RESEARCH ARTICLE

The effect of esketamine in patients with treatment-resistant depression with and without comorbid anxiety symptoms or disorder

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Abstract

Background: Comorbid anxiety is generally associated with poorer response to antidepressant treatment. This post hoc analysis explored the efficacy of esketamine plus an antidepressant in patients with treatment-resistant depression (TRD) with or without comorbid anxiety.

Methods: TRANSFORM-2, a double-blind, flexible-dose, 4-week study (NCT02418585), randomized adults with TRD to placebo or esketamine nasal spray, each with a newly-initiated oral antidepressant. Comorbid anxiety was defined as clinically noteworthy anxiety symptoms (7-item Generalized Anxiety Disorder scale [GAD-7] score ≥10) at screening and baseline or comorbid anxiety disorder diagnosis at screening. Treatment effect based on change in Montgomery–Åsberg Depression Rating Scale (MADRS) total score, and response and remission were examined by presence/absence of comorbid anxiety using analysis of covariance and logistic regression models.

Results: Approximately 72% (162/223) of patients had baseline comorbid anxiety. Esketamine-treated patients with and without anxiety demonstrated significant reductions in MADRS (mean [SD] change from baseline at day 28: −21.0 [12.51] and −22.7 [11.98], respectively). Higher rates of response and remission, and a significantly greater decrease in MADRS score at day 28 were observed compared to antidepressant/placebo, regardless of comorbid anxiety (with anxiety: difference in LS means [95% CI] −4.2 [−8.1, −0.3]; without anxiety: −7.5 [−13.7, −1.3]). There was no significant interaction of treatment and comorbid anxiety (*p* = .371). Notably, in the antidepressant/placebo group improvement was similar in those with and without comorbid anxiety.

Conclusion: Post hoc data support efficacy of esketamine plus an oral antidepressant in patients with TRD, regardless of comorbid anxiety.

KEYWORDS
anxiety, anxious depression, comorbid anxiety, esketamine, treatment-resistant depression

1 | INTRODUCTION

Major depressive disorder (MDD) commonly presents with co-morbid anxiety (53%–67%, depending on definition used) (Fava et al., 2008; Lamers et al., 2011). Patients with depression and comorbid anxiety have greater depressive illness severity and chronicity, more suicide attempts and completions (Fava et al., 2006, 2008; Fawcett, 2001; McIntyre et al., 2016; Zimmerman et al., 2014), and poorer response and remission rates to anti-depressant medications than those without comorbid anxiety (Andreescu et al., 2007; Fava et al., 2008; Souery et al., 2007; Wiethoff et al., 2010). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, response and remission rates were significantly lower and took longer to achieve in pa-tients with, than in those without, comorbid anxiety symptoms (Fava et al., 2008). Taken together, new treatment options are clearly needed for patients with MDD and comorbid anxiety.

Depression with comorbid anxiety symptoms or "anxious de-pression" has been defined in many different ways in the literature, leading to varying clinical profiles. Some investigators have used a syndromal approach to establish a diagnosis of anxious depression (e.g., based on Diagnostic and Statistical Manual of Mental Disorders [DSM] criteria), whereas others have based the diagnosis on di-mensional criteria (using a cut-off score from a standardized scale), with a score of ≥7 on the Hamilton Depression Rating Scale (HAM-D) anxiety/somatization factor most commonly used (Ionescu et al., 2013). There is no consensus as to the most appropriate approach.

Data with intravenous ketamine, an N-methyl D-aspartate (NMDA) antagonist, in patients with depression and comorbid anxi-ety are limited. Two small studies, one in patients with treatment-resistant major depressive disorder (TRD) and one in patients with bipolar depression suggested an antidepressant effect of ketamine in those with comorbid anxiety symptoms (Ionescu, Luckenbaugh, et al., 2014; Ionescu et al., 2015). A recent double-blind, placebo-controlled pilot study of 99 patients with TRD (Salloum et al., 2019) found intravenous ketamine to be equally efficacious in patients with or without baseline comorbid anxiety symptoms at days 1 and 3 after a single infusion. Esketamine, the S-enantiomer of ketamine, with up to 2-fold higher affinity than ketamine for the NMDA receptor (Zanos et al., 2018), was recently approved by the US Food and Drug Administration and European Medicines Agency, in conjunction with an oral antidepressant, for TRD in adults (Spravato Prescribing In-formation 2019; Spravato Summary of Product Characteristics, 2021). This approval was based, in large part, on the results of the pivotal, flexible-dose short-term TRANSFORM-2 study in which mean Montgomery–Åsberg Depression Rating Scale (MADRS) total score decreased from 37 at baseline through day 28 with esketa-mine/antidepressant (LS mean change [95% CI]: −21.4 [−21.2 to −18.3]) and with antidepressant/placebo (−15.8 [−17.6 to −14.1]), with greater improvement among the esketamine-treated patients (difference of LS means at day 28: −4.0, 95% CI: −7.3 to −0.6, p = .020) (Popova et al., 2019).

To evaluate the effect of comorbid anxiety symptoms or dis-order on the antidepressant effects of esketamine in TRD, we con-ducted post hoc analyses of data from the TRANSFORM-2 study (Popova et al., 2019). The aims of these analyses were to explore whether there is a difference in efficacy or the safety profile be-tween esketamine nasal spray plus an oral antidepressant and anti-depressant plus placebo in patients with TRD, with or without comorbid anxiety symptoms or disorder.

2 | METHODS

2.1 | Study design

This is a post hoc analysis of data from TRANSFORM-2, a 4-week, flexible-dose, double-blind, active-controlled, multicenter trial of outpatients with TRD who received either esketamine or placebo nasal spray and a newly-initiated oral antidepressant (Popova et al., 2019).

The study was approved by independent review boards/ethics committees and written informed consent was obtained from all patients (clinicaltrials.gov identifier: NCT02418585).

2.2 | Patients

TRANSFORM-2 enrolled outpatients aged 18–64 years with re-current MDD (per DSM-5 criteria [American Psychiatric Associa-tion, 2013]), without psychotic features, and a total score ≥34 on the clinician-rated Inventory of Depressive Symptomatology (Rush et al., 1996, 2000). At the start of screening, eligible participants had documented nonresponse to ≥1 but ≤5 oral antidepressants based on historical report and the Massachusetts General Hospital Anti-depressant Treatment Response Questionnaire (Chandler et al., 2010). Per protocol, participants had been adherent to an ongoing oral antidepressant for at least the most recent 2 weeks, which was continued prospectively for 4 additional weeks during a screening/prospective observational phase. Exclusion criteria in-cluded moderate-to-severe substance or alcohol use disorder within the prior 6 months, obsessive compulsive disorder (current only), and use of a total daily dose of benzodiazepines equivalent to >6 mg/day of lorazepam. Of note, comorbid anxiety disorders were otherwise not excluded.

Those with nonresponse to their ongoing oral antidepressant and meeting criteria for TRD following the 4-week screening/pro-spective observational phase discontinued all current antidepressant treatment(s) and were randomized to 4 weeks of double-blind treatment, comprised of twice-weekly, flexible-dose esketamine na-sal spray (56 or 84 mg) or placebo nasal spray, each in combination with a newly-initiated open-label oral antidepressant taken daily. Dosing of the oral antidepressant followed a fixed titration schedule, and patients were titrated to the maximally tolerated dose per the product label.

2.3 | Assessments

A standardized diagnostic interview, the Mini International Neuropsychiatric Inventory (MINI) (Sheehan et al., 1998), was conducted by the investigator at screening to confirm the presence of MDD and to assess for presence of other comorbid disorders, including comorbid anxiety disorder.

The MADRS (Williams & Kobak, 2008) was administered at baseline and on days 2, 8, 15, 22, and 28 of the double-blind treatment phase by off-site, independent blinded raters. In addition, the 7-item Generalized Anxiety Scale (GAD-7), a patient-reported assessment, was completed at Screening and pre-dose on day 1 and day 28. The GAD-7 is a brief, validated measure of overall anxiety; a cut-off of ≥10 has been used in the literature to establish presence of at least moderate severity of anxiety (Spitzer et al., 2006).

Safety evaluations included incidence of reported adverse events, which were assessed throughout the study, and dissociation based on Clinician Administered Dissociative States Scale (Bremner et al., 1998) (CADSS) which was assessed at multiple timepoints during all dosing visits.

2.4 | Statistical analyses

Efficacy analyses included all randomized patients who received at least 1 dose of intranasal study drug and 1 dose of oral antidepressant. Adverse events and CADSS total scores were analyzed in a data set that included all patients who received at least one dose of either medication.

Analyses of efficacy and safety endpoints were evaluated in groups of patients according to the presence or absence of comorbid anxiety. Comorbid anxiety was ascribed when either (1) a current anxiety disorder (including current generalized anxiety, panic, social anxiety, posttraumatic stress [PTSD], or obsessive-compulsive disorder [OCD]) was established as present by the MINI at screening, or (2) the GAD-7 (Spitzer et al., 2006) total score was ≥10 at screening and baseline (day 1). Of note, the GAD-7 scale criteria was required at both screening and baseline in an effort to ensure patients did not have fluctuating levels of anxiety. Patients with PTSD or OCD in the comorbid anxiety disorder group were included to be consistent with prior reports, though neither condition is included in DSM-5 anxiety disorders (American Psychiatric Association, 2000). That said, no patient met the criteria for current OCD, which was an exclusion criterion for the study.

Between-group differences for baseline demographics and disease characteristics were analyzed by t-test for continuous variables and by χ^2 test for categorical variables.

Change in MADRS total score from baseline to day 28 was compared within treatment groups by paired t test and between treatment groups using analysis of covariance (ANCOVA) with fixed effects for treatment group, comorbid anxiety condition, and baseline value as a covariate. Interaction terms between treatment and comorbid anxiety conditions were also included in models. Least

squares (LS) mean differences between treatment groups and 95% confidence interval (CI) are provided by comorbid anxiety status.

Response (defined as ≥50% improvement in MADRS total score from baseline) and remission (defined as MADRS total score ≤12) rates at day 28 were compared between treatment groups using the Cochran–Mantel–Haenszel (CMH) test controlling for region, and class of oral antidepressant (SNRI or SSRI). Multiple logistic regression models were used to examine whether observed treatment differences at day 28 were dependent on the presence or absence of comorbid anxiety. Terms included treatment, comorbid anxiety, and the interaction of treatment and comorbid anxiety status. Probability of response and remission were computed between treatment groups by presence of comorbid anxiety, and odds ratios (OR) and 95% CIs were calculated.

Adverse events were summarized for patients with and without comorbid anxiety. Incidence of dissociative symptoms (defined a priori as CADSS total score >4) at any time during the 4-week treatment was compared between treatment groups within and between comorbid anxiety groups within each treatment group by CMH test.

3 | STUDY RESULTS

Overall, 227 patients were randomized to double-blind treatment; of these, 3 did not receive any study drug and 1 did not receive a dose of study antidepressant. Thus, the data set for the efficacy analyses included 223 patients (114 in the esketamine plus antidepressant group and 109 the antidepressant plus placebo group). The majority of these participants (esketamine/antidepressant: 86.0% [98/114]; antidepressant/placebo: 90.8% [99/109]) completed 28 days of treatment. Few patients discontinued the study due to an adverse event (8/114 [7.0%] and 1/109 [0.9%], respectively).

At baseline of the double-blind treatment phase, 72.6% (162/223) of patients had either comorbid anxiety symptoms or disorder, with 69.1% (154/223) of patients having a GAD-7 total score ≥10 at both screening and baseline and 13.5% (30/223) of patients meeting criteria for current anxiety disorder on the MINI (Table 1). Patients with comorbid anxiety appeared to have more chronic depressive symptoms compared to patients without comorbid anxiety based on longer mean duration of current episode and higher mean MADRS score at baseline (Table 1). Otherwise, those with or without comorbid anxiety were similar with respect to demographic and most disease characteristics.

The median mean daily dose for each of the oral antidepressants during the 4-week treatment phase was similar for patients in the esketamine/antidepressant group compared to those in the antidepressant/placebo group: duloxetine (each 60.0 mg each), escitalopram (17.3 and 17.4 mg, respectively), sertraline (110.3 and 115.5 mg), and venlafaxine XR (each 168.8 mg).

At day 28, esketamine-treated patients with and without anxiety demonstrated significant reductions in MADRS (mean [SD] change from baseline: patients with comorbid anxiety [n = 72]: −21.0 [12.51],

TABLE 1 Baseline demographics and disease characteristics by status of comorbid anxiety among patients with treatment-resistant depression

| | Comorbid anxiety | | No comorbid anxiety | |
| | Esketamine + Antidepressant | Antidepressant + placebo | Esketamine + antidepressant | Antidepressant + placebo |
Parameter	n = 83	n = 79	n = 31	n = 30
Mean age, years (SD)	44.9 (12.91)	45.4 (11.09)	45.1 (11.84)	49.1 (11.01)
Sex, n (%)				
Female	32 (38.5)	31 (39.2)	7 (22.6)	15 (50.0)
Male	51 (61.5)	48 (60.8)	24 (77.4)	15 (50.0)
Race, n (%)				
White	77 (92.8)	74 (93.7)	29 (93.6)	28 (93.3)
Black/African American	5 (6.0)	3 (3.8)	1 (3.2)	2 (6.7)
Other	1 (1.2)	2 (2.5)	1 (3.2)	0 (0)
Region				
Europe	52 (62.7)	52 (65.8)	17 (54.8)	13 (43.3)
North America	31 (37.3)	27 (34.2)	14 (45.2)	17 (56.7)
Mean duration of current episode, weeks (SD)	122.3 (133.6)	130.6 (208.9)	82.3 (90.4)	84.8 (108.7)
History of suicidal ideation during prior 6 months, assessed by C-SSRS, n (%)	29 (34.9)	23 (29.1)	8 (25.8)	11 (36.7)
No. of previous antidepressants, n (%)[a]				
1 or 2	75 (90.4)	68 (86.1)	27 (87.1)	26 (86.7)
≥3	8 (9.6)	11 (13.9)	4 (12.9)	4 (13.3)
Class of oral antidepressant, n (%)				
SNRI	57 (68.7)	58 (73.4)	20 (64.5)	17 (56.7)
SSRI	26 (31.3)	21 (26.6)	11 (35.5)	13 (43.3)
Mean MADRS total score (SD)	37.4 (5.43)	38.5 (5.48)	36.0 (6.33)	34.1 (4.92)
GAD-7 total score at baseline				
Mean (SD)	15.2 (4.0)	15.1 (3.5)	7.8 (3.7)	7.7 (3.6)
≥10[b], n (%)	80 (96.4)	74 (93.7)	0	0
Comorbid anxiety disorder[c] at screening, n (%)	17 (20.5)	13 (16.5)	0	0

Note: Comorbid anxiety was determined if the patient had one of the following at screening: generalized anxiety disorder current, panic disorder current, social anxiety disorder current, posttraumatic stress disorder current, or obsessive-compulsive disorder current by MINI, or GAD-7 total score of ≥10 at screening and baseline.

Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MGH-ATRQ, Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; MINI, Mini-International Neuropsychiatric Interview; SD, standard deviation; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a]Number of antidepressant medications with nonresponse (defined as ≤25% improvement) taken for at least 6 weeks during the current episode as obtained at screening from MGH-ATRQ.

[b]At screening and at baseline.

[c]Comorbid anxiety disorder was determined if the patient had one of generalized anxiety disorder current, panic disorder current, social anxiety disorder current, posttraumatic stress disorder current, or obsessive-compulsive disorder current by MINI.
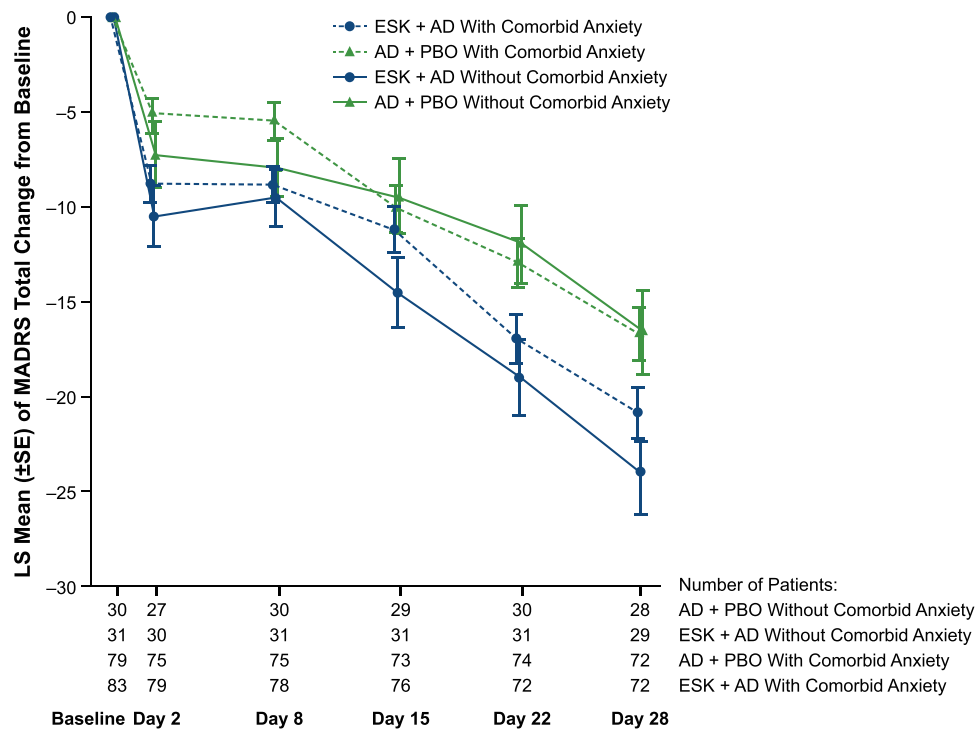
FIGURE 1 Least square mean change (SE) in Montgomery–Åsberg depression rating scale total score over time in the double-blind treatment phase. *Note:* Treatment effect based on change in Montgomery–Åsberg depression rating scale (MADRS) total score from baseline to day 28 was not statistically significantly different (interaction term $p = .371$) between the without/with anxiety groups (difference in LS means 3.3, 95% CI −4.0 to 10.6), with a greater improvement in MADRS scores among those treated with esketamine/antidepressant as compared to antidepressant/placebo (patients without comorbid anxiety: −7.5, −13.7 to −1.3; $p = .017$; patients with comorbid anxiety: −4.2, −8.1 to −0.3; $p = .036$). Abbreviations: AD, antidepressant; ESK, esketamine; LS, least squares; PBO, placebo; SE, standard error

95% CI: −23.6 to −18.1; and patients without comorbid anxiety [$n = 29$]: −22.7 [11.98], 95% CI: −28.4 to −19.8). In analyses of depressive symptoms by comorbid anxiety status (either symptoms *or* disorder) across both treatment groups, treatment effect based on change in MADRS total score from baseline to day 28 was significantly different, with a greater improvement in MADRS scores among those treated with esketamine/antidepressant as compared to antidepressant/placebo (Figure 1) (difference of LS means – patients with comorbid anxiety [$n = 144$ at day 28]: −4.2, 95% CI: −8.1 to −0.3; patients without comorbid anxiety [$n = 57$ at day 28]: −7.5, 95% CI: −13.7 to −1.3). The treatment differences observed did not differ between those without and with comorbid anxiety (interaction term $p = .371$; difference in LS means 3.3, 95% CI: −4.0 to 10.6; Table 2).

By day 28 there was a greater likelihood of meeting response criteria with esketamine/antidepressant versus antidepressant/placebo (patients with comorbid anxiety (65.3% vs. 54.2%, respectively; OR = 1.59, 95% CI: 0.81 to 3.11; patients without comorbid anxiety (79.3% vs. 46.4%, respectively; OR = 4.42, 95% CI: 1.38 to 14.19) (Figure 2). Similarly, there was a greater likelihood of achieving remission at day 28 with esketamine/antidepressant compared with antidepressant/placebo (patients with comorbid anxiety [47.2% vs. 33.3%, respectively; OR = 1.79, 95% CI: 0.91 to 3.51]; patients without comorbid anxiety [65.5% vs. 25.0%, respectively; OR = 5.70,

95% CI: 1.81 to 17.97]) (Figure 2). The interaction of treatment and comorbid anxiety was not statistically significant for response ($p = .136$) or for remission ($p = .088$).

In terms of safety, the most common adverse events reported for esketamine-treated patients (>10% of all patients) were anxiety, blurred vision, dissociation, dizziness, dysgeusia (metallic taste), headache, nausea, paresthesia, somnolence, and vertigo (Table 3), with a higher incidence in the esketamine/antidepressant group than the antidepressant/placebo group. Of these, the placebo-adjusted rates of anxiety, dissociation, nausea, and paresthesia were higher among esketamine-treated patients with versus without comorbid anxiety (Table 3). Most adverse events in both treatment groups were mild or moderate and resolved on the treatment day.

Two patients of 227 (0.9%), both with comorbid anxiety, experienced a serious adverse event during the 4-week treatment period. The serious adverse events included road traffic accident (with subsequent patient death) in the esketamine/antidepressant group, which the investigator considered doubtfully related to esketamine or to antidepressant, and an event of positional vertigo in the antidepressant/placebo group.

During double-blind treatment, the incidence of dissociative symptoms, based on CADSS total score >4, was higher among patients in the esketamine/antidepressant group compared to the antidepressant/placebo group (comorbid anxiety: 67.5% [56/83] vs.

TABLE 2 Change in MADRS total score from baseline to day 28 in patients with TRD and comorbid anxiety

	Comorbid Anxiety		No comorbid anxiety	
	Esketamine + antidepressant	Antidepressant + Placebo	Esketamine + Antidepressant	Antidepressant + Placebo
Baseline				
N	83	79	31	30
Mean (SD)	37.4 (5.42)	38.5 (5.48)	36.0 (6.33)	34.1 (4.92)
Change from baseline to day 28				
N	72	72	29	28
Mean (SD)	−21.0 (12.51)	−18.3 (13.99)	−22.7 (11.98)	−13.6 (13.25)
p value based on pared t-test	< .001	< .001	< .001	< .001
ANCOVA analysis[a] of treatment groups within same status of comorbid anxiety				
Difference of LS means[b] (SE)	−4.2 (1.97)		−7.5 (3.12)	
95% CI on difference	−8.1 to −0.3		−13.7 to − 1.3	
p value on difference	.036		.017	
ANCOVA analysis[c] of treatment groups under comorbid anxiety, yes versus no				
Difference of LS means[d] (SE)				3.3 (3.71)
95% CI on difference				−4.0 to 10.6
p value				.371

Notes: Anxious depression was determined if the patient had one of the following at screening: generalized anxiety disorder current, panic disorder current social anxiety disorder current, posttraumatic stress disorder current, or obsessive-compulsive disorder current, or had GAD-7 total ≥10 both at screening and at baseline. MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition. Negative change in score indicates improvement. Negative difference favors esketamine.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; SE, standard error.

[a]ANCOVA model with fixed effects for treatment and comorbid anxiety and baseline value as a covariate.

[b]Esketamine + antidepressant minus antidepressant + placebo within same status of comorbid anxiety (yes, no).

[c]Model also includes the interaction term between treatment and comorbid anxiety.

[d]Esketamine + antidepressant minus antidepressant + placebo in comorbid anxiety group versus no comorbid anxiety group.

12.7% [10/79], respectively; p < .001; no comorbid anxiety: 74.2% [23/31] vs. 6.7% [2/30], respectively; p < .001). In each treatment group, the presence/absence of comorbid anxiety appeared unrelated to incidence of dissociation.

4 | DISCUSSION

These post-hoc data support the efficacy of esketamine plus an oral antidepressant in patients with TRD regardless of comorbid anxiety. As noted in the introduction, previous studies indicate that patients with MDD and comorbid anxiety have poorer response with monoaminergic antidepressant medications than those without comorbid anxiety (Andreescu et al., 2007; Fava et al., 2008; Souery et al., 2007; Wiethoff et al., 2010). In line with these findings, in the current post-hoc analyses, patients with lower levels of anxiety symptoms appeared to achieve greater depressive symptom improvement than their counterparts with comorbid anxiety symptoms or disorder (LS mean difference between subgroups on-treatment differences: 3.3 points [95% CI −4.0 to 10.6]). However, a clinically meaningful and statistically significant treatment effect was observed in esketamine-treated patients with comorbid anxiety, with no significant interaction of treatment and comorbid anxiety (p = .371). Esketamine-treated patients with TRD and comorbid anxiety symptoms or disorder(s) demonstrated evidence of a clinically meaningful improvement compared to antidepressant/placebo (LS mean difference between groups: −4.2 points [95% CI, −8.1 to −0.3]). This difference is almost double the 2-point between-group difference found in clinical trials of the most recently approved biogenic amine antidepressants compared with only a placebo rather than an active comparator (Preskorn, 2013). This is important to note, as esketamine may provide an additional treatment option for this traditionally difficult-to-treat group of patients.
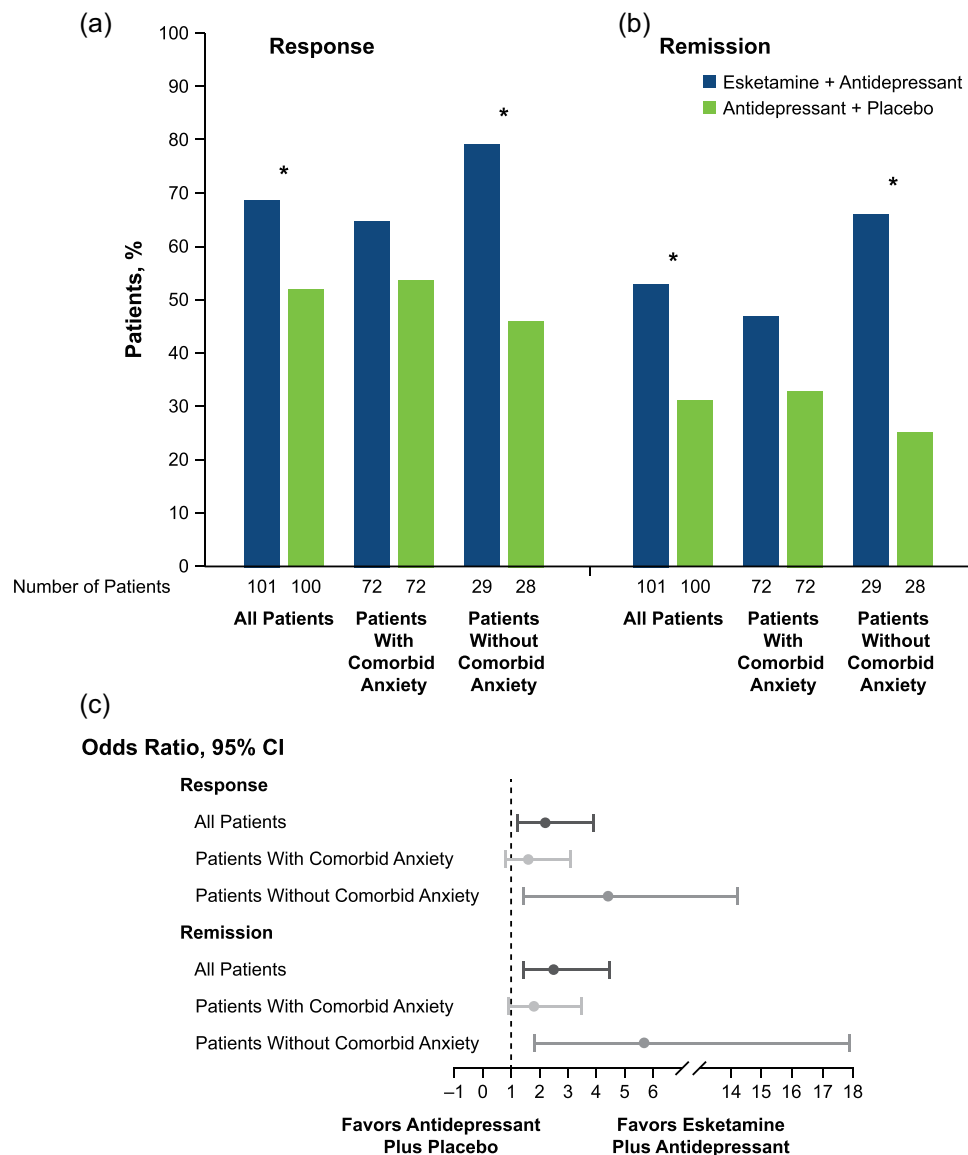
FIGURE 2 Response and remission rates at day 28 based on Montgomery–Åsberg depression rating scale total score. *p < .05 from CMH test. *Note:* Response was defined as a ≥50% improvement in MADRS total score from baseline. Remission was defined as MADRS total score ≤12. For both response and remission rates at day 28, treatment-by-subgroup interactions were formally tested using logistic regression models. p values for testing the interactions were .136 and .088 for response and remission rate differences, respectively. CI, confidence interval; CMH, Cochran–Mantel–Haenszel; MADRS, Montgomery–Åsberg depression rating scale

After 4 weeks of treatment, higher response and remission rates and a significantly greater decrease in MADRS total score were observed in the esketamine/antidepressant group than in the antidepressant/placebo group, with or without comorbid anxiety. As noted above, previously conducted studies with ketamine in patients with TRD have also shown evidence of antidepressant effect in those with and without anxiety (Ionescu, Luckenbaugh, et al., 2014; Salloum et al., 2019). In a post-hoc analysis, Ionescu, Luckenbaugh, et al. (2014) found greater antidepressant improvement in patients with anxious depression (n = 15), defined by HAM-D anxiety/somatization factor score, compared to nonanxious depression (n = 11). While the current study did not find an antidepressant advantage to esketamine treatment in patients with TRD with, versus without,

comorbid anxiety, there are several differences between the earlier study and our study that limit the ability to compare findings (e.g., differences in sample size, definition of comorbid anxiety, study design [single vs. multiple dose, placebo-controlled vs. active control]). Although the current data should be interpreted with caution given the limitations outlined below, in this large sample of patients receiving treatment over 4 weeks, esketamine/antidepressant appears to be an effective treatment for adults with TRD and comorbid anxiety symptoms.

Prior studies indicate that patients with MDD and comorbid anxiety have a reduced rate of response or remission following treatment with monoaminergic antidepressants and may have a greater risk for side effects compared to patients without comorbid

TABLE 3 Most frequently reported treatment-emergent adverse events in the double-blind treatment phase of randomized controlled trials of treatment-resistant depression

| Adverse event | Number (%) of patients | | | |
| | Comorbid anxiety | | No comorbid anxiety | |
	Esketamine + antidepressant n = 83	Antidepressant + placebo n = 79	Esketamine + antidepressant n = 31	Antidepressant + placebo n = 30
Nausea	24 (28.9)	6 (7.6)	6 (19.4)	1 (3.3)
Dissociation	22 (26.5)	2 (2.5)	8 (25.8)	2 (6.7)
Vertigo	20 (24.1)	3 (3.8)	10 (32.3)	0
Dysgeusia	18 (21.1)	10 (12.7)	10 (32.3)	3 (10.0)
Dizziness	16 (19.3)	3 (3.8)	7 (22.6)	2 (6.7)
Headache	15 (18.1)	16 (20.3)	8 (25.8)	3 (10.0)
Somnolence	14 (16.9)	3 (3.8)	1 (3.2)	4 (13.3)
Anxiety	11 (13.3)	4 (5.1)	1 ((3.2)	1 (3.3)
Paresthesia	11 (13.3)	1 (1.3)	2 (6.5)	0
Insomnia	10 (12.1)	5 (6.3)	1 (3.2)	0
Vomiting	10 (12.1)	1 (1.3)	1 (3.2)	1 (3.3)
Paresthesia oral	9 (10.8)	1 (1.3)	0	0
Vision blurred	9 (10.8)	2 (2.5)	5 (16.1)	1 (3.3)
Hypoesthesia oral	8 (9.6)	0	1 (3.2)	1 (3.3)
Nasal discomfort	8 (9.6)	1 (1.3)	0	1 (3.3)
Blood pressure increased	7 (8.4)	0	4 (12.9)	1 (2.1)
Diarrhea	7 (8.4)	7 (8.9)	3 (9.7)	3 (10.0)
Dry mouth	7 (8.4)	2 (2.5)	2 (6.5)	1 (3.3)
Hypoesthesia	7 (8.4)	0	1 (3.2)	1 (3.3)
Throat irritation	7 (8.4)	2 (2.5)	2 (6.5)	3 (10.0)
Feeling drunk	6 (7.2)	1 (1.3)	2 (6.5)	0
Sedation	5 (6.0)	0	0	1 (3.3)
Dizziness postural	4 (4.8)	1 (1.3)	4 (12.9)	0
Fatigue	3 (3.6)	5 (6.3)	2 (6.5)	1 (3.3)
Irritability	3 (3.6)	0	2 (6.5)	1 (3.3)

Note: The table lists adverse events with an incidence ≥5% in either treatment group, listed in decreasing order based on incidence within the group of patients with comorbid anxiety treated with esketamine plus antidepressant, and in alphabetical order for events with the same incidence.

anxiety (reviewed by Ionescu, Niciu, et al., 2014]). In STAR*D, remission was less likely and more slowly achieved in the presence of comorbid anxiety symptoms (Fava et al., 2008). In a large European study, a strong association was found between anxious comorbidity and failure to respond to treatment in patients with TRD (OR 2.6, p < .001) (Souery et al., 2007). Patients with depression and comorbid anxiety have also been reported as having greater depressive illness severity and chronicity (Fava et al., 2006, 2008). This finding is in line with the current analysis, in which patients with comorbid anxiety appeared to have more chronic and severe depressive symptoms compared to patients without comorbid anxiety, reporting a longer

mean duration of current episode and a higher mean MADRS score at baseline.

Consistent with results across the esketamine development program (Spravato Prescribing Information, 2019; Spravato Summary of Product Characteristics, 2021), in the current analysis most adverse events were mild-moderate and resolved on treatment day. Few patients in either treatment group experienced a serious adverse event or discontinued study drug due to an adverse event. Among esketamine-treated patients, placebo-adjusted rates of anxiety, dissociation, nausea, and paresthesia were numerically higher among those with versus without comorbid anxiety, perhaps due to

anxious patients being more attentive to somatic symptoms and side effects (Paulus & Stein, 2010; Shankman et al., 2017). Rates of dissociation based on the CADSS were not different between patients with and without comorbid anxiety.

4.1 | Study limitations

The TRANSFORM-2 study was not designed to evaluate efficacy or safety in patients with comorbid anxiety. Interpretation of current findings is limited by the definition of comorbid anxiety being made on a post-hoc basis, rather than being defined based on using pre-specified criteria at the time of patient enrollment.

For this report, we defined comorbid anxiety based on syndromal criterion (current anxiety disorder from the MINI) or dimensional criterion (both screening and baseline GAD-7 total score ≥10). Based on the choice of definition of comorbid anxiety used in the current analysis and the study inclusion criteria, this data may not necessarily reflect the true prevalence of comorbid anxiety in the overall TRD population.

The definition of anxiety does impact findings. For example, in a post hoc analysis of 1171 adults with MDD and inadequate response to antidepressants, Thase et al. (2018) reported there was low overlap between anxious distress defined by proxies for DSM-5 criteria and anxious depression defined by the STAR*D definition (≥7 on the HAM-D anxietysomatization factor). In the current analysis, the discrepancy between the percentage of patients who met criteria for comorbid anxiety based on the GAD-7 (total score ≥10) compared to those who met criteria for current comorbid anxiety disorder (on the MINI), with more patients meeting criteria for the former, may be partially explained by the difference in state versus trait anxiety. Those who met criteria for anxiety disorder based on the MINI were required to fully meet criteria at the time of administration ("state" anxiety). However, at study entry patients were being treated with traditional antidepressant therapies, with some also receiving anxiolytic medications, which may have resulted in patients who no longer met criteria for an anxiety disorder. Despite treatment effects, residual anxiety may have remained, allowing them to still meet criteria for being included in the analysis ("trait" anxiety). Of note, the current analysis did not account for differences in dose of antidepressant or concomitant benzodiazepine use, which could have an impact on observed outcomes.

Another limitation is that the design of the TRANSFORM-2 study may also have an impact on the interpretability of the findings. Patients in both treatment arms were seen twice weekly at the study site for extensive visits. Although the literature suggests a poorer response to monoaminergic oral antidepressants for those with versus without anxiety, this was not the case for patients in the antidepressant/placebo group in the current analysis, suggesting that potentially increased contact with site staff may have had a greater effect on those with comorbid anxiety for that treatment group. Additionally, recent preliminary research indicates evidence of higher placebo response when patients expect to receive a medication with dissociative or hallucinogenic effects (Olson et al., 2020).

The generalizability of these findings is limited in that we excluded patients with moderate-to-severe substance and alcohol use disorder and those taking high-dose benzodiazepines. Additionally, whether longer treatment duration would have produced even higher response and remission rates in the context of comorbid anxiety with TRD remains unknown. Taken together, the authors recommend that the current findings be interpreted with caution, with further studies clearly warranted.

5 | CONCLUSIONS

In this post hoc analysis, esketamine nasal spray combined with a newly-initiated antidepressant was more effective than a newly-initiated antidepressant combined with placebo nasal spray in patients with TRD, regardless of the presence or absence of comorbid anxiety, suggesting a beneficial effect for esketamine in this population of adults with challenging-to-treat depression. Given the limitations of this analysis, further studies designed to look specifically at this patient population are warranted.

CONFLICT OF INTERESTS

Ella J. Daly, Ibrahim Turkoz, Giacomo Salvadore, Maggie Fedgchin, Dawn F. Ionescu, H. Lynn Starr, and Stephane Borentain are employees of Janssen Scientific Affairs, LLC or Janssen Research & Development, LLC and are stockholders of Johnson & Johnson, Inc. While employed by Janssen Research & Development, LLC, Jaskaran B. Singh worked on the clinical development program of esketamine for TRD; he is currently employed by Neurocrine Biosciences. Madhukar H. Trivedi has consulted for or served on the advisory board of Acadia Pharmaceuticals, Alto Neuroscience, Axsome Therapeutics, Boegringer Ingelheim, Engage Health Media, GreenLight VitalSign6 Inc., Janssen Research & Development, Lundbeck Research USA, Medscape, Merck & Co. Inc., Myriad Neuroscience, Navitor Pharmaceutical Inc, Neurocrine, Otsuka America Pharmaceutical Inc., Perception, Pharmerit International, Sage Therapeutics, Signant Health, and Takeda Global Research. Dr. Trivedi has received research support from the Agency for Healthcare Research and

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