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Research Directions

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Real-world esketamine treatment for treatment-resistant depression: an analysis of comorbid post-traumatic stress disorder, comorbid anxiety disorder and line of therapy subgroups

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Abstract

This paper describes subgroup analyses of a recent real-world study examining the impact of esketamine nasal spray combined with a newly initiated oral antidepressant (OAD) on quality-of-life and depression severity in participants with treatment-resistant depression (TRD). Patients with TRD, defined as major depressive disorder in adults who have not responded adequately to ≥2 different OADs of adequate dose and duration to treat the current depressive episode, were recruited from the esketamine early access program in Australia and New Zealand. Subgroups were defined by prior antidepressant medications received in the current depressive episode (2, 3–5, or ≥6) and post-traumatic stress disorder (PTSD) or anxiety disorder comorbidity (with or without). Comorbid PTSD or anxiety disorder was identified by treating psychiatrists. Outcome measurements included Assessment of Quality-of-Life (AQoL-8D) and Hamilton Depression Rating (HAM-D) scales. From baseline to Week 16, all subgroups saw significant improvements in AQoL-8D and HAM-D. There was no statistical difference between outcome improvements for participants with or without comorbid anxiety or PTSD. When separated by prior therapy, participants with 2 prior therapies demonstrated the greatest outcome improvements. Real-world esketamine treatment in conjunction with a newly initiated OAD benefits real-world participants with TRD and comorbid anxiety or PTSD, regardless of previously failed treatments.

Introduction

Depression is the largest contributor to disability and suicide worldwide, with over 300 million individuals affected by major depressive disorder (MDD) globally (Jamieson et al. 2023). Over 1.3 million people in Australia and over 200 thousand people in New Zealand live with a depressive disorder (World Health Organization 2017). In Australia, 4.9% of people experienced a depressive episode and 1.5% experienced dysthymia over 12 months in 2020 to 2022 (Australian Bureau of Statistics 2023). While treatment for depression is effective in many people, an estimated one-third of people with MDD have treatment-resistant depression (TRD) (Al-Harbi 2012; Malhi et al. 2021; World Health Organization 2017). The Royal Australian and New Zealand College of Psychiatrists defines TRD as depression that fails to respond to 2 or more antidepressants of an adequate dose and duration (Al-Harbi 2012; Malhi et al. 2015).

TRD is a multifaceted condition, with many factors contributing to treatment resistance and disease burden (Rost et al. 2024; Souery et al. 2007). The burden of TRD includes progressive social and functional decline and substantial economic burden due to extensive use of healthcare resources and patients' incapacity to work. In the real-world, patients with TRD experience moderate to severe depressive symptoms, low health-related quality-of-life (QoL) and multiple instances of failed treatment response, corresponding to a high burden of disease (Oliveira-Maia et al. 2024). Results of a European real-world cohort study found all participants (n = 411) to have at least moderate depression severity, with 45.7% of participants having experienced ≥3 prior lines of antidepressant treatment over a maximum follow-up period of 21 months. Participants were found to have to have experienced poor QoL (Heerlein et al. 2021).

The impacts of TRD increase with time and treatment failure. Extended ineffective treatment prolongs the suffering of patients with TRD, diminishes their expectations of treatment effectiveness and potentially contributes to further lack of response (Al-Harbi 2012; Halaris et al. 2021; Leuchter et al. 2009; Malhi et al. 2015; Oluboka et al. 2018). Depression severity and the

risk of relapse is increased in patients who have failed prior lines of therapy (Oliveira-Maia et al. 2024). The Sequenced Treatment Alternatives to Relieve Depression (STAR * D) report, which enrolled 4,041 participants, demonstrated a higher rate of relapse in participants with more prior treatments over a follow-up period of 1 year. Relapse in this study was defined as a Quick Inventory of Depressive Symptomatology (QIDS) self-report score of ≥11, corresponding to moderate to very severe depression (Rush et al. 2006). Increasing resistance in TRD is also associated with a decrease in patient QoL (Johnston et al. 2019). In STAR * D, patients who did not experience remission after up to 4 treatment steps experienced a significant decline in QoL (IsHak et al. 2015).

TRD may be complicated further by comorbid psychiatric conditions which contribute to treatment resistance (Al-Harbi 2012; Malhi et al. 2015; McIntyre et al. 2023; Rothärmel et al. 2022). Post-traumatic stress disorder (PTSD) and anxiety disorders are common comorbidities in patients with MDD. The prevalence of comorbid PTSD and MDD ranges from 30% to 50% (Angelakis and Nixon 2015). Within a given 12-month period, comorbid anxiety disorders are experienced by 41.6% of the MDD population (Kalin 2020).

In patients with TRD, comorbid PTSD (Angelakis and Nixon 2015; Flory and Yehuda 2015; Kalin 2020; McIntyre et al. 2023) and comorbid anxiety disorder (Daly et al. 2021; Kalin 2020; McIntyre et al. 2023) can increase depression symptoms, depression severity and suicidality, while reducing response and adherence to TRD treatment, conferring high patient burden and contributing to treatment resistance. Considering the impact of comorbid PTSD and anxiety disorder in patients with depression, further research and more therapeutic options are needed (Angelakis and Nixon 2015; Daly et al. 2021).

Esketamine is a novel antidepressant registered by both the Australian Therapeutic Goods Administration (TGA) and New Zealand Medicines and Medical Devices Safety Authority (Medsafe) for use in TRD (Medsafe 2019; Therapeutic Goods Administration 2021), based on the results of a comprehensive clinical trial development program demonstrating efficacy and tolerability (Daly et al. 2021; Jamieson et al. 2023; Popova et al. 2019; Wajs et al. 2020). The cited evidence demonstrates the benefit of esketamine in complex patients with TRD, including those with psychiatric comorbidities and multiple prior lines of therapy. In the TRANSFORM-2 clinical study, patients with TRD were treated with esketamine nasal spray and an oral antidepressant (OAD) compared to placebo nasal spray and an OAD. In the esketamine arm, 89% of participants had received 1 to 2 prior antidepressant medications, with 11% of participants receiving ≥3 previous antidepressant medications. Comorbid anxiety symptoms were exhibited in 73% of these participants and 15% had an anxiety disorder, including PTSD, at baseline (Daly et al. 2021). Significant improvements in QoL and health status were observed in the esketamine patient population when compared to placebo (Jamieson et al. 2023). Additionally, a significant reduction in depression severity score and higher rates of response and remission were seen with esketamine treatments in patients both with and without comorbid anxiety, compared to placebo (Daly et al. 2021). An open-label, retrospective, single arm study in 11 patients with TRD and comorbid PTSD demonstrated an improvement in depression symptoms with esketamine treatment (Rothärmel et al. 2022). A recent real-world cohort of French patients with TRD, who were resistant to an average of 4.2 previous antidepressants, showed esketamine efficacy comparable to trends seen in Phase 3 trials (Samalin et al. 2022).

Due to the complexity of TRD, clinical management should involve early and effective treatment, optimised for individual patient characteristics (Oluboka et al. 2018). Characteristics including multiple failed lines of therapy, comorbid anxiety disorders and comorbid PTSD can complicate TRD and be detrimental for treatment outcomes. Therefore, study of TRD treatments, such as esketamine, in these subgroups is important. Additionally, real-world evidence is important to allow translation of evidence into clinical decision-making and to obtain insights into patient management in clinical practice (Koch et al. 2024; Oliveira-Maia et al. 2024). While esketamine has demonstrated utility in treating across the complexities of TRD, in Australia and New Zealand this evidence is limited to clinical trial settings. Real-world evidence for esketamine efficacy in these populations is lacking.

A recently published real-world evidence study examined esketamine treatment in conjunction with a newly initiated OAD in patients with TRD in Australia and New Zealand. The primary objective was to describe the change from baseline to 16 weeks after esketamine treatment using the Australian Quality-of-Life-8D (AQoL-8D) questionnaire. The secondary objectives included changes from baseline to 16 weeks after esketamine treatment in work productivity metrics (WPAI), Hamilton Depression (HAM-D) and Treatment Satisfaction Questionnaire for Medication (TSQM) assessments. Esketamine treatment was found to confer significant improvements in QoL and depression severity score at 16 weeks of treatment (Hopwood et al. 2024). PTSD and anxiety disorders were the most frequently reported comorbidities in this full analysis and approximately 77% of participants had received at least 3 prior lines of therapy (Hopwood et al. 2024).

This paper aimed to analyse the impact of real-world esketamine nasal spray treatment in conjunction with a newly initiated OAD for patients with TRD who have comorbidities and have failed multiple prior lines of therapy. This study aimed to investigate this question through analysis of prespecified post-hoc subgroups from the full real-world study. Subgroups were defined as participants with TRD who had received 2, 3–5 or ≥6 prior lines of antidepressant medications and who had comorbid PTSD or anxiety disorder. The primary objective of the subgroup analyses presented in this paper was to assess change in QoL from baseline to Week 16, with a secondary objective to assess change in depression severity from baseline to Week 16.

Materials and methods

Study design

This is a post-hoc subgroup analysis of a prospective, multi-site, non-interventional study of esketamine nasal spray treatment in conjunction with a newly initiated OAD (Hopwood et al. 2024). The study treatment was aligned with the registered indication for esketamine treatment in both Australia and New Zealand (Medsafe 2019; Therapeutic Goods Administration 2021) and has been referred to henceforth as esketamine+OAD treatment. The subgroup analyses were pre-specified in the study protocol, which was approved by Bellberry Limited Human Research Ethics Committee (HREC) 2021-06-606-AF-PRE-1.

Participants

This study enrolled participants with TRD included in the esketamine early access program (EAP), supported by Johnson and Johnson Australia New Zealand (then Janssen-Cilag Australia and New Zealand). These participants were eligible for esketamine+

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OAD treatment through the TGA and MedSafe indications, which define TRD as MDD in adults who have not responded adequately to at least 2 different OADs of adequate dose and duration to treat the current depressive episode. Participants were enrolled from 8 specialty psychiatry clinics in Australia (7 sites) and New Zealand (1 site). Participants were excluded if they had a diminished capacity for decision making in the opinion of the investigator, were under 18 years old, or were not fluent in English. Comorbid PTSD and/or anxiety disorder were identified in participants via clinical assessment by their treating psychiatrist using the DSM-V criteria (American Psychiatric Association 2013). Those participants with comorbid PTSD or anxiety disorder who completed both baseline and Week 16 assessments were included in this subgroup analysis. Written informed consent was obtained from all participants.

Assessments

AQoL-8D data was collected directly from consenting participants using questionnaires which were administered to participants online through a mobile application (ClaimIt). This enabled remote participation in the study. Participants' HAM-D scores were assessed by the study investigator in person and uploaded through the ClaimIt application.

Assessment of quality-of-Life-8D (AQoL-8D)

The AQoL-8D questionnaire has been contextualised and validated for the assessment of QoL in Australian patients with any disease (Richardson et al. 2013). The questionnaire contains 35 items which assess physical and psychosocial QoL, considering independent living, relationships, mental health, coping, pain, senses, happiness and self-worth (Centre for Health Economics Monash University 2017). A high AQOL-8D score indicates a lower QoL. The AQoL-8D was used in this study to assess the primary objective of change in QoL from baseline to Week 16. AQoL-8D scores were reported by the participants at baseline and Week 16 of treatment. In these subgroup analyses, unweighted (psychometric) AQoL-8D scores were calculated.

Hamilton depression rating scale index (HAM-D)

HAM-D is a widely used clinician-administered depression assessment scale, containing 17 items relating to depression symptoms the patient has experienced over the previous week. These items include depressed mood, feelings of guilt, feeling suicidal, insomnia, work and interests, retardation, agitation, psychic anxiety, somatic anxiety, appetite, fatigue, sexual interest, hypochondriasis, weight loss and insight. A high HAM-D score indicates high depression severity. In this study, HAM-D thresholds were used to indicate mild (10 to 13), mild to moderate (14 to 17) and moderate to severe depression (>17) (Hamilton 1960; Hamilton 1967). HAM-D was used to assess the secondary objective of change in depression severity from baseline to Week 16. Participants' HAM-D scores were assessed at baseline and Week 16 of treatment. The minimum clinically important difference for HAM-D ranges from 3 to 5 points (Hengartner and Plöderl 2022).

Statistical analysis

For both the primary endpoint (AQoL-8D-8D) and secondary endpoint (HAM-D) evaluated in these subgroup analyses, mean score changes from baseline to Week 16 were calculated and summarised descriptively. The significance of score changes were evaluated using a multivariate linear regression model with p-values considered significant at 95% level ($p < 0.05$). Two-sided confidence intervals (CI) were calculated at the 95% confidence level. Continuous variables were summarised as the number of observations, mean, median and standard deviation (SD). Categorical variables were summarised by count and percentage. In these subgroup analyses, participants were categorised by the number of prior lines of antidepressant medication received (2, 3–5, or ≥6) and by their PTSD or anxiety disorder comorbidity status (with or without). Participants could have had both PTSD and anxiety disorder. No corrections were made for multiple comparisons in this study. SAS V9.4 statistical software was used to analyse the endpoints.

Results

Participant characteristics

In the full study, 127 participants received at least one dose of esketamine+OAD. Of these participants, 94 had comorbid anxiety disorder, and 31 had comorbid PTSD. A total of 71 participants who completed both baseline and Week 16 study assessments were included in these subgroup analyses. Participant characteristics are presented in Table 1. In the total population, 57.7% of participants were female. Comorbid PTSD was reported in 26.8% of participants and the majority of participants had comorbid anxiety disorder (74.7%). All participants with or without comorbid PTSD and anxiety experienced a similar number of depressive episodes at baseline, with an average of 2.4 to 2.7 episodes.

Most participants had received 3 to 5 prior lines of antidepressant medication (49.3%). The most reported prior treatments were selective serotonin reuptake inhibitors (SSRIs) (76.1%) and serotonin–norepinephrine reuptake inhibitors (SNRIs) (76.1%) (Table 2).

Quality-of-Life

Number of prior antidepressants subgroups

Between baseline and Week 16, statistically significant improvements in QoL as measured by AQoL-8D were seen across all number of prior antidepressant medications subgroups (p-value <0.01). When separated by number of prior antidepressants, the largest AQoL-8D improvement (−21.4 points) was seen in participants who had failed 2 prior lines of antidepressants. A reduction of 19.8 points was seen for the 3–5 prior antidepressants subgroup, and a reduction of 19.2 points was seen for the ≥6 prior antidepressants subgroup (Figure 1). There were no significant differences in AQoL-8D change between the prior lines of antidepressants subgroups.

Comorbidity subgroups

Similarly, statistically significant improvements in QoL from baseline were seen in participants both with and without PTSD and anxiety disorder from baseline to Week 16 (p-value <0.01). Participants with comorbid PTSD saw a larger 23.4-point reduction in AQoL-8D score from baseline, compared to a 19.0-point reduction in those participants without comorbid PTSD. Participants with comorbid anxiety disorder saw a smaller 18.8-point reduction in AQoL-8D score from baseline, compared to a 23.1-point reduction in participants without comorbid anxiety disorder. There was no statistically significant difference between AQoL-8D improvement for participants with and without comorbid PTSD (p-value 0.37, 95% CI [−5.27, 14.07]) or anxiety disorder (p-value 0.36, 95% CI [−13.65, 5.05]) (Figure 2).

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Table 1. Patient characteristics by comorbidity and number of prior antidepressants subgroups

	Comorbidity (n = 71)				Number of prior antidepressants in current episode (n = 71)		
Subgroups	With PTSD	Without PTSD	With anxiety disorder	Without anxiety disorder	2 prior lines	3-5 prior lines	6+ prior lines
Number of participants, n (%)[a]	**19 (26.8%)**	**52 (73.2%)**	**53 (74.7%)**	**18 (25.4%)**	**15 (21.1%)**	**35 (49.3%)**	**21 (29.6%)**
Demographics							
Sex, n (%)[b]							
Female	11 (57.9)	30 (57.7)	29 (66.7)	12 (54.7)	4 (26.7)	23 (65.7)	14 (66.7)
Male	8 (42.1)	22 (42.3)	24 (33.3)	6 (45.3)	11 (73.3)	12 (34.3)	7 (33.3)
Age (years), mean (SD)	35.7 (10.8)	40.1 (15.3)	36.6 (13.1)	45.8 (15.7)	38.1 (15.6)	39.1 (13.0)	39.2 (16.0)
Disease characteristics							
Years from diagnosis, mean (SD)	13.0 (7.8)	18.4 (12.0)	14.5 (9.5)	24.3 (12.9)	16.7 (12.1)	15.5 (10.8)	14.1 (8.9)
Number of previous depressive episodes, mean (SD)	2.4 (2.5)	2.6 (2.0)	2.5 (2.0)	2.7 (2.5)	4.1 (2.3)	2.9 (2.4)	2 (1.8)
History of suicide ideation, n (%)[b]	7 (36.8)	22 (42.3)	24 (45.3)	5 (27.8)	11 (73.3)	14 (40.0)	4 (19.0)
History of self-harm, n (%)[b]	5 (26.3)	13 (25.0)	17 (32.1)	1 (5.6)	5 (33.3)	11 (31.4)	2 (9.5)
Past suicide attempts, n (%)[b]	1 (5.2)	4 (7.7)	5 (9.4)	0 (0)	3 (20.0)	0 (0)	2 (9.5)

PTSD = post-traumatic stress disorder; SD = standard deviation.
[a]Percentages expressed as a proportion of the study total (n = 71).
[b]Percentages expressed as a proportion of the number of participants in the subgroup (column).

Table 2. Prior lines of antidepressants separated by participant comorbidity subgroup

	PTSD		Anxiety disorder		
Comorbidity	With PTSD (n = 19)	Without PTSD (n = 52)	With anxiety disorder (n = 53)	Without anxiety disorder (n = 18)	Total (n = 71)
Prior antidepressants received n (%)					
2 prior lines	3 (15.8)	12 (23.1)	13 (24.5)	2 (11.1)	15 (21.1)
3-5 prior lines	12 (63.2)	23 (44.2)	27 (50.9)	8 (44.4)	35 (49.3)
6 or more	4 (21.1)	17 (32.7)	13 (24.5)	8 (44.4)	21 (29.6)
Prior MDD therapy classes received, n (%)					
SSRI	14 (73.7)	40 (76.9)	40 (75.5)	14 (77.8)	54 (76.1)
SNRI	16 (84.2)	38 (73.1)	39 (73.6)	15 (83.3)	54 (76.1)
Atypical antipsychotics	7 (36.8)	24 (46.2)	24 (45.3)	7 (38.9)	31 (43.7)
NaSSA	6 (31.6)	21 (40.4)	21 (39.6)	6 (33.3)	27 (38.0)
TCA	7 (36.8)	18 (34.6)	18 (34.0)	7 (38.9)	25 (35.2)
Lithium	5 (26.3)	18 (34.6)	14 (26.3)	9 (34.6)	23 (32.4)
Melatonin agonists	2 (10.5)	11 (21.2)	9 (17.0)	4 (22.2)	13 (18.3)
Serotonin modulators	2 (10.5)	9 (17.3)	6 (11.3)	5 (27.8)	11 (15.5)
MAOIs	2 (10.5)	8 (15.4)	7 (13.2)	3 (16.7)	10 (14.1)

MDD = major depressive disorder; SSRI = selective serotonin reuptake inhibitors; SNRI = serotonin–norepinephrine reuptake inhibitors; NaSSA = noradrenaline and specific serotonergic antidepressants; TCA = tricyclic antidepressants; MAOI = monoamine oxidase inhibitors.

Depression severity

Number of prior antidepressants subgroups

A statistically significant improvement in depression scores from baseline to Week 16 of esketamine+OAD treatment, as measured by HAM-D, were seen across all number of prior antidepressants subgroups (p-value <0.01). The 2 prior lines of antidepressants subgroup had a significantly larger average HAM-D improvement (−11.1 points) compared to the ≥6 prior antidepressants subgroup (−5.2 points) (p-value <0.01, 95% CI [1.86, 9.94]) (Figure 3). At Week 16, the number of participants whose HAM-D scores corresponded to an experience of severe or moderate depression across prior antidepressants subgroups had decreased from

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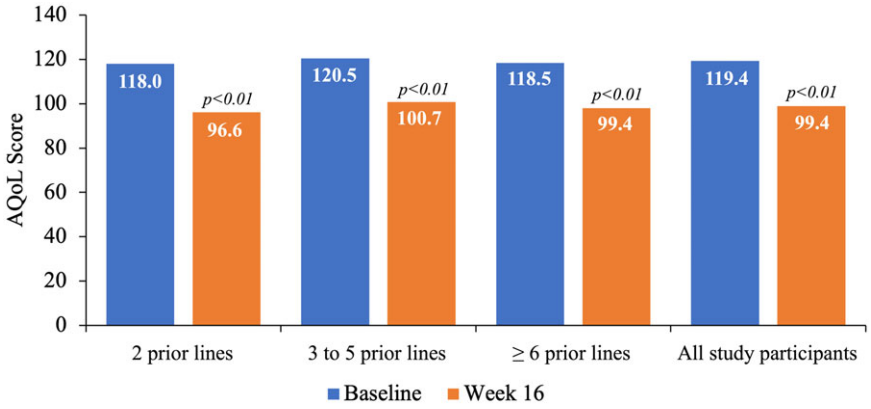

Figure 1. Change in average AQoL-8D score by number of prior antidepressants subgroups.

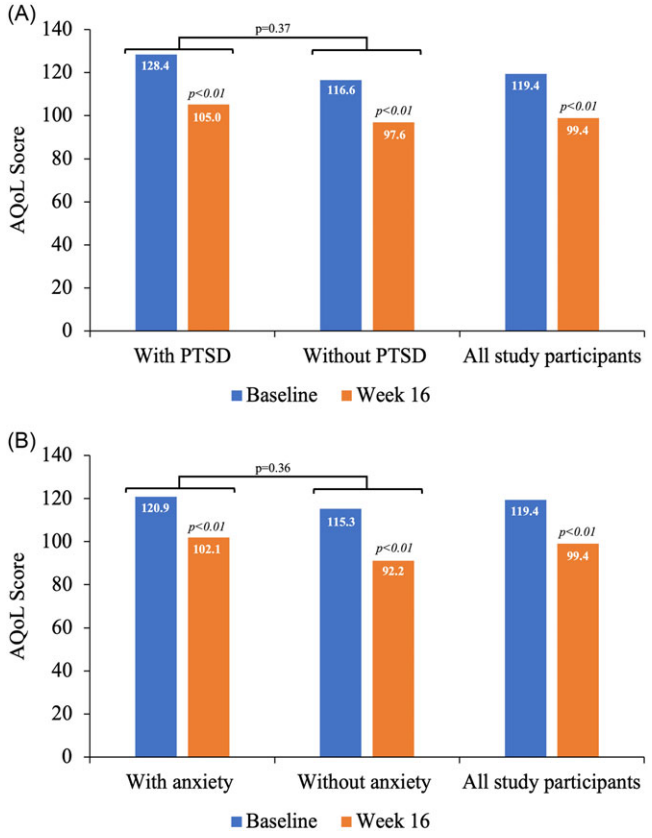

Figure 2. Change in average AQoL-8D score by comorbidity subgroup. A: PTSD subgroup, B: anxiety subgroup.

baseline. In the 2 prior lines of antidepressants subgroup, no participants were found to have severe depression at Week 16. This had reduced from 20.0% of these participants at baseline. In the 3–5 and ≥6 prior antidepressants subgroups, the percentage of participants with moderate and severe depression was reduced from baseline by 48.6% and 57.2% respectively at Week 16 (Figure 4).

Comorbidity subgroups

Statistically significant improvements in average HAM-D scores (p-value <0.01) were also seen in participants both with and without PTSD and anxiety disorder from baseline to Week 16. Participants without comorbid PTSD (−8.1 points) and anxiety disorder (−10.0 points) had slightly larger reductions in HAM-D compared to those with comorbid PTSD and anxiety. However, the reductions in HAM-D scores between participants with comorbid PTSD (−7.7 points) and anxiety disorder (−7.3 points) were comparable. There were no statistically significant differences in HAM-D improvement between anxiety disorder subgroups (with and without, p-value 0.12, 95% CI [−6.07, 0.67]) and PTSD subgroups (with and without, p-value 0.83, 95% CI [−4.00, 3.20]) (Figure 5).

The majority of participants with comorbid anxiety disorder (83.0%) had severe to moderate depression at baseline, as indicated by the HAM-D score. This number decreased to 43.4% by Week 16, with 1 in 4 participants experiencing no or minimal depression symptoms by Week 16.

At baseline, 89.5% of participants with comorbid PTSD had HAM-D scores corresponding to severe or moderate depression. This number decreased to 52.7% by Week 16. At Week 16, 15.8% of participants were found to be in the "normal" category for HAM-D scores, defined as having minimal depression symptoms (Figure 6).

Discussion

This study described the use of esketamine treatment in conjunction with a newly initiated OAD as per approved indications (Medsafe 2019; Therapeutic Goods Administration 2021), in participants with comorbid anxiety disorder, comorbid PTSD and multiple prior lines of therapy recruited from the Australia and New Zealand esketamine EAP. As such, our study provides insights into real-world esketamine treatment and subgroup populations representative of complex real-world patients with TRD (Oliveira-Maia et al. 2024). Most participants experienced ≥3 prior treatment attempts with standard antidepressant treatment, with high prevalence of comorbid PTSD and anxiety disorder.

Improvements in participant-reported AQoL-8D and investigator-assessed HAM-D from baseline to Week 16 were significant across PTSD and anxiety disorder comorbidities and prior number of antidepressants subgroups. Improvements in AQoL-8D across all subgroups ranged from 18.8 to 23.4 points. In participants with comorbid PTSD and anxiety disorder, HAM-D changed by a minimum of 5.2 and a maximum of 11.1 points, across all line of therapy subgroups. These improvements also correspond to a minimally important difference of 3 to 5 points in

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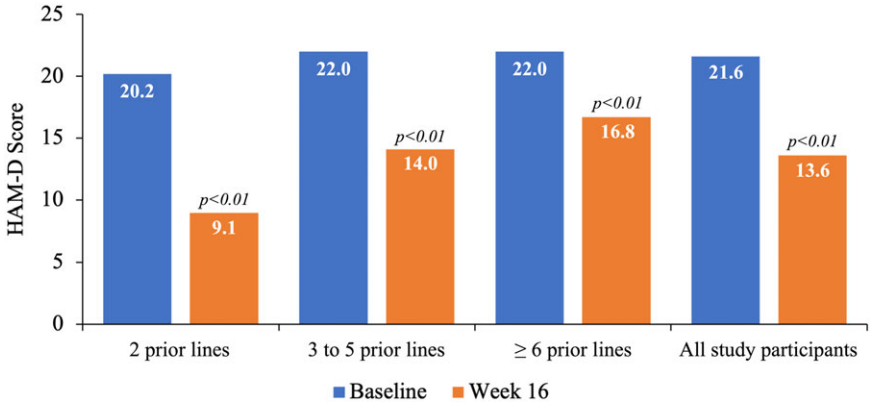

Figure 3. Change in average HAM-D score by number of prior antidepressants subgroups.

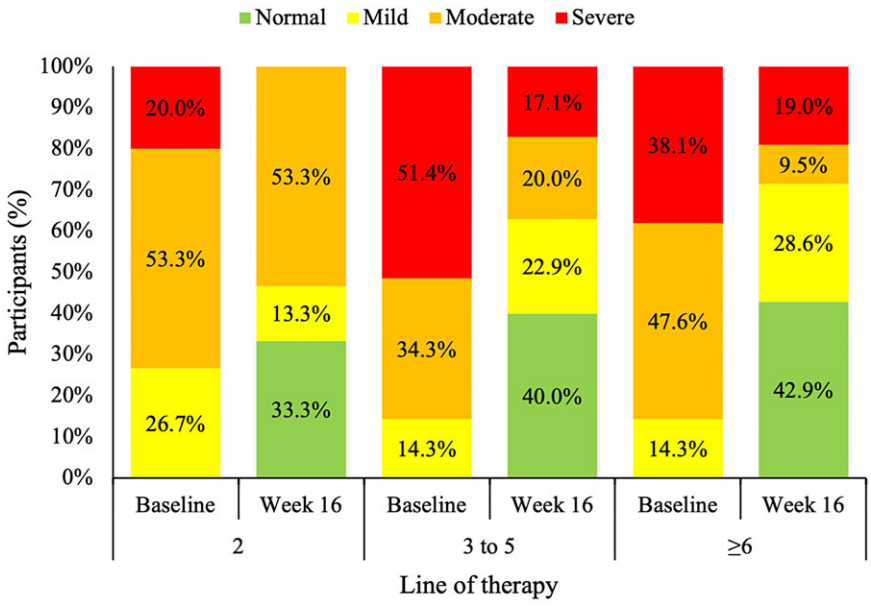

Figure 4. Change in HAM-D category by number of prior antidepressants subgroups.

depression severity from baseline to Week 16 (Hengartner and Plöderl 2022).

These results, showing significant improvements in AQoL-8D scores and exceeding minimally clinically important improvements for HAM-D, are highly meaningful considering the treatment-resistant patient subgroups analysed in this study. Particularly, the clinically meaningful 5-point reduction in HAM-D score for participants who had failed ≥6 prior antidepressant medications represent a consequential improvement. Additionally, the results seen across all subgroups represent holistic improvement beyond depressed mood alone, as factors such as independent living, relationships, suicidal feelings, work, interests and fatigue are considered through AQoL-8D and HAM-D (Centre for Health Economics Monash University 2017; Hamilton 1960; Hamilton 1967).

These clinically significant improvements in AQoL-8D and HAM-D suggest a meaningful benefit with esketamine+OAD treatment and are consistent with the results of the full study analysis (Hopwood et al. 2024). In the full study, the percentage of participants with HAM-D scores indicative of moderate to severe depression reduced by 47% from baseline to Week 16. This is comparable to a reduction of moderate to severe depression in the comorbid PTSD subgroup (36.8%), comorbid anxiety disorder subgroup (39.6%) and in the 2 (20.0%), 3–5 (48.6%) and 6 (57.2%) prior lines of therapy subgroups. Weighted utility AQoL-8D scores were not calculated for these subgroup analyses. As such, the clinical importance of the results is unknown. However, weighted AQoL-8D scores reported in the full study were found to exceed a minimal clinically important difference of 0.04 (Walters and Brasier 2005).

Available clinical trial results for esketamine treatment typically have not separated participant data beyond 4 prior lines of antidepressants. In TRANSFORM-2, the study population was classified as having 1 to 2 or ≥3 previous antidepressants, the results for which favoured esketamine+OAD (Daly et al. 2021; Popova et al. 2019). In SUSTAIN-2, the number of prior antidepressants the study population did not respond to in their current depressive episode were reported (1, 2, 3 or ≥4), but not analysed separately (Wajs et al. 2020). The results of our subgroup analysis, categorising participants with up to ≥6 prior antidepressants, suggests that clinically meaningful improvement in treatment-resistant participants is associated with real-world use of

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esketamine. The results of this study also highlight that outcome improvements decreased with increasing number of prior antidepressants. Participants who received 2 lines of prior therapy achieved the highest improvements in QoL and depression severity. While all subgroups had significant outcome improvements on esketamine+OAD treatment, this association between outcome improvement and less prior lines of antidepressants suggests that esketamine+OAD treatment may potentially be more beneficial earlier in TRD. This supports earlier TRD treatment, aligning with recommendations in existing research. However, this result may be nonspecific to esketamine+OAD treatment and instead be attributed to factors associated with MDD, such as increased burden over time (Oluboka et al. 2018). As such, further investigation is required.

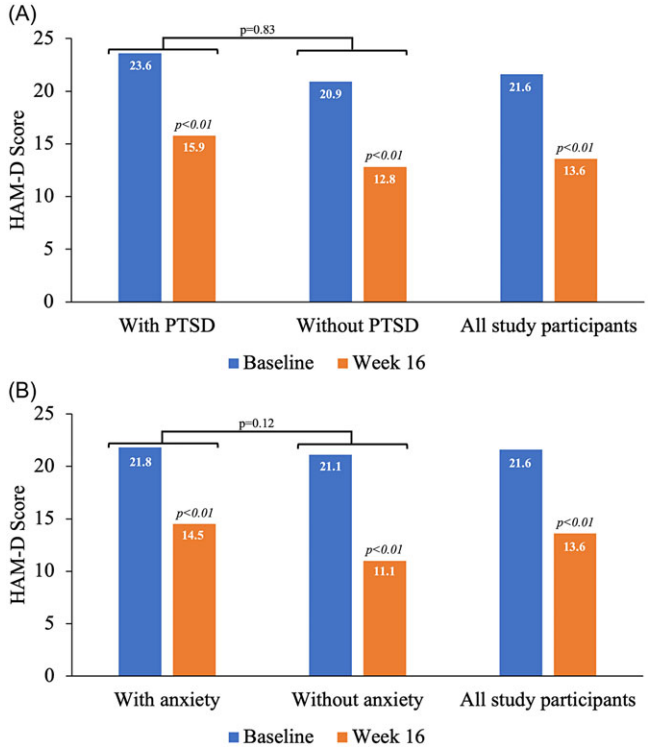

Figure 5. Change in average HAM-D score by comorbidity subgroup. A: PTSD subgroup, B: anxiety subgroup.

In this study, comparable improvements in QoL and depression severity were seen in participants both with and without comorbid anxiety disorder or PTSD. This suggests that esketamine+OAD treatment can be efficacious regardless of comorbid anxiety disorder or PTSD in the real-world. This is valuable, considering the contributions of comorbid anxiety disorders to lack of response in patients with TRD (Al-Harbi 2012), and currently limited research on treatment for comorbid TRD and PTSD or anxiety disorder (Angelakis et al. 2020; Daly et al. 2021).

The findings of this study are limited, primarily by the non-randomised, unblinded study design. Recruitment from the EAP may have also introduced selection and reporting bias. The exclusion of non-English speaking participants, in addition to the conduct of the research in only 8 treatment centres in Australia and New Zealand, may also limit the applicability of this study to the broad patient population seen in clinical practice. Collection of AQoL-8D data using online questionnaires, while allowing remote participation, may have excluded eligible participants who were unable to complete online assessments due to barriers accessing technology or the internet. While significant results were observed in this study, the assessment timeframe of 16 weeks is short in comparison to the real-world duration of TRD. Therefore, the sustainability of the outcome improvements observed in this study is unclear and should be studied further. Furthermore, although the post-hoc analyses reported here were stipulated in the statistical analyses plan, the study was not powered to find differences between the reported subgroups. The number of participants included in these subgroup analyses are small. Therefore, reported statistical differences may be influenced by low power, as opposed to the true effect of subgroup on outcome

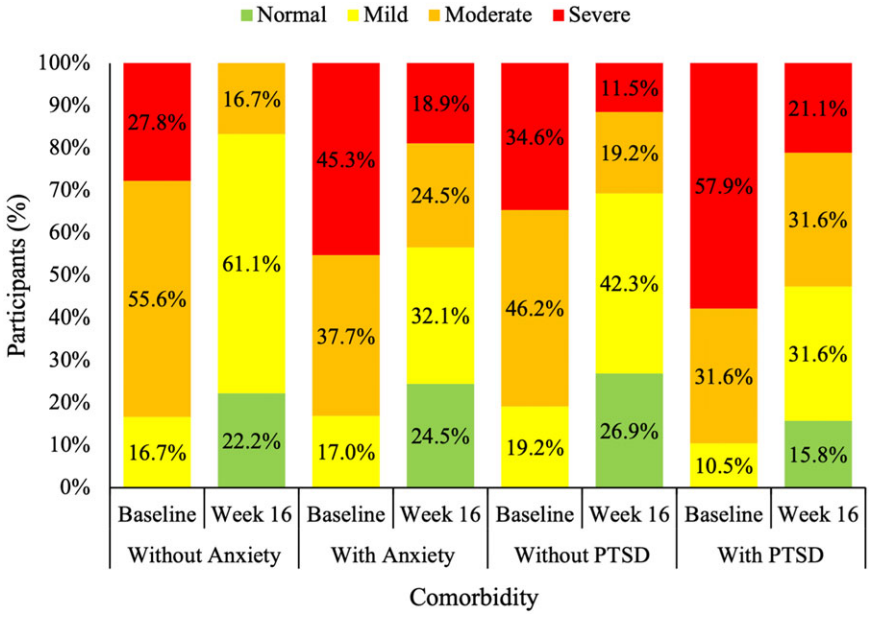

Figure 6. Change in HAM-D category by comorbidity subgroup.

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improvement. The study results should therefore be interpreted cautiously. The results of this study provide insights into the outcomes of esketamine treatment as administered in real-world practice. However, the results are also limited by the uncontrolled study design. Recruitment of participants from the EAP prevented the inclusion of a control arm in the study, in order to provide patients with access to esketamine prior to its reimbursement. Treatment with esketamine was in conjunction with a newly initiated OAD and therefore benefits seen may have been partially attributed to the OAD. Improvement in outcomes for patients with TRD is possible with standard treatment over less than 16 weeks, as seen in existing research (Daly et al. 2021; Jamieson et al. 2023; Turkoz et al. 2021). Due to the lack of a placebo or esketamine monotherapy control arm, causal association between outcome improvements and esketamine alone cannot be made.

The heterogeneity of depression and other mood disorders is a barrier in research and treatment (Hickie et al. 2024). This study provides insight into patterns of response to esketamine+OAD treatment in patients with multiple failed prior antidepressants and comorbid anxiety or PTSD, which may facilitate an understanding of factors that drive subgroups of TRD in future research.

While demonstrating efficacy across participants with TRD and comorbid PTSD or anxiety disorder, the persistence of this benefit across multimorbid patients and patients with other psychiatric comorbidities remains unassessed.

To wholistically investigate the broad benefit of esketamine treatment across patients with TRD and further validate the interpreted trends identified in this subgroup analysis, future research should be adequately powered, controlled and comparative. Reporting both clinical and patient-reported long-term outcomes should a focus of future research.

Conclusions

TRD patients frequently present with moderate to severe depression and poor QoL. Multiple failed prior treatments and psychiatric comorbidity can exacerbate disease burden and attenuate response to treatment. This post-hoc subgroup analysis suggests that esketamine+OAD treatment is associated with a clinically important, real-world benefit in participants with TRD and comorbid PTSD and/or anxiety disorder, regardless of the number of prior antidepressants trialled. Statistically significant improvements in QoL and depression severity were seen across subgroups of participants both with and without comorbid PTSD or anxiety disorder. This suggests that esketamine+OAD treatment can provide benefit independent of mental health comorbidity. Additionally, the association between outcome improvements on esketamine+OAD treatment and fewer antidepressants trialled suggests that esketamine+OAD initiation earlier in a patient's experience with TRD may confer optimal benefit. However, this requires further investigation. This study provides real-world evidence for the use of esketamine+OAD in TRD that is consistent with previous clinical trial results. The participant population of this study is reflective of clinical settings across Australia and New Zealand and may provide insight for psychiatrists, potentially informing broader use of esketamine+OAD across complex TRD patients in clinical practice. Limitations of the study results include uncertainty due to the short timeframe of 16 weeks and the underpowered nature of the study due to small subgroup populations. Additionally, due to the uncontrolled study design and esketamine administration in conjunction with a newly initiated antidepressant, the observed outcome improvements cannot be attributed to esketamine alone. The results of this study should be interpreted with consideration of these limitations. Future long-term evaluation of esketamine benefit in TRD patients with multiple lines of prior antidepressant medications and comorbidities in broad clinical practice is needed to facilitate the real-world use of esketamine for the complex TRD patient.

Data availability statement. The authors confirm that the data supporting the findings of this study are available from the corresponding author, AP, upon reasonable request.

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Author contributions. *Malcolm Hopwood:* Conceptualisation, Investigation, Methodology, Visualisation, Writing – original draft, Writing – review & editing. *David Codyre:* Formal analysis, Visualisation, Writing – review & editing. *David Barton:* Formal analysis, Visualisation, Writing – review & editing. *Elizabeth M. Scott:* Visualisation, Writing – review & editing. *Andrea Puig:* Conceptualisation, Methodology, Visualisation, Writing – original draft, Writing – review & editing. *Jarrad King:* Visualisation, Writing – original draft, Writing – review & editing. *Ian B. Hickie:* Conceptualisation, Methodology, Visualisation, Writing – original draft, Writing – review & editing.

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Competing interests. *MH* has received speaker's fees/honoraria, has attended advisory boards and has received research support from Janssen-Cilag (Janssen Pty Ltd), Servier Australia, Seqirus, Otsuka and Lundbeck Australia.

DC has received honoraria for advisory services provided to Janssen-Cilag New Zealand. He has also been an investigator in past research funded by Janssen-Cilag International and Eli Lilly.

DB declares his interest as Co-director of NeuroCentrix, Director of Clinical Services at South Eastern Private Hospital and Chair of the Aurora Health Research Committee. Dr Barton is/has been on the advisory boards for Eisai, Janssen, Lilly and Biogen. Clinical trials completed at NeuroCentrix are supported with funding from NHMRC grants and the following pharmaceutical companies: Douglas; Praxis; Anavex; Alkermes; Cerecin; Athira; Janssen; Roche; Pfizer; Lilly; Eisai; Actinogen; BMS; Biogen; ImmuneBio. NeuroCentrix acknowledges financial support for Education and Research programs by (but not limited to) Servier; Lundbeck; Lily; Pfizer; GSK; Janssen-Cilag.

EMS declares her interest as a Principal Research Fellow at the Brain and Mind Centre, The University of Sydney. She is Discipline Leader of Adult Mental Health, School of Medicine, University of Notre Dame and a Consultant Psychiatrist. She was the Medical Director, Young Adult Mental Health Unit, St Vincent's Hospital Darlinghurst until January 2021. She has received honoraria for educational seminars related to the clinical management of depressive disorders supported by Servier, Janssen and Eli Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored by Servier.

AP and JK are employees of Janssen-Cilag Pty Ltd Australia.

IBH is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney, Australia. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. IBH has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca, Janssen-Cilag) projects focused on the identification and better management of anxiety and depression.

IBH is the Chief Scientific Advisor to, and a 3.2% equity shareholder in, InnoWell Pty Ltd which aims to transform mental health services through the use of innovative technologies. IBH is the current editor-in-chief for the Cambridge University Press journal Research Directions: Depression.

Ethical standards. The protocol for this study was approved by Bellberry Limited Human Research Ethics Committee (HREC) 2021-06-606-AF-PRE-1. Written informed consent was obtained from all participants.

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