106:61-68. doi:10.1016/j.jpsychires.2018.09.013
23. McIntyre RS, Rodrigues NB, Lipsitz O, et al. The effectiveness of intravenous ketamine in adults with treatment-resistant major depressive disorder and bipolar disorder presenting with prominent anxiety: results from the Canadian Rapid Treatment Center of Excellence. *J Psychopharmacol*. 2021;35(2):128-136. doi:10.1177/0269881120954048
24. McIntyre RS, Rodrigues NB, Lee Y, et al. The effectiveness of repeated intravenous ketamine on depressive symptoms, suicidal ideation and functional disability in adults with major depressive disorder and bipolar disorder: results from the Canadian Rapid Treatment Center of Excellence. *J Affect Disord*. 2020;274:903-910. doi:10.1016/j.jad.2020.05.088
25. McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: An international expert opinion on the available evidence and implementation. *Am J Psychiatry*. 2021;178(5):383-399. doi:10.1176/appi.ajp.2020.20081251
26. An D, Wei C, Wang J, Wu A. Intranasal ketamine for depression in adults: a systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials. *Front Psychol*. 2021;12:648691. doi:10.3389/fpsyg.2021.648691
27. Wajs E, Aluisio L, Holder R, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). *J Clin Psychiatry*. 2020;81(3). doi:10.4088/JCP.19m12891
28. Skriptshak C, Reich A. Intranasal esketamine use in bipolar disorder: a case report. *Ment Heal Clin*. 2021;11(4):259-262. doi:10.9740/mhc.2021.07.259
29. Martinotti G, Vita A, Fagiolini A, et al. Real-world experience of esketamine use to manage treatment-resistant depression: a multicentric study on safety and effectiveness (REAL-ESK study). *J Affect Disord*. 2022;319:646-654. doi:10.1016/j.jad.2022.09.043
30. Vahia VN. Diagnostic and statistical manual of mental disorders 5: a quick glance. *Indian J Psychiatry*. 2013;55(3):220-223. doi:10.4103/0019-5545.117131
31. Murphy BL, Babb SM, Ravichandran C, Cohen BM. Oral SAMe in persistent treatment-refractory bipolar depression: a double-blind, randomized clinical trial. *J Clin Psychopharmacol*. 2014;34(3):413-416. doi:10.1097/JCP.0000000000000064
32. Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. *Am J Psychiatry*. 2019;176(6):428-438. doi:10.1176/appi.ajp.2019.19020172
33. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry*. 1991;48(9):851-855. doi:10.1001/archpsyc.1991.01810330075011
34. WMA. Dichiarazione di Helsinki della World Medical Association. *Evidence*. 2013;5(10):1-5.
35. Miller JN, Black DW. Bipolar disorder and suicide: a review. *Curr Psychiatry Rep*. 2020;22(2):6. doi:10.1007/s11920-020-1130-0
36. Sheehan DV. Attaining remission in generalized anxiety disorder: venlafaxine extended release comparative data. *J Clin Psychiatry*. 2001;62(Suppl 1):26-31.
37. Delfino RS, Del-Porto JA, Surjan J, et al. Comparative effectiveness of esketamine in the treatment of anhedonia in bipolar and unipolar depression. *J Affect Disord*. 2021;278:515-518. doi:10.1016/j.jad.2020.09.056
38. Shen J, Tomar JS. Elevated brain glutamate levels in bipolar disorder and pyruvate carboxylase-mediated anaplerosis. *Front Psych*. 2021;12:640977. doi:10.3389/fpsyt.2021.640977
39. Bae JN, MacFall JR, Krishnan KRR, Payne ME, Steffens DC, Taylor WD. Dorsolateral prefrontal cortex and anterior cingulate cortex white matter alterations in late-life depression. *Biol Psychiatry*. 2006;60(12):1356-1363. doi:10.1016/j.biopsych.2006.03.052
40. Goldberg D, Fawcett J. The importance of anxiety in both major depression and bipolar disorder. *Depress Anxiety*. 2012;29(6):471-478. doi:10.1002/da.21939
41. Bauer MS, Altshuler L, Evans DR, Beresford T, Williford WO, Hauger R. Prevalence and distinct correlates of anxiety, substance, and combined comorbidity in a multi-site public sector sample with bipolar disorder. *J Affect Disord*. 2005;85(3):301-315. doi:10.1016/j.jad.2004.11.009
42. Sampogna G, Del Vecchio V, Giallonardo V, Luciano M, Fiorillo A. Diagnosis, clinical features, and implications of agitated depression. *Psychiatr Clin North Am*. 2020;43(1):47-57. doi:10.1016/j.psc.2019.10.011
43. Serra F, Gordon-Smith K, Perry A, et al. Agitated depression in bipolar disorder. *Bipolar Disord*. 2019;21(6):547-555. doi:10.1111/bdi.12778
44. McIntyre RS, Lipsitz O, Rodrigues NB, et al. The effectiveness of ketamine on anxiety, irritability, and agitation: implications for treating mixed features in adults with major depressive or bipolar disorder. *Bipolar Disord*. 2020;22:831-840. doi:10.1111/bdi.12941
45. Nasir M, Trujillo D, Levine J, Dwyer JB, Rupp ZW, Bloch MH. Glutamate systems in DSM-5 anxiety disorders: their role and a review of glutamate and GABA psychopharmacology. *Front Psych*. 2020;11:548505. doi:10.3389/fpsyt.2020.548505
46. Kang MJY, Hawken E, Vazquez GH. The mechanisms behind rapid antidepressant effects of ketamine: a systematic review with a focus on molecular neuroplasticity. *Front Psych*. 2022;13:860882. doi:10.3389/fpsyt.2022.860882
47. Weckmann K, Deery MJ, Howard JA, et al. Ketamine's effects on the glutamatergic and GABAergic systems: a proteomics and

metabolomics study in mice. *Mol Neuropsychiatry*. 2019;5(1):42-51. doi:10.1159/000493425

48. Vellante F, Ferri F, Baroni G, et al. Euthymic bipolar disorder patients and EEG microstates: a neural signature of their abnormal self experience? *J Affect Disord*. 2020;272(March):326-334. doi:10.1016/j.jad.2020.03.175
49. Bi B, Che D, Bai Y. Neural network of bipolar disorder: toward integration of neuroimaging and neurocircuit-based treatment strategies. *Transl Psychiatry*. 2022;12(1):143. doi:10.1038/s41398-022-01917-x

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