

Real-world effectiveness and treatment duration by psychiatric comorbidity status: esketamine nasal spray for treatment-resistant depression

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Introduction

- There is a high prevalence of psychiatric comorbidity among people with treatment resistant depression (TRD),¹ underscoring the importance of effective and sustainable therapy for TRD in the context of other psychiatric diagnoses.
- Esketamine nasal spray (NS), in combination with a selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI), is indicated for TRD in adults lacking a response to ≥2 pharmacological treatments in the current moderate to severe depressive episode.²
- Existing evidence from small-scale studies suggests that in patients with TRD and comorbid post-traumatic stress disorder (PTSD) or anxiety disorder, esketamine NS treatment improves major depressive severity, symptoms and health-related quality of life.^{3–6}
- The Esketamine CoHort (ECHO) study investigated esketamine NS effectiveness and safety in real-world clinical settings, offering an opportunity to investigate these outcomes in a large real-world cohort of patients with TRD and psychiatric comorbidities.
- Here, we evaluate the effectiveness of esketamine NS, by psychiatric comorbidity status, in adults with TRD from real-world clinical settings, using data from the ECHO study.

Methods

- ECHO was a long-term, prospective, non-interventional study comprising a variable duration treatment period and a 6-month post-treatment follow-up period.
- Eligible patients were adults diagnosed with TRD from Belgium, Germany, Israel, Italy, Netherlands, Spain and Sweden prescribed esketamine NS per local clinical practice independent of study participation.
- Effectiveness in the treatment period was assessed by current psychiatric comorbidity status (yes/no) and presence of current specific psychiatric comorbidities at baseline (anxiety disorder[s], PTSD, obsessive compulsive disorder [OCD] and any personality disorder[s]).
 - Anxiety disorders included panic disorder, social anxiety disorder (social phobia) and generalised anxiety disorder.
- Outcomes included treatment duration and dosing, and assessments of effectiveness from baseline up to 48 weeks in the treatment period, including mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score, and the proportion of patients achieving remission (MADRS total score ≤10) and response (≥50% improvement in MADRS from treatment initiation).
- Treatment duration and dosing data were summarised as means (standard deviation [SD]), change from baseline in MADRS scores with 95% confidence intervals (CIs), and remission and response outcomes as frequencies and percentages.

Results

Patient population

- Of the 570 patients who started the treatment period, 568 patients had their comorbidity status assessed at baseline, 259 (45.6%) of which had a current psychiatric comorbidity.
 - The most common current psychiatric comorbidities were personality disorder(s) (n=45; 7.9%), generalised anxiety disorder (n=41; 7.2%) and PTSD (n=40; 7.0%).
- Patients had severe and chronic TRD at baseline as indicated by their MADRS scores, long duration of current episode and high number of previous treatment failures (**Table 1**).
 - Measures of disease severity (MADRS and SDS scores) were numerically highest in patients with current comorbid PTSD.
 - Treatment resistance was high across all comorbidity subgroups; patients with current anxiety disorder(s) had the numerically highest number of treatment failures in the current episode.

Treatment duration and dosing

- In the overall cohort, patients received esketamine NS for an average of ~9 months; approximately a quarter of patients received treatment for over a year (**Table 2**).
 - Treatment duration was numerically longer for patients with current PTSD or OCD compared with other comorbidities.
- The mean daily dose of esketamine NS was similar across current psychiatric comorbidity groups.

Effectiveness

- MADRS total scores at baseline in patients with and without psychiatric comorbidities were similar, and both groups showed similar clinically-meaningful and statistically significant (p<0.001 at all timepoints) early improvements and through Week 48 (**Figure 1A**).
 - All specific current psychiatric comorbidity subgroups demonstrated statistically significant reductions (p<0.01 at all timepoints) from baseline in MADRS score from Week 2, which continued to Week 48 (**Figure 1B**).
- The proportion of patients achieving remission and response generally increased over time in patients with and without current psychiatric comorbidities (**Figures 2A and 2B**); among patients with current psychiatric comorbidities, rates peaked at Week 36 and were numerically lower at Week 48.
 - Remission and response rates were similar regardless of current psychiatric comorbidity status. However, patients with PTSD and OCD had lower Week 48 remission and response rates (10.0–11% and 20.0–33.3%, respectively) than patients in other subgroups (21.1–30.0% and 52.6–60.0%, respectively).

Strengths and limitations

- Data from ECHO represent the largest real-world dataset for esketamine NS, and reflect the complexity of the real-world population of patients with TRD, although limitations include the small subgroup size for certain comorbidities, patient dropout and lack of comparator arm.

Table 1. Demographics, baseline characteristics and psychiatric history

Mean (SD), unless otherwise specified	Overall cohort (N=570)	No current psychiatric comorbidity (N=309)	Any current psychiatric comorbidity (N=259)	Current anxiety disorder(s) ^a (N=89)	Current PTSD (N=40)	Current OCD (N=28)	Current personality disorder(s) ^b (N=45)
Age, years	48.9 (13.8)	51.7 (13.0)	45.7 (14.0)	44.3 (14.1)	41.0 (12.0)	37.3 (11.0)	43.6 (13.4)
Sex, female, n (%)	296 (51.9)	156 (50.5)	139 (53.7)	47 (52.8)	26 (65.0)	13 (46.4)	29 (64.4)
Age at first MDD diagnosis, years	32.8 (13.7)	35.2 (13.9)	30.0 (12.9)	29.5 (13.3)	27.6 (11.5)	23.5 (7.1)	27.3 (10.9)
Total number of depressive episodes	4.7 (5.6)	4.6 (5.8)	4.9 (5.4)	4.8 (5.4)	5.4 (6.3)	6.6 (8.7)	5.7 (7.1)
Duration of current episode, years	3.3 (4.4)	3.3 (4.0)	3.3 (4.8)	3.8 (4.0)	5.1 (8.4)	2.1 (2.0)	3.0 (3.0)
MADRS score	33.3 (6.8)	32.7 (6.5)	33.9 (7.0)	34.1 (7.3)	35.4 (7.3)	35.1 (7.3)	34.5 (7.2)
SDS score	23.9 (5.1)	23.6 (5.5)	24.2 (4.7)	24.7 (4.7)	25.2 (3.8)	23.7 (5.7)	24.8 (4.6)
Number of treatment failures in current episode	3.8 (1.9)	3.8 (2.0)	3.8 (1.8)	3.9 (1.9)	3.6 (2.0)	3.1 (0.8)	3.2 (1.4)

^aIncluding panic disorder, social anxiety disorder (social phobia) and generalised anxiety disorder; ^bIncluding any personality disorder.

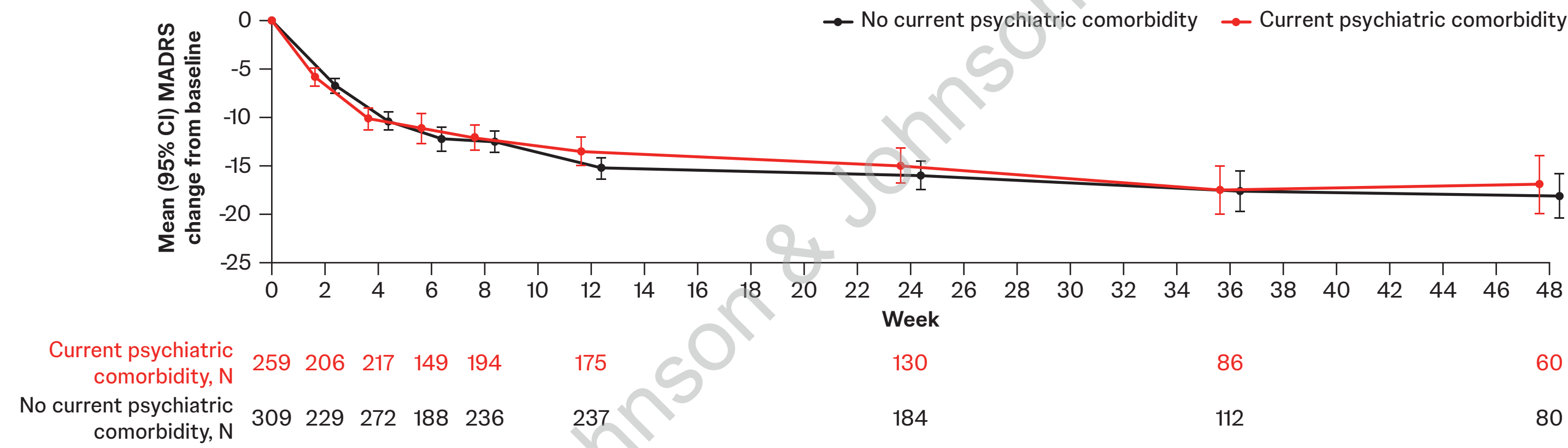
Table 2. Treatment duration and dosing in patients with current psychiatric comorbidities

Mean (SD)	Overall cohort (N=570)	No current psychiatric comorbidity (N=309)	Any current psychiatric comorbidity (N=259)	Current anxiety disorder(s) ^a (N=89)	Current PTSD (N=40)	Current OCD (N=28)	Current personality disorder(s) ^b (N=45)
Treatment duration, days	266.5 (279.6)	271.9 (263.6)	255.6 (294.1)	227.1 (264.7)	310.3 (329.3)	309.4 (379.3)	165.6 (214.8)
Dose, mg	71.2 (13.6)	70.8 (13.5)	71.9 (13.6)	71.3 (13.7)	76.5 (10.1)	79.5 (6.6)	70.5 (16.3)
Total treatment duration, months							
<3	174 (30.5)	81 (26.2)	93 (35.9)	38 (42.7)	10 (25.0)	12 (42.9)	21 (46.7)
3–6	100 (17.5)	59 (19.1)	41 (15.8)	12 (13.5)	7 (17.5)	2 (7.1)	10 (22.2)
6–9	114 (20.0)	64 (20.7)	50 (19.3)	17 (19.1)	11 (27.5)	3 (10.7)	3 (6.7)
9–12	50 (8.8)	31 (10.0)	19 (7.3)	5 (5.6)	2 (5.0)	5 (17.9)	8 (17.8)
>12	132 (23.2)	74 (23.9)	56 (21.6)	17 (19.1)	10 (25.0)	6 (21.4)	3 (6.7)

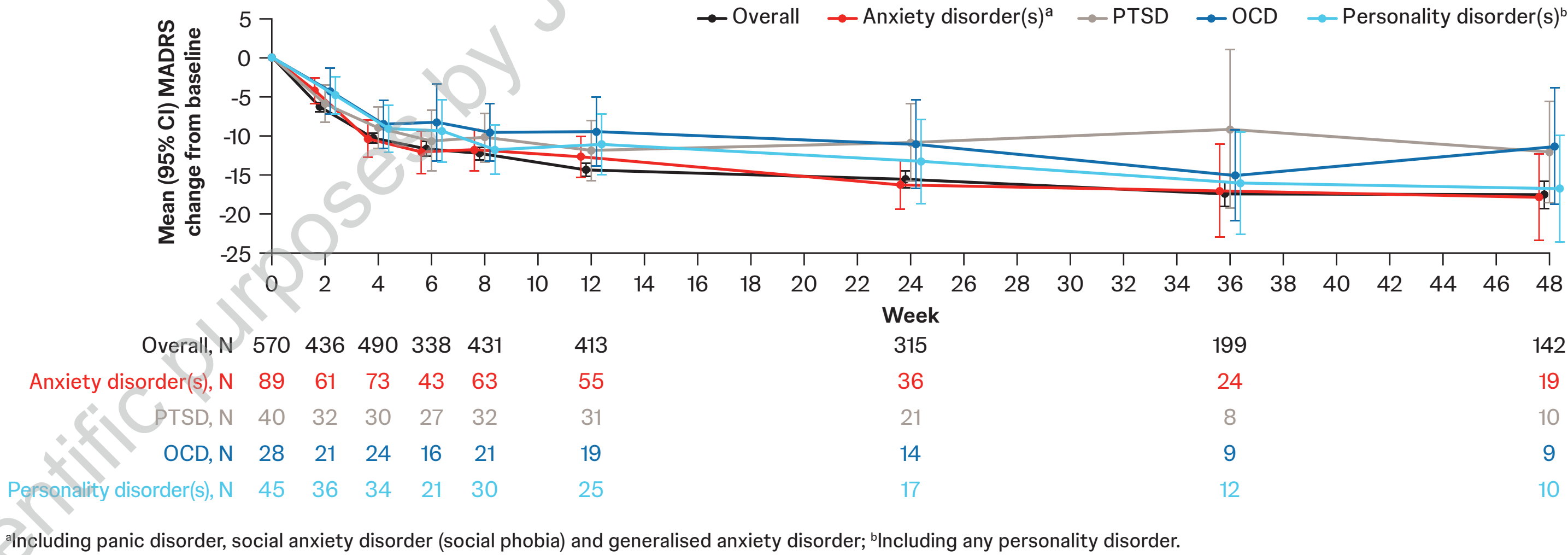
^aIncluding panic disorder, social anxiety disorder (social phobia) and generalised anxiety disorder; ^bIncluding any personality disorder.

Figure 1. Mean (95% CI) change from baseline in MADRS total score

A) Stratified by current psychiatric comorbidity status



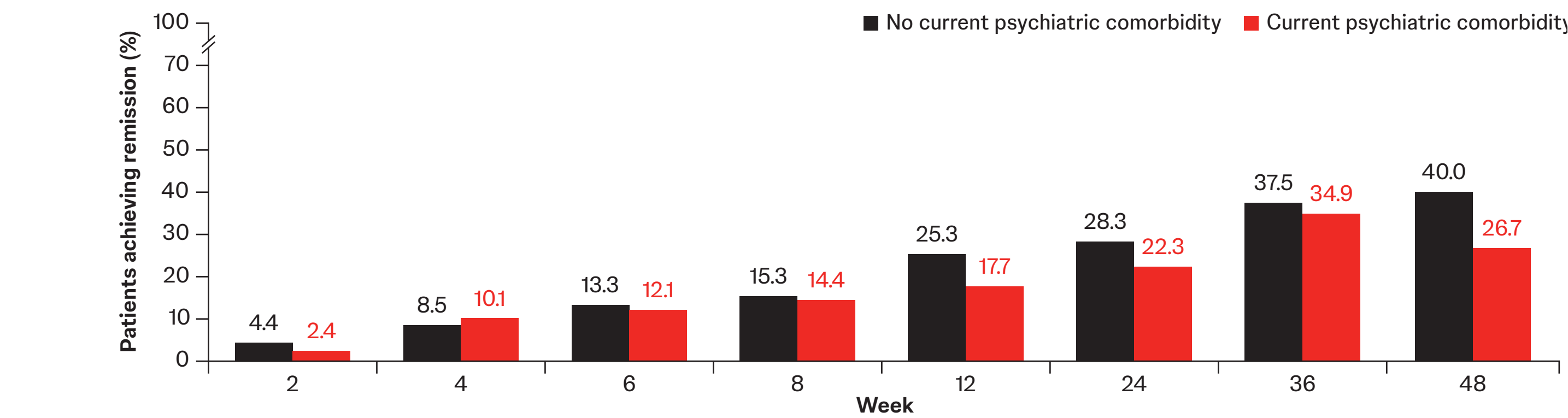
B) Stratified by specific current psychiatric comorbidities present at baseline



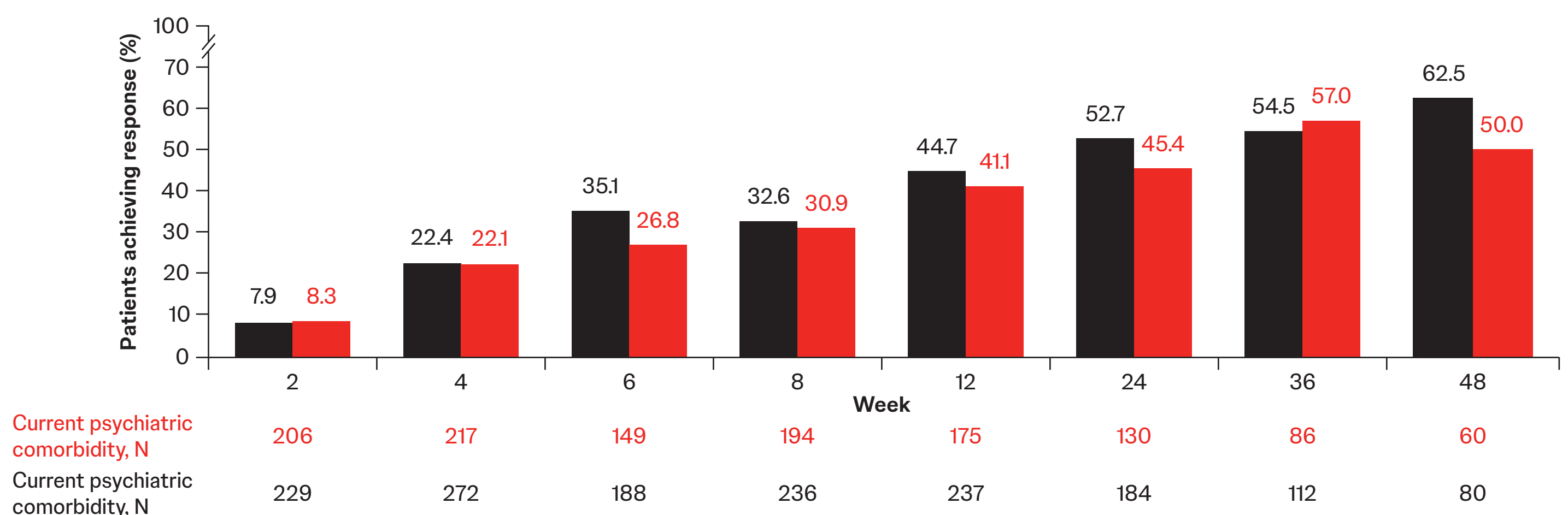
^aIncluding panic disorder, social anxiety disorder (social phobia) and generalised anxiety disorder; ^bIncluding any personality disorder.

Figure 2. Achievement of remission and response in patients with and without a current psychiatric comorbidity

A) Proportion of patients achieving remission^a



B) Proportion of patients achieving response^b



^aMADRS total score ≤10; ^b≥50% improvement in MADRS from treatment initiation.

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Key takeaway



- These prospective real-world data provide evidence to support the use of esketamine NS in the treatment of patients with TRD and psychiatric comorbidities, and may be useful for informing treatment decision-making in clinical practice for patients with TRD.

Conclusions



- In this prospective real-world population of patients with TRD, nearly half (45.6%) had a current comorbidity at baseline, highlighting the clinical complexity of patients with TRD treated with esketamine NS in these settings.
- Patients with comorbid PTSD and OCD received generally longer treatment with esketamine NS than other patients.
- Esketamine NS treatment was effective regardless of whether patients had psychiatric comorbidities, with rapid and continued, clinically meaningful improvements from baseline in depressive symptoms through 48 weeks of treatment, indicating broad treatment effectiveness.
- For patients with specific current psychiatric comorbidities, esketamine NS effectiveness may vary across conditions, although all groups demonstrated reductions from baseline in depressive symptoms.

Abbreviations

CI: confidence interval; ECHO: Esketamine CoHort; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NS: nasal spray; OCD: obsessive compulsive disorder; PTSD: post-traumatic stress disorder; SD: standard deviation; SDS: Sheehan Disability Scale; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TRD: treatment resistant depression.

Author contributions

Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: VM, BTB, KF, YK, SK, JMO, IT, CvH, GR; drafting of the publication, or reviewing it critically for important intellectual content: VM, BTB, KF, YK, SK, JMO, IT, CvH, GR; final approval of the publication: VM, BTB, KF, YK, SK, JMO, IT, CvH, GR.

Disclosures

VM: Served on advisory boards, received consulting fees and speaker's honoraria from Johnson & Johnson (Europe and Italy), Lundbeck, Otsuka, Teva Europe and Teva Italia; received travel grants from Angelini, Johnson & Johnson, Lundbeck, Otsuka and Teva. BTB: Received consulting fees for roles with the National Health and Medical Research Council, Australia; received honoraria from Angelini, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, GH Research, Johnson & Johnson, LivaNova, Lundbeck, Medscape, Otsuka, Pfizer, Roche, Servier, Sumitomo Dainippon Pharma, Sunovion, Viartis and Wyeth; served on advisory boards for Biogen, Boehringer Ingelheim, GH Research, Janssen-Cilag, LivaNova, Lundbeck, Medscape, Novartis, Viartis and Otsuka; received research grants from private industries or non-profit funds from AstraZeneca, Janssen, Lundbeck and Sanofi-Synthelabo; received research grants from the BMBF and BMG, Germany, the DFG, Germany, EraPerMed, Horizon Europe 2021, Medical Research Future Fund (MRFF, Australia), the National Health and Medical Research Council (NHMRC, Australia), and the Wellcome Trust (UK); received research grants from the Fay Fuller Foundation and James & Diana Ramsay Foundation, Adelaide. KF: Received honoraria from Eli Lilly, Janssen Cilag and Sigma and travel support from Brainsway, Janssen Cilag and Liva-Nova. YK, IT, CvH: Employees of Johnson & Johnson; hold Johnson & Johnson company stock/stock options. SK: Participated in advisory boards and received speaker's honoraria over the last 3 years from ARISTO Pharma, Johnson & Johnson, Medice and Otsuka; participated in clinical studies on esketamine. JMO: Received grants and served as consultant, advisor or CME speaker for AstraZeneca, Bristol Myers Squibb, Eli Lilly and Company, Glaxo-Smith-Kline, Johnson & Johnson, Lundbeck, Novartis, Otsuka, Pfizer and Sanofi-Aventis. GR: Speaker/consultant for Angelini, Johnson & Johnson, Lundbeck, Neuraxpharm, Otsuka and Rovi.

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