Received: 5 October 2021 | Revised: 16 May 2022 | Accepted: 27 May 2022

DOI: 10.1002/mpr.1927

WILEY

ORIGINAL ARTICLE

Montgomery-Åsberg Depression Rating Scale factors in treatment-resistant depression at onset of treatment: Derivation, replication, and change over time during treatment with esketamine

Stephane Borentain[1] | Jagadish Gogate[2] | David Williamson[3] | Thomas Carmody[4] | Madhukar Trivedi[4] | Carol Jamieson[5] | Patricia Cabrera[6] | Vanina Popova[7] | Ewa Wajs[7] | Allitia DiBernardo[1] | Ella J. Daly[3]

[1]Department of Global Medical Affairs, Janssen Research & Development, LLC, Titusville, New Jersey, USA

[2]Department of Statistics & Decision Sciences, Janssen Research & Development LLC, Raritan, New Jersey, USA

[3]Clinical Medical Affairs, Janssen Scientific Affairs LLC, Titusville, New Jersey, USA

[4]Department of Psychiatry, UT Southwestern Medical Center, Dallas, Texas, USA

[5]Patient Reported Outcomes, Janssen Research & Development LLC, Milpitas, California, USA

[6]Department of Global Medical Affairs, Janssen Global Services LLC, Titusville, New Jersey, USA

[7]Department of Neuroscience, Janssen Research & Development, Beerse, Belgium

Correspondence

Stephane Borentain, Department of Global Medical Affairs, Janssen Research & Development, LLC, 1125 Trenton-Harbourton Road, Titusville, NJ 08560, USA.
Email: SBorent1@ITS.JNJ.com

Funding information

Janssen Research & Development LLC

Abstract

Objective: Derive and confirm factor structure of the Montgomery-Åsberg Depression Rating Scale (MADRS) in patients with treatment-resistant depression (TRD) and evaluate how the factors evident at baseline change over 4 weeks of esketamine treatment.

Methods: Two similarly-designed, short-term TRANSFORM trials randomized adults to esketamine or matching placebo nasal spray, each with a newly-initiated oral antidepressant, for 4 weeks (TRANSFORM-1: $N = 342$ patients; TRANSFORM-2: $N = 223$ patients). The factor structure of MADRS item scores at baseline was determined by exploratory factor analysis in TRANSFORM-2 and corroborated by confirmatory factor analysis in TRANSFORM-1. Change in MADRS factor scores from baseline (day 1) to the end of the 28-day double-blind treatment phase of TRANSFORM-2 was analyzed using a mixed-effects model for repeated measures (MMRM).

Results: Three factors were identified based on analysis of MADRS items: Factor 1 labeled affective and anhedonic symptoms (apparent sadness, reported sadness, lassitude, inability to feel), Factor 2 labeled anxiety and vegetative symptoms (inner tension, reduced sleep, reduced appetite, concentration difficulties), and Factor 3 labeled hopelessness (pessimistic thoughts, suicidal thoughts). The three-factor structure observed in TRANSFORM-2 was verified in TRANSFORM-1. Treatment benefit at 24 h with esketamine versus placebo was observed on all 3 factors and continued throughout the 4-week double-blind treatment period.

David Williamson and Ella J. Daly were employed by Janssen Scientific Affairs LLC while this work was performed. Dr. Williamson has current affiliations with the Departments of Psychiatry and Neurology at the University of South Alabama College of Medicine, Mobile, AL and the Department of Psychiatry and Health Behavior at Augusta University, Augusta, GA.

Conclusions: A three-factor structure for MADRS appears to generalize to TRD. All three factors improved over 4 weeks of treatment with esketamine nasal spray.

KEYWORDS
depression, esketamine, factor analysis, MADRS

1 | INTRODUCTION

Major depressive disorder (MDD) can present in a variety of ways, with hundreds to thousands of possible combinations of symptoms meeting the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (American Psychiatric Association, 2013), depending on method. (Fried & Nesse, 2015; Zimmerman et al., 2015) Nonetheless, a relatively small number of the most frequent possible combinations account for the majority of patients with MDD. (Zimmerman et al., 2015) Understanding how best to quantify these relatively more consistent combinations of symptoms, and determining if these are affected differentially by different forms of treatment, may inform clinicians and researchers alike.

The Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) is a validated, widely-used, 10-item, clinician-rated measure of depression severity. Individual items of the MADRS may contribute differently to the same overall depression severity across patients. Moreover, treatment effect may vary across symptoms. Several studies have identified possible MADRS subscales and symptom clusters in patients with MDD by applying factor analytic strategies to the set of 10 items. (Galinowski & Lehert, 1995; Quilty et al., 2013; Suzuki et al., 2005; Williamson et al., 2006) The number of factors identified has varied, depending on the characteristics of the sample (e.g., severity, chronicity, treatment resistance, inclusion of patients in the depressed phase of bipolar I or bipolar II), time of assessment relative to treatment course (e.g., at baseline or after treatment has been initiated), and method chosen to identify the number of relevant factors (e.g., Kaiser criterion, parallel analysis). (Carmody, Rush, Bernstein, Brannan, et al., 2006; Carmody, Rush, Bernstein, Warden, et al., 2006) For instance, whereas the MADRS is often found to be multifactorial at baseline (generally three (Benazzi, 2001; Galinowski & Lehert, 1995; Suzuki et al., 2005) or four (Quilty et al., 2013; Williamson et al., 2006) factors), single-factor solutions are often found at the conclusion of treatment, (Borentain et al., 2019; Carmody, Rush, Bernstein, Warden, et al., 2006) although this finding is not universal. (Quilty et al., 2013; Uher et al., 2008)

The extent to which symptom pattern may vary as a function of treatment resistance has received relatively little attention. (Akil et al., 2018) In a sample of 233 patients with highly treatment-resistant depressive episodes, 208 of whom were diagnosed with MDD, Carmody and colleagues (Carmody, Rush, Bernstein, Brannan, et al., 2006) noted a unifactorial structure to MADRS responses after completion of 12 months of treatment. Dimensionality of the MADRS at baseline was not characterized. To improve clinical decision-making and symptom characterization, it may be useful to establish if multiple factors are evident at baseline in treatment-resistant samples. Identifying relevant symptom clusters in patients with TRD and evaluating their response to a novel glutamatergic antidepressant with a unique mechanism of action, such as esketamine, may inform treatment selection and offers the potential for a targeted therapeutic intervention.

Esketamine, the S-enantiomer of racemic ketamine, is approved in conjunction with an oral antidepressant for the treatment of adults with TRD by the United States Food and Drug Administration, (Spravato™, 2020) the European Medicines Agency (2021) and other regulatory authorities. These approvals were based, in part, on the results of the pivotal, short-term flexible-dose TRANSFORM-2 study, in which improvement in depressive symptoms was observed beginning as early as at 24 h post-initial dose and consistently thereafter throughout the 28-day double-blind treatment phase of the study. (Popova et al., 2019) These findings were further supported by results from a second short-term fixed-dose study, TRANSFORM-1. (Fedgchin et al., 2019)

1.1 | Aims of the post hoc investigation

A post hoc analysis of data from the TRANSFORM-2 study was conducted to (1) identify statistically valid and clinically meaningful clusters of depressive symptoms at the onset of esketamine treatment from among the MADRS items using factor analysis and confirm the MADRS factor structure using data from TRANSFORM-1 study, and (2) measure the effect of esketamine compared to placebo nasal spray, each in conjunction with an oral antidepressant, on trajectories of the clinical clusters identified by factor analysis.

2 | METHODS

2.1 | Study design

TRANSFORM-2 (Popova et al., 2019) and TRANSFORM-1 (Fedgchin et al., 2019) were phase 3 short-term, randomized, double-blind, active-controlled, multicenter studies of esketamine nasal spray. These TRANSFORM studies were designed to compare the efficacy and safety of esketamine nasal spray combined with a newly initiated oral antidepressant to that of a newly initiated oral antidepressant plus placebo nasal spray in adult patients with TRD.

The studies were approved by independent review boards/ethics committees, and written informed consent was obtained from all patients (clinical trials.gov identifier: NCT02418585 and NCT02417064).

2.2 | Patients

Both TRANSFORM studies enrolled outpatients, aged 18–64 years, inclusive, with MDD (per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (American Psychiatric Association, 2013)), without psychotic features, and who met criteria for TRD, defined as non-response to an adequate trial (dose, duration, adherence) of at least 2 antidepressants in the current episode of depression. MDD diagnosis was established using clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998); a total score of ≥34 on the clinician-rated Inventory of Depressive Symptomatology (Rush et al., 1996, 2000) was required, defining moderate-to-severe depression. Patients with current or recent (past 6 months) homicidal ideation/intent or suicidal ideation with intent to act or suicidal behavior within the past year were excluded from study participation.

At screening, eligible participants had documented non-response to ≥1 but ≤5 oral antidepressants, based on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire. Patients must have been adherent to an ongoing different oral antidepressant for at least the prior 2 weeks, which was continued prospectively for 4 additional weeks during a screening/prospective observational phase. Those with non-response to their ongoing oral antidepressant and who met criteria for TRD following the screening phase, discontinued all current antidepressant treatment(s) and were randomized to receive double-blind treatment with esketamine nasal spray or placebo nasal spray, administered twice weekly, each combined with a newly initiated, open-label oral antidepressant (duloxetine, escitalopram, sertraline, or extended-release venlafaxine) administered daily for 4 weeks. Patients received either esketamine or placebo nasal spray 1:1 – flexible dose in TRANSFORM-2 (i.e., 56 mg on day 1, then either 56 mg or 84 mg on days 4, 8, 11, or 15 based on efficacy and tolerability, after which the dose remained stable) and fixed dose in TRANSFORM-1 (i.e., esketamine 56 mg, esketamine 84 mg, or placebo 1:1:1).

2.3 | MADRS assessments

The MADRS (Montgomery & Åsberg, 1979) comprises the following 10 items: apparent sadness; reported sadness; inner tension; reduced sleep; reduced appetite; concentration difficulties; lassitude; inability to feel; pessimistic thoughts; and suicidal thoughts. Clinicians rate each item on a 7-point Likert scale; the sum of the item scores produces a MADRS total score that ranges from 0 to 60, with higher scores reflecting greater depression severity.

As treatment with esketamine may produce transient dissociative effects that are difficult to blind, possibly biasing the site staff supervising the dosing, all MADRS assessments were performed remotely (via telephone) by site-independent, remote raters who were blinded to the protocol details, including study visit, the patient's clinical status, and side effects during the trial. (Fedgchin et al., 2019; Popova et al., 2019) MADRS assessments were performed prior to dosing at baseline (pre-treatment) and on days 8, 15, and 22. In addition a MADRS assessment was performed on day 2 (24 h following the first dose) and on day 28.

2.4 | Statistical analyses

Exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) were conducted using data from the TRANSFORM-2 (Popova et al., 2019) and TRANSFORM-1 (Fedgchin et al., 2019) studies, respectively. TRANSFORM-2, which served as one of the two pivotal trials supporting the drug's approval by FDA, was used as the primary dataset for assessing change in factor scores over time because it employed flexible dosing of esketamine (vs. fixed dosing in TRANSFORM-1), thus better reflecting real-world use of esketamine in clinical practice as well as the intended use of esketamine per prescribing information. (Spravato™, 2020)

2.4.1 | Factor analyses

Exploratory factor analysis with principal components analysis (PCA) as the extraction method and promax (oblique) rotation (using SAS version 9.4; SAS Institute, Cary, NC, USA) was performed on MADRS items from TRANSFORM-2 at baseline. The oblique promax rotation, appropriate for correlated factors, was used due to the inherent correlation often observed between psychiatric symptoms. (Fabrigar et al., 1999; Peralta & Cuesta, 2001; Russell, 2002) The number of factors chosen was based on (a) the Kaiser criterion (number of factors with eigenvalues >1), (b) good model fit, (c) clear loadings of items on a specific factor, and (d) clinical meaningfulness. Items were selected onto factors where the loading was greater than 0.50; with this criterion, an individual item could not load onto more than one factor. CFA was then used to confirm the factor structure derived from the baseline MADRS item scores of TRANSFORM-2 in the independent TRANSFORM-1 sample. Models were tested (SAS 9.4 TS Level 1M4, SAS Institute Inc., Cary, NC, USA) using maximum-likelihood estimation. Following the recommendations of (Kline, 2016), model fit was evaluated in CFA using a mix of global and local fit indices: chi square (χ^2), residual-based measures (root mean square of approximation [RMSEA]), standardized root mean square residual (SRMR), and an index assessing incremental goodness-of-fit (Comparative Fix Index [CFI]). Given our sample size ($n > 200$), χ^2 is viewed as problematic for evaluating model fit, because the statistic is more likely to signal a significant difference between distributions as samples grow larger. (Hu & Bentler, 1999) However, the relative χ^2, calculated as the chi-square statistic divided by degrees of freedom, has been found to mitigate this issue to some extent, with the target value being between 2 and 5. (Fabrigar et al., 1999; Wheaton et al., 1977) RMSEA is an absolute fit index that examines the discrepancy between the hypothesized model and an optimal model. Values closer to zero indicate better fit, (Xia & Yang, 2019)

with "acceptable" values being <0.08. (Fabrigar et al., 1999) In contrast, CFI examines the discrepancy between the data and a baseline model (i.e., a model with the worst fit), while adjusting for sample size. Values range from 0 to 1, with higher values indicating a better fit. Values for acceptable models will generally be 0.90 or above.

2.4.2 | Change in baseline factors over the course of treatment

For each MADRS factor, the factor score was derived by summing the scores for the individual items comprising the factor. Change in MADRS factor scores from baseline (day 1) over time during the double-blind treatment phase of TRANSFORM-2 was analyzed for each factor using a mixed-effects model for repeated measures (MMRM). The model included treatment group, baseline value, time (visit), and treatment group by time interaction as covariates. An unstructured covariance matrix was used to model the correlation among repeated measures within patients. Visit (study day) is considered a categorical variable. The repeated measures correspond to MADRS items-based factor total scores at each visit (study day) by patient, and all visits were included simultaneously in the model. Least squares means (adjusted means) are based on the estimates corresponding to the treatment by time (visit) interaction term. The magnitude of change of each factor in the esketamine plus antidepressant group relative to the antidepressant plus placebo group was also examined in terms of effect sizes (Cohen's *d*).

3 | RESULTS

The analysis sets for the TRANSFORM-2 and TRANSFORM-1 studies included 223 and 342 patients, respectively. In TRANSFORM-2, the majority (61.9%) of the patients were female and the mean (SD) age was 45.7 (11.89) years old. At baseline, mean (SD) duration of the current episode exceeded 2 years (114.6 (157.96) weeks) and mean (SD) MADRS total score was 37.1 (5.7). The treatment groups of TRANSFORM-2 were similar with respect to demographics, baseline clinical characteristics, and the type/rate of oral antidepressant study drug selected. (Popova et al., 2019) Demographic and other baseline characteristics of the patients in TRANSFORM-1 were similar to those of patients in TRANSFORM-2 (Table 1). Individual MADRS item scores are summarized in Table S1.

3.1 | Exploratory factor analysis of TRANSFORM-2

The correlation between individual MADRS items at baseline is presented in Table S2. Three factors (eigenvalue ≥1.0) were identified at baseline; those three factors accounted for 54.3% of the variance (Table S3), with each item of the scale clearly loading (>0.5) onto a specific factor.

The three factors from PCA with promax (oblique) rotation included the following items (Table 2): The first factor, labeled "affective and anhedonic symptoms" includes apparent sadness, reported sadness, lassitude, and inability to feel, and represents the highest proportion of the scale variance (22.4%). The second factor, labeled "anxiety and vegetative symptoms", includes inner tension, reduced sleep, reduced appetite, and concentration difficulties, and represents a meaningful proportion of the variance (18%). The third factor, labeled "hopelessness", includes items of pessimistic thoughts and suicidal thoughts. Inter-factor correlations were 0.36729 between Factors 1 and 2, 0.23675 between Factors 1 and 3, and 0.06959 between Factors 2 and 3.

3.2 | Confirmatory factor analysis of TRANSFORM-1

Results of the CFA suggest that the three-factor structure identified in EFA was an acceptable model fit. Values of the relative χ^2 (2.92), RMSEA (0.075, 95% CI: 0.058–0.093), and SRMR (0.0617) were all consistent with an acceptable fit, while CFI just missed the conventional cutoff (0.865). Monte Carlo simulations have suggested that when mild disagreement is noted between an acceptable RMSEA and a less acceptable CFI, the issue may more likely be a function of sampling variability than model specification. (Lai & Green, 2016)

3.3 | Change over time in factors identified at baseline

Change in total MADRS score from baseline (Figure 1) has been reported. (Popova et al., 2019) In TRANSFORM-2, improvement in scores for all three MADRS factors was observed at all post-baseline timepoints with treatment, more so for esketamine plus antidepressant than for antidepressant plus placebo, with a significant treatment effect ($p < 0.05$) at all timepoints for Factor 2 (anxiety and vegetative symptoms), at days 2, 22, and 28 for Factor 1 (affective and anhedonic symptoms), and at day 2 only for Factor 3 (hopelessness) (Table 3; Figure 1). At day 28, the beneficial effects of esketamine plus antidepressant relative to antidepressant plus placebo on each factor, in terms of effect sizes, were 0.29, 0.35, and 0.25 for Factors 1, 2, and 3, respectively (Table 3).

4 | DISCUSSION

Factor analysis, a data-driven approach, can be used to identify meaningful dimensions within a heterogeneous construct. Change in subscales may occur over different timeframes and to different degrees in response to treatment and may therefore provide a more focused assessment of treatment effect compared to the overall scale score. In this regard, the MADRS has been evaluated in prior factor analyses, with the aim of identifying symptom profiles and assessing

TABLE 1 Demographic and baseline characteristics

	TRANSFORM-2 study cohort *N* = 223	TRANSFORM-1 study cohort *N* = 342
Age, years		
Mean (SD)	45.7 (11.89)	46.3 (11.19)
Range	19 – 64	18 – 64
Sex, *n* (%)		
Male	85 (38.1)	101 (29.5)
Female	138 (61.9)	241 (70.5)
Race, *n* (%)		
Asian	2 (0.9)	5 (1.5)
Black or African American	11 (4.9)	19 (5.6)
White	208 (93.3)	262 (76.6)
Multiple	2 (0.9)	1 (0.3)
Not reported	0	25 (7.3)
Baseline body mass index, kg/m^2		
Mean (SD)	28.1 (6.05)	28.8 (6.42)
Range	16 – 56	17 – 56
Age when diagnosed with MDD, years		
Mean (SD)	33.7 (12.86)	31.4 (12.54)
Range	5 – 64	9 – 63
Duration of current episode, weeks		
Mean (SD)	114.6 (157.96)	202.9 (290.24)
Range	8 – 1196	6 – 2288
No. of previous antidepressant medications[a], *n* (%)		
1 or 2	150 (67.3)	205 (60.3)
≥3	73 (32.7)	135 (39.7)
Class of oral antidepressant, *n* (%)		
SNRI	152 (68.2)	196 (57.3)
SSRI	71 (31.8)	146 (42.7)
Oral antidepressant, *n* (%)		
Duloxetine	121 (54.3)	136 (39.8)
Escitalopram	38 (17.0)	73 (21.3)
Sertraline	32 (14.3)	73 (21.3)
Venlafaxine extended release	32 (14.3)	60 (17.5)

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a]Number of antidepressant medications at screening with non-response (defined as ≤25% improvement) taken for at least 6 weeks during the current episode as obtained from Massachusetts General Hospital Antidepressant Treatment Response Questionnaire, in addition to one prospective antidepressant.

if some of those profiles are associated with better treatment outcomes. Previous investigations of MADRS structure, in various patient populations, have not converged upon a consistent model, and data are particularly lacking in the structure of the MADRS at the onset (rather than conclusion) of a course of treatment for patients with TRD. In our strictly-defined TRD cohort, factor analysis of the MADRS at baseline identified three interpretable and clinically meaningful clusters of MADRS items – affective and anhedonic

symptoms (Factor 1), anxiety and vegetative symptoms (Factor 2), hopelessness (Factor 3) – that may have a different timeframe and degree of response to esketamine treatment than to conventional monoaminergic antidepressants. These three factors accounted for 54.3% of variance of the items, in line with other studies that explored the factor structure of the MADRS. (Cassano et al., 2009; Vrieze et al., 2014)

While the number of factors often varies among prior studies, without any convergent model emerging, some symptom aggregations have been consistently observed. The symptom aggregation results from patients with TRD in both TRANSFORM studies are generally consistent with those from previous studies of patients with MDD and TRD. (Galinowski & Lehert, 1995; Johnson et al., 2016; Suzuki et al., 2005; Williamson et al., 2006)

TABLE 2 TRANSFORM-2: Items comprising each factor[a] at baseline from promax oblique rotation

Item	Factor 1	Factor 2	Factor 3
Apparent sadness	0.78387	−0.04101	0.08674
Reported sadness	0.73677	0.13369	−0.00841
Inner tension	−0.08232	0.66736	0.28730
Reduced sleep	−0.05306	0.68732	−0.08777
Reduced appetite	0.03163	0.64685	0.03974
Concentration difficulties	0.20470	0.55798	−0.19033
Lassitude	0.64831	0.09548	−0.03712
Inability to feel	0.75628	−0.11097	0.03444
Pessimistic thoughts	0.02630	0.19922	0.74539
Suicidal thoughts	0.03727	−0.18780	0.81997
Variance explained by Factor	26.1%	21.4%	15.3%

[a]factor loading score >0.5.

The observation that the first factor, including anhedonia-related symptoms (inability to feel, lassitude) and sadness, accounted for most of the explained variance is not unexpected given that these symptoms are related to depression severity. (Burke et al., 2005; Fawcett et al., 1983) Anhedonia and depressed mood constitute core features of major depression: according to the DSM-V, at least five symptoms must occur for a diagnosis of MDD, one of which must be either depressed mood or anhedonia. The second factor includes anxiety and vegetative symptoms, which have been associated with increased duration of depressive episodes, decreased likelihood of response, and higher risk of chronic course and recurrences, which are key attributes of patients with TRD. (Cassano et al., 1997) Interestingly, in the current study, concentration difficulties loaded with inner tension and neurovegetative symptoms. This result differs from previous studies in which an anhedonia factor was defined including concentration difficulties as well as the four items (i.e., apparent sadness, reported sadness, lassitude, inability to feel) included in our affective and anhedonic factor. (Cao et al., 2019) Impaired concentration is frequently reported in MDD and has been found to be relatively unstable, likely related to several potential underlying mechanisms, (Oquendo et al., 2004) potentially explaining the variability in this item loading across various studies and population. The third factor identified in our current analysis, hopelessness (including items of pessimistic thoughts and suicidal thoughts) is consistent with most of the previous study results which loaded pessimistic thoughts and suicidal ideation on the same factor. (Suzuki et al., 2005) Pessimistic thoughts are related with hopelessness, which has been strongly correlated with suicidal thoughts and behavior. (Hawton et al., 2013)

A statistically significant treatment benefit with esketamine was observed on the magnitudes of all three factors (clinical dimensions) at the first post-dose evaluation timepoint, 24 h after the first dose of study drug (day 2) compared to the oral antidepressant plus placebo.

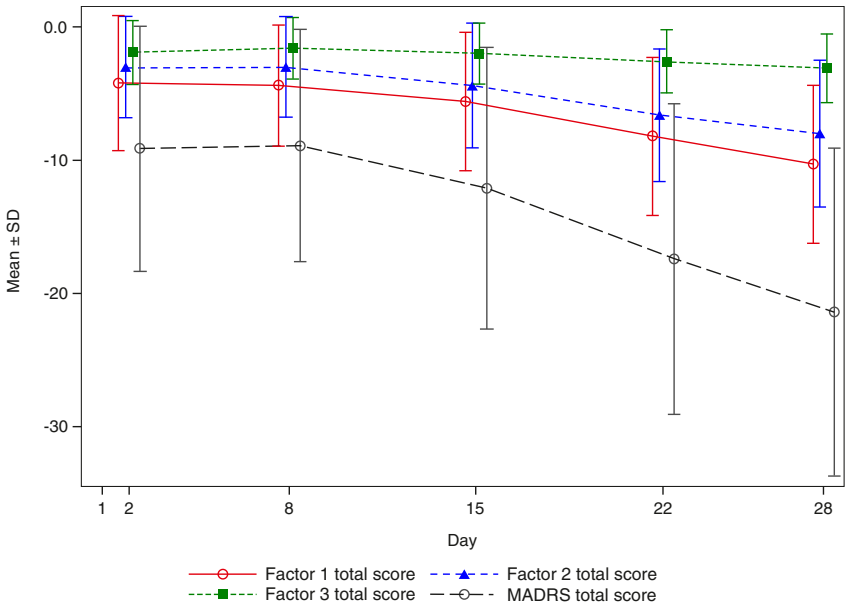

FIGURE 1 Mean Change (±SD) in MADRS Items Factor Scores and Total Score with Esketamine Plus Antidepressant (Observed Cases in TRANSFORM-2). MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation. Factor 1: affective symptoms (apparent sadness, reported sadness, lassitude, inability to feel); Factor 2: anxiety and vegetative symptoms (inner tension, reduced sleep, reduced appetite, and concentration difficulties); Factor 3: hopelessness (pessimistic thoughts and suicidal thoughts)

TABLE 3 Least squares mean (SE) change in MADRS by factor and treatment group

Factor	Esketamine plus antidepressant	Antidepressant plus placebo	Difference between groups[a]			
			LS mean (SE)	95% CI	*p* value	Cohen's *d*[b]
Factor 1						
Day 2	−4.39 (0–0.46)	−2.76 (0.47)	−1.63 (0.66)	−2.93, −0.33	0.014	−0.30
Day 8	−4.49 (0.43)	−3.40 (0.43)	−1.09 (0.61)	−2.29, 0.11	0.076	−0.17
Day 15	−5.66 (0.50)	−4.91 (0.51)	−0.75 (0.71)	−2.16, 0.65	0.293	−0.10
Day 22	−7.97 (0.55)	−6.25 (0.56)	−1.72 (0.79)	−3.27, −0.17	0.030	−0.31
Day 28	−10.18 (0.58)	−8.33 (0.59)	−1.85 (0.83)	−3.48, −0.23	0.026	−0.29
Factor 2						
Day 2	−3.05 (0.34)	−1.91 (0.35)	−1.14 (0.49)	−2.11, −0.16	0.022	−0.31
Day 8	−2.94 (0.31)	−1.38 (0.31)	−1.56 (0.44)	−2.43, −0.70	0.001	−0.43
Day 15	−4.32 (0.40)	−3.18 (0.41)	−1.15 (0.57)	−2.27, −0.03	0.045	−0.26
Day 22	−6.23 (0.44)	−4.41 (0.44)	−1.81 (0.62)	−3.03, −0.60	0.004	−0.43
Day 28	−7.74 (0.47)	−6.01 (0.48)	−1.73 (0.67)	−3.05, −0.41	0.011	−0.35
Factor 3						
Day 2	−1.83 (0.19)	−1.24 (0.20)	−0.59 (0.27)	−1.13, −0.05	0.031	−0.32
Day 8	−1.51 (0.20)	−1.28 (0.20)	−0.23 (0.28)	−0.79, 0.33	0.415	−0.13
Day 15	−1.90 (0.20)	−1.76 (0.20)	−0.14 (0.28)	−0.70, 0.42	0.613	−0.10
Day 22	−2.48 (0.22)	−2.13 (0.22)	−0.35 (0.31)	−0.96, 0.26	0.265	−0.21
Day 28	−3.04 (0.23)	−2.54 (0.23)	−0.50 (0.32)	−1.13, 0.14	0.1261	−0.25

Note: The sum of the item scores produces a MADRS factor score that ranges from 0 to 24 for factor 1 and for factor 2, and from 0 to 12 for factor 3, with a negative change in score indicating improvement. MADRS items factor 1: affective and anhedonic symptoms (apparent sadness, reported sadness, lassitude, inability to feel); MADRS items factor 2: anxiety and vegetative symptoms (inner tension, reduced sleep, reduced appetite, and concentration difficulties); MADRS items factor 3: hopelessness (pessimistic thoughts and suicidal thoughts).

Abbreviations: CI, confidence interval; LS, least squares; SE, standard error.

[a]Analyzed by a repeated measure model for change from baseline value that included treatment group, baseline value, time (visit), and treatment group by time interaction as covariates. An unstructured covariance matrix was used to model the correlation among repeated measures within patients.

[b]Difference between treatment groups [esketamine/antidepressant minus antidepressant/placebo] in factor total score divided by the pooled standard deviation.

Additionally, improvement in scores for all three MADRS item factors was observed at all subsequent timepoints throughout the 28-day double-blind treatment phase, more so for esketamine plus antidepressant than for antidepressant plus placebo, with a statistically significant treatment effect at all timepoints for Factor 2 (anxiety and vegetative symptoms), at days 2, 22, and 28 for Factor 1 (affective and anhedonic symptoms), and day 2 only for Factor 3 (hopelessness), with the latter result limited by the fact that patients with recent significant suicidal ideation (past year) or behavior (6 months) were excluded from enrollment in the TRANSFORM studies. Effect sizes clustered around 0.30, an effect size consistent with that reported for newer antidepressants relative to placebo (Hengartner et al., 2020); however, it is important to keep in mind that the demonstrated benefits in this trial are in comparison to placebo in addition to newly-initiated antidepressant medication, not placebo alone. Overall, these findings reflect the early onset, robust, and sustained effect of esketamine across depressive symptoms in patients with TRD, as compared to placebo nasal spray combined with a newly-initiated oral antidepressant.

Our results are limited by the relatively small size of the TRANSFORM-2 population in the context of PCA. Other limitations include the exclusion of patients with significant psychiatric or medical co-morbidities, including moderate to severe substance use disorder, patients with current or recent suicidal ideation or behavior (studied in a separate program), prior non-response to (es)ketamine in the current episode, and by the lower proportion of non-white patients. An inherent limitation is related to the number of symptoms explored through the 10 items of the MADRS, which does not assess some clinically relevant symptoms in this population (e.g., irritability, impulsivity). And, given that our analyses were conducted on a post hoc exploratory basis, we did not correct for multiple comparisons. Despite these limitations, our findings support a dimensional model of TRD that may help to define relevant patient sub-types.

In conclusion, factor analyses identified three groups of MADRS items, each representing distinct, clinically meaningful dimensions of MDD symptoms. Specifically, MADRS factors 1 and 2 improved over 4 weeks of treatment with esketamine nasal spray. These factors identify meaningful clinical dimensions that may define TRD subtypes. The findings merit further investigation in prospective studies.

ACKNOWLEDGMENTS

We acknowledge Sandra Norris, PharmD, of the Norris Communications Group LLC for medical writing assistance and Ellen Baum, PhD (Janssen Global Services, LLC), for additional editorial support. This work was supported by funding from Janssen Research & Development LLC, Titusville, NJ USA.

CONFLICT OF INTEREST

Drs. Borentain, Gogate, Jamieson, Cabrera, Popova, Wajs, and DiBernardo are employees of Janssen Research & Development, LLC or Jan-Cil Colombia, Drs. Williamson and Daly were employees of Janssen Scientific Affairs, LLC at the time this work was performed, and some authors hold company equity. Dr. Carmody has consulted for Alkermes, Inc., Dr. Trivedi has consulted for or served on the advisory board of Acadia Pharmaceuticals, Inc., Alkermes Inc., Alto Neuroscience Inc., Axsome Therapeutics, GH Research Limited, GreenLight VitalSign6 Inc., Janssen, Merck Sharp & Dohme Corp., Mind Medicine (MindMed) Inc., Neurocrine Biosciences Inc., Orexo US Inc., Otsuka, SAGE Therapeutics, Signant Health, and Titan Pharmaceuticals, Inc. Dr. Trivedi has received research support from the Cancer Prevention and Research Institute of Texas, Janssen Research & Development, LLC, National Institute of Drug Abuse, National Institute of Mental Health, and the Patient-Centered Outcomes Research Institute; and he has received editorial compensation from Oxford University Press.

DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. Requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

ORCID

Stephane Borentain https://orcid.org/0000-0003-3312-1557
Madhukar Trivedi https://orcid.org/0000-0002-2983-1110

REFERENCES

Akil, H., Gordon, J., Hen, R, Javitch, J., Mayberg, H, McEwen, B., Meaney, M. J. & Nestler, E. J. (2018). Treatment resistant depression: A multi-scale, systems biology approach. *Neuroscience & Biobehavioral Reviews*, *84*, 272–288. https://doi.org/10.1016/j.neubiorev.2017.08.019

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5)* (5th ed.). American Psychiatric Association.

Benazzi, F. (2001). Factor analysis of the Montgomery Åsberg Depression Rating Scale in 251 bipolar II and 306 unipolar depressed outpatients. *Progress In Neuro-Psychopharmacology & Biological Psychiatry*, *25*(7), 1369–1376. https://doi.org/10.1016/s0278-5846(01)00190-7

Borentain, S., Gogate, J., Jamieson, C., Fombu, E., Cabrera, P., Périco, C. A. M., Popova, V., Wajs, E., Daly, E. J., Singh, J. B., & DiBernardo, A. (2019). Factor analysis of the MADRS over the course of treatment with esketamine nasal spray in patients with treatment-resistant depression. Poster presented at the 32nd ECNP Congress, 7–10. https://www.ecnp.eu/about-ecnp/history/past-ecnp-meetings/past-congresses/Copenhagen2019/Programme#!abstractdetails/0000393860

Burke, H. M., Davis, M. C., Otte, C., & Mohr, D. C. (2005). Depression and cortisol responses to psychological stress: A meta-analysis. *Psychoneuroendocrinology*, *30*(9), 846–856. https://doi.org/10.1016/j.psyneuen.2005.02.010

Cao, B., Park, C., Subramaniapillai, M., Lee, Y., Iacobucci, M., Mansur, R. B., Zuckerman, H., Phan, L.,& McIntyre, R. S. (2019). The efficacy of vortioxetine on anhedonia in patients with major depressive disorder. *Frontiers in Psychiatry*, *10*, 17. https://doi.org/10.3389/fpsyt.2019.00017

Cassano, G. B., Benvenuti, A., Miniati, M., Calugi, S., Mula, M., Maggi, L., Rucci, P., Fagiolini, A., Perris, F., Frank, E. (2009). The factor structure of lifetime depressive spectrum in patients with unipolar depression. *Journal of Affective Disorders*, *115*(1–2), 87–99. https://doi.org/10.1016/j.jad.2008.09.006

Cassano, G. B., & Savino, M. (1997). Chronic and residual major depressions. In H. S. Akiskal & G. B. Cassano (Eds.), *Dysthymia and the spectrum of chronic depression* (pp. 54–65). The Guilford Press.

Carmody, T. J., Rush, A. J., Bernstein, I. H., Brannan, S., Husain, M. M., & Trivedi, M. H. (2006). Making clinicians lives easier: Guidance on use of the QIDS self-report in place of the MADRS. *Journal of Affective Disorders*, *95*(1–3), 115–118. https://doi.org/10.1016/j.jad.2006.03.024

Carmody, T. J., Rush, A. J., Bernstein, I., Warden, D., Brannan, S., Burnham, D., Woo, A., & Trivedi, M. H. (2006). The Montgomery Åsberg and the Hamilton ratings of depression: A comparison of measures. *European Neuropsychopharmacology*, *16*(8), 601–611. https://doi.org/10.1016/j.euroneuro.2006.04.008

Fabrigar, L. R., Wegener, D. T., MacCallum, R. C., & Strahan, E. J. (1999). Evaluating the use of exploratory factor analysis in psychological research. *Psychological Methods*, *4*(3), 272–299. https://doi.org/10.1037/1082-989X.4.3.272

Fawcett, J., Clark, D. C., Scheftner, W. A., & Gibbons, R. D. (1983). Assessing anhedonia in psychiatric patients. *Archives of General Psychiatry*, *40*(1), 79–84. https://doi.org/10.1001/archpsyc.1983.01790010081010

Fedgchin, M., Trivedi, M, Daly, E. J., Melkote, R., Lane, R., Lim, P., Vitagliano, D., Blier, P., Fava, M., Liebowitz, M., Ravindran, A., Gaillard, R., Ameele, H. V. D, Preskorn, S., Manji, H., Hough, D., Drevets, W. C., & Singh, J. B. (2019). Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: Results of a randomized, double-blind, active-controlled study (TRANSFORM-1). *The International Journal of Neuropsychopharmacology*, *22*(10), 616–630. https://doi.org/10.1093/ijnp/pyz039

Fried, E. I., & Nesse, R. M. (2015). Depression is not a consistent syndrome: An investigation of unique symptom patterns in the STAR*D study. *Journal of Affective Disorders*, *172*, 96–102. https://doi.org/10.1016/j.jad.2014.10.010

Galinowski, A., & Lehert, P. (1995). Structural validity of MADRS during antidepressant treatment. *International Clinical Psychopharmacology*, *10*(3), 157–161. https://doi.org/10.1097/00004850-199510030-00004

Hawton, K., Casañas, I., Comabella, C., Haw, C., & Saunders, K. (2013). Risk factors for suicide in individuals with depression: A systematic

review. *Journal of Affective Disorders*, *147*(1–3), 17–28. https://doi.org/10.1016/j.jad.2013.01.004

Hengartner, M. P., Jakobsen, J. C., Sorensen, A., & Plöderl, M. (2020). Efficacy of new-generation antidepressants assessed with the montgomery-Åsberg depression rating scale, the gold standard clinician rating scale: A meta-analysis of randomised placebo-controlled trials. *PLoS One*, *15*(2), e0229381. Published 2020 Feb 26. https://doi.org/10.1371/journal.pone.0229381

Hu, L., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling*, *66*, 1–55.

Johnson, K. M., Devine, J. M., Ho, K. F., Howard, K. A., Saretsky, T. L., & Jamieson, C. A. (2016). Evidence to support Montgomery-Åsberg Depression Rating Scale administration every 24 hours to assess rapid onset of treatment response. *Journal of Clinical Psychiatry*, *77*(12), 1681–1686. https://doi.org/10.4088/JCP.15m10253

Kline, R. B. (2016). *Principles and practice of structural equation modeling* (4th ed.). Guilford Press.

Lai, K., & Green, S. B. (2016). The problem with having two watches: Assessment of fit when RMSEA and CFI disagree. *Multivariate Behavioral Research*, *51*(2–3), 220–239. https://doi.org/10.1080/00273171.2015.1134306

Medicines Agency, European Esketamine nasal spray summary of product characteristics. Accessed 1 July 2021. https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_en.pdf. Accessed 1 July 2021.

Montgomery, S. A., & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, *134*, 382–389. https://doi.org/10.1192/bjp.134.4.382

Oquendo, M. A., Barrera, A., Ellis, S. P., Li, S., Burke, A. K., Grunebaum, M., Endicott, J., & John Mann, J. (2004). Instability of symptoms in recurrent major depression: A prospective study. *American Journal of Psychiatry*, *161*(2), 255–261. https://doi.org/10.1176/appi.ajp.161.2.255

Peralta, V., & Cuesta, M. J. (2001). How many and which are the psychopathological dimensions in schizophrenia? Issues influencing their ascertainment. *Schizophrenia Research*, *49*(3), 269–285. https://doi.org/10.1016/s0920-9964(00)00071-2

Popova, V, Daly, E. J., Trivedi, M., Cooper, K., Lane, R., Lim, P., Mazzucco, C., Hough, D., Thase, M. E., Shelton, R. C., Molero, P., Vieta, E., Bajbouj, M., Manji, H., Drevets, W. C., & Singh, J. B. (2019). 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. *American Journal of Psychiatry*, *176*(6), 428–438. https://doi.org/10.1176/appi.ajp.2019.19020172

Quilty, L. C., Robinson, J. J., Rolland, J. P., Fruyt, F. D., Rouillon, F., & Bagby, R. M. (2013). The structure of the Montgomery-Åsberg depression rating scale over the course of treatment for depression. *International Journal of Methods in Psychiatric Research*, *22*(3), 175–184. https://doi.org/10.1002/mpr.1388

Rush, A. J., Carmody, T., & Reimitz, P.-E. (2000). The inventory of depressive Symptomatology (IDS): Clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. *Int Methods Psychiatr Res*, *9*(2), 45–59.

Rush, A. J., Gullion, C. M., Basco, M. R., & JarrettTrivedi, R. B. M. H. (1996). The inventory of depressive Symptomatology (IDS): Psychometric properties. *Psychological Medicine*, *26*(3), 477–486. https://doi.org/10.1017/s0033291700035558

Russell, D. W. (2002). In search of underlying dimensions: The use (and abuse) of factor analysis in the personality and social psychology bulletin. *Personality and Social Psychology Bulletin*, *12*, 1629–1646.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The mini-international neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59*(Suppl 20), 22–33. quiz 34-57.

Spravato™ (esketamine) nasal spray Prescribing Information. © 2020 Janssen Pharmaceutical Companies.

Suzuki, A., Aoshima, T., Fukasawa, T., Yoshida, K., Higuchi, H., Shimizu, T., & Otani, K. (2005). A three-factor model of the MADRS in major depressive disorder. *Depression and Anxiety*, *21*(2), 95–97. https://doi.org/10.1002/da.20058

Uher, R., Farmer, A., Maier, W., Rietschel, M., Hauser, J., Marusic, A., Mors, O., Elkin, A., Williamson, R. J., Schmael, C., Henigsberg, N., Perez, J., Mendlewicz, J., Janzing, J. G., Zobel, A., Skibinska, M., Kozel, D., Stamp, A. S., Bajs, M., …, & Aitchison, K. J. (2008). Measuring depression: Comparison and integration of three scales in the GENDEP study. *Psychological Medicine*, *38*(2), 289–300. https://doi.org/10.1017/S0033291707001730

Vrieze, E., Demyttenaere, K., Bruffaerts, R., Hermans, D., Pizzagalli, D. A., Sienaert, P., Hompes, T., de Boer, P., Schmidt, M., & Claes, S. (2014). Dimensions in major depressive disorder and their relevance for treatment outcome. *Journal of Affective Disorders*, *155*, 35–41. https://doi.org/10.1016/j.jad.2013.10.020

Wheaton, B., Muthen, B., Alwin, D. F., & Summers, G. (1977). Assessing reliability and stability in panel models. *Sociological Methodology*, *8*, 84–136. https://doi.org/10.2307/270754

Williamson, D., Brown, E., Perlis, R. H., Ahl, J., Baker, R. W., & Tohen, M. (2006). Clinical relevance of depressive symptom improvement in bipolar I depressed patients. *Journal of Affective Disorders*, *92*(2–3), 261–266. https://doi.org/10.1016/j.jad.2006.02.011

Xia, Y., & Yang, Y. (2019). RMSEA, CFI, and TLI in structural equation modeling with ordered categorical data: The story they tell depends on the estimation methods. *Behavior Research Methods*, *51*, 409–428. https://doi.org/10.3758/s13428-018-1055-2

Zimmerman, M., Ellison, W., Young, D., Chelminski, I., & Dalrymple, K. (2015). How many different ways do patients meet the diagnostic criteria for major depressive disorder? *Comprehensive Psychiatry*, *56*, 29–34. https://doi.org/10.1016/j.comppsych.2014.09.007

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Borentain, S., Gogate, J., Williamson, D., Carmody, T., Trivedi, M., Jamieson, C., Cabrera, P., Popova, V., Wajs, E., DiBernardo, A., & Daly, E. J. (2022). Montgomery-Åsberg Depression Rating Scale factors in treatment-resistant depression at onset of treatment: Derivation, replication, and change over time during treatment with esketamine. *International Journal of Methods in Psychiatric Research*, *31*(4), e1927. https://doi.org/10.1002/mpr.1927