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Estimating the Benefit of Esketamine Nasal Spray Versus Real-World Treatment on Patient-Reported Functional Remission: Results from the ICEBERG Study

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OBJECTIVE

- To compare functional remission rates in patients receiving esketamine nasal spray with patients receiving real-world treatment from the Indirect adjusted Comparison Estimating the long-term Benefit of Esketamine nasal spray when compared with Routine treatment of treatment resistant depression in General psychiatry (ICEBERG) analysis.

BACKGROUND

- Treatment resistant depression (TRD) affects 10–30% of patients with major depressive disorder; most patients do not respond to real-world treatments (RWT).[1]
- Esketamine nasal spray (NS), in combination with a selective serotonin or serotonin-norepinephrine reuptake inhibitor (SSRI/SNRI), is approved for treatment of TRD.[2]
- Esketamine NS has demonstrated significant benefit on response and remission rates compared with placebo (plus SSRI/SNRI), and when compared with RWT strategies.[3,4]
- Functional improvement and remission often represent key treatment goals for patients and clinicians. Any benefit of esketamine NS on patient-reported daily function remains to be established.

METHODS

Study details

- ICEBERG was performed using data from two studies of patients with TRD:
  - SUSTAIN-2: an open-label study of esketamine NS plus SSRI/SNRI.[5]
  - The Tretament Resistant Depression Cohort in Europe (EOTC): a prospective, non-interventional study in real-world practice.[1]

Treatment outcomes and analysis

- Patient-reported functioning was assessed using the Sheehan Disability Scale (SDS), which measures the disruption from TRD on patients' daily lives. Functional remission was defined as a total SDS score ≤6 at Month 6.
- Clinical response and remission were defined as ≥50% improvement in total Montgomery-Åsberg Depression Rating Scale (MADRS) score and total MADRS score ≤10, respectively.

Statistical analysis

- Analyses were conducted using propensity score re-weighting based on 18 covariates.
- Non-working patients were excluded from the analysis as the work item score of the SDS could not be assessed.
- For SUSTAIN-2, only patients that enrolled ≥6 months before study termination were included. Patients that dropped out before Month 6 were imputed as non-responders, except those patients from SUSTAIN-2 that dropped out due to study termination.
- Due to updates in the model, this poster reports data from an updated data set compared with the submitted abstract.

RESULTS

Baseline characteristics

- Baseline characteristics were similar across studies (**Table 1**).

Predicted probability of response and remission

- At Month 6, the probability of functional remission was 25.6% (95% confidence interval [CI] 21.8–29.4) for patients receiving esketamine NS; the adjusted probability for RWT was 11.5% (95% CI 6.9–16.1; unadjusted RWT: 12.5% [95% CI 7.7–17.3]; **Figure 1**).
- The relative risk (RR) significantly favoured esketamine NS (2.226 [95% CI 1.451–3.416]; p=0.0003, **Table 2**). The risk difference (RD) also significantly favoured esketamine NS over RWT for 6-month functional remission (0.141 [95% CI 0.081–0.201]; p<0.0001).
- For every eight patients treated with esketamine NS and RWT, one additional patient on esketamine NS achieved functional remission (number needed to treat [NNT]: 8 [95% CI 5–13]; **Table 2**).

Comparison of functional remission with clinical outcomes

- Of the total population (combined SUSTAIN-2 and EOTC n=696):
  - Patients who did not achieve clinical response or clinical remission, had a very low probability of achieving functional remission (5.84% and 8.76%, respectively; **Table 3**).
  - For patients who did achieve clinical response or clinical remission, the probability of achieving functional remission was greater, although still not achieved for many patients (43.38% and 54.15%, respectively; **Table 3**).

Threshold analysis

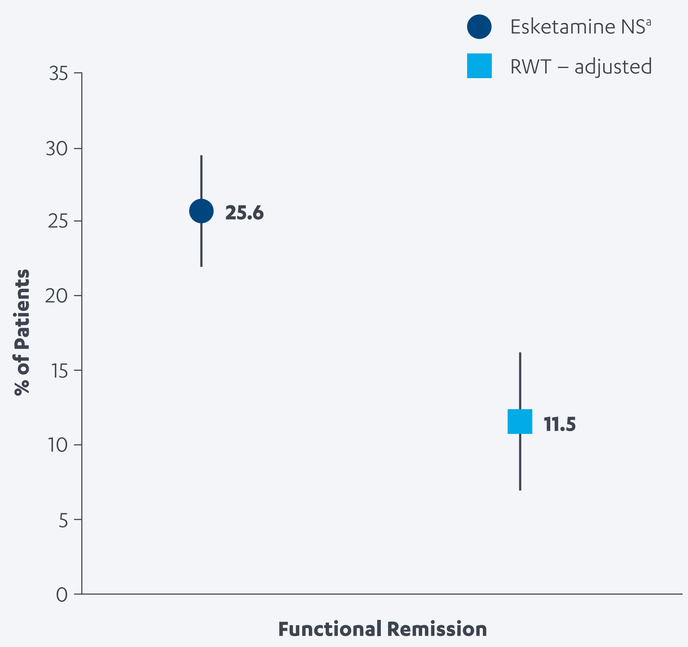
- Threshold analysis showed that a 7.6–8.4% loss of functional remission rate could occur before loss of significance (**Table 4**).
- Results were similar across sensitivity analyses and using alternative re-weighting comparisons.

SUMMARY

- This indirect treatment comparison suggests esketamine NS has a significant functional benefit over 6 months versus RWT for patients with TRD.
- Following adjustment for the 18 covariates, consistent results demonstrate the robustness of the comparison.
- Compared with clinical response and remission, functional remission is a more stringent treatment target. Patients who achieve clinical remission are more likely to achieve functional remission, further supporting that clinical remission should be preferred over clinical response to allow patients the best chance of day-to-day functional improvements.

NEUROPSYCHIATRY

FIGURE 1. Probability of functional remission (%)



[a]Esketamine NS is taken in addition to an SSRI/SNRI.

TABLE 1. Baseline demographics and patient characteristics

Mean (SD)	Esketamine NS[a] (N=512)	RWT (N=184)
Age, years	48.8 (12.4)	50.2 (9.9)
Age at diagnosis, years	34.3 (13.0)	37.5 (13.0)
Time since diagnosis, years	14.5 (11.2)	12.7 (11.0)
Number of episodes	4.1 (3.4)[b]	3.8 (3.6)
Duration of current episode, weeks	132.6 (223.8)	131.9 (180.1)
Average treatment duration, weeks	43.3 (69.8)	52.5 (74.5)
Number of treatment failures in the current MDE	2.6 (1.0)	2.6 (0.9)
SDS total score	22.5 (5.0)	21.9 (5.5)
MADRS total score at baseline	31.3 (5.0)	32.0 (5.9)
CGI-S score	4.9 (0.7)	4.8 (0.8)
EuroQoL VAS score	44.3 (19.8)[b]	40.7 (18.5)

[a]Esketamine NS is taken in addition to an SSRI/SNRI. [b]Two missing patients.

TABLE 2. Chance of functional remission at Month 6

Esketamine NS[a] vs RWT	Result (95% CI)	p-value
OR	2.648 (1.613–4.346)	0.0001
RR	2.226 (1.451–3.416)	0.0003
RD	0.141 (0.081–0.201)	<0.0001
NNT	8 (5–13)	N/A

[a]Esketamine NS is taken in addition to an SSRI/SNRI. RWT data were adjusted using the ATT covariate adjustment method. OR>1, RR>1 and RD>0 all indicate esketamine NS is superior to the comparator treatment.

TABLE 3. Chance of achieving functional remission at Month 6 based on clinical outcome

	No functional remission	Functional remission achieved
No clinical response	94.16% (n=371)	5.84% (n=23)
Clinical response achieved	56.62% (n=171)	43.38% (n=131)

	No functional remission	Functional remission achieved
No clinical remission	91.24% (n=448)	8.76% (n=43)
Clinical remission achieved	45.85% (n=94)	54.15% (n=111)

TABLE 4. Threshold analysis based on OR, RR and RD for chance of 6-month functional remission

	Predicted probability, % (95% CI)		
Efficacy measure	**Observed**	**Lowest significant simulated result[a]**	**Difference,[b] %**
OR	25.6 (21.8–29.4)	17.8 (14.5–21.1)	7.8
RD	25.6 (21.8–29.4)	17.2 (13.9–20.5)	8.4
RR	25.6 (21.8–29.4)	18.0 (14.6–21.3)	7.6

[a]Pre-determined significance value was p<0.05. [b]Maximum difference in response/remission before loss of significance in outcomes.

ABBREVIATIONS: **ATT**: rescaled average treatment effect among treated; **CI**: confidence interval; **CGI-S**: Clinical Global Impressions-Severity; **EOTC**: European Observational TRD Cohort; **EuroQoL**: European Quality of Life; **ICEBERG**: Indirect adjusted Comparison Estimating the long-term Benefit of Esketamine nasal spray when compared with Routine treatment of treatment resistant depression in General psychiatry; **MADRS**: Montgomery-Åsberg Depression Rating Scale; **MDE**: major depressive episode; **N/A**: not applicable; **NNT**: number needed to treat; **NS**: nasal spray; **OR**: odds ratio; **RD**: risk difference; **RR**: relative risk; **RWT**: real-world treatment; **SD**: standard deviation; **SDS**: Sheehan Disability Scale; **SNRI**: serotonin-norepinephrine reuptake inhibitor; **SSRI**: selective serotonin reuptake inhibitor **TRD**: treatment resistant depression; **VAS**: visual analogue scale.

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