

LONG-TERM OUTCOMES OF INTRANASAL ESKETAMINE IN TREATMENT-RESISTANT DEPRESSION: EVIDENCE FROM CLINICAL TRIALS AND REAL-WORLD STUDIES

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BACKGROUND AND AIM: Treatment-Resistant Depression (TRD) is defined as failure to respond to at least two adequate antidepressant trials in the current episode.

Esketamine, a non-competitive NMDA receptor antagonist, promotes synaptogenesis through mTORC1 activation and BDNF release. This study aims to evaluate esketamine's relapse prevention capacity, long-term safety (up to 6.5 years), and comparative efficacy by synthesizing data from clinical trials (SUSTAIN, ESCAPE-TRD) and real-world evidence (REAL-ESK).

METHODS: (Ethics Committee Approval must be obtained and the number should be specified). A comprehensive literature review was conducted using PubMed, Cochrane Library, and Google Scholar (2019–2025). Phase studies (SUSTAIN-1, SUSTAIN-2, SUSTAIN-3), comparative trials (ESCAPE-TRD), and observational real-world data (REAL-ESK) were included. Ethics committee approval is not required for systematic reviews.

RESULTS: In SUSTAIN-1 (N=297), esketamine reduced relapse risk by 70% ($p<0.001$) in stable responders and 51% ($p=0.003$) in stable remitters. SUSTAIN-2 reported a 58.2% remission rate at

one year. In ESCAPE-TRD (N=676), esketamine demonstrated superiority over quetiapine, achieving 27.1% remission at week 8 ($p=0.003$) and 21.7% relapse-free remission through week 32. SUSTAIN-3 (N=1148) showed that remission rates approached 50% and were maintained for up to 6.5 years under intermittent dosing. REAL-ESK, a multicenter real-world cohort, reported a 40.6% remission rate; in the subsequent trajectory study ($n=78$), 55.1% of patients maintained clinical benefit during continuation treatment. Across studies, 40–50% non-response rates reflect the persistent clinical burden of TRD.

CONCLUSIONS: Esketamine represents an important long-term treatment option for TRD, supported by sustained efficacy and safety data from clinical trials and extension studies. Nevertheless, reported success rates should be interpreted considering enriched trial designs, open-label extensions, and potential sponsor relationships. This poster synthesizes long-term clinical and real-world data to provide a balanced overview of esketamine's role in sustained TRD management.

Keywords: Treatment-resistant depression, intranasal esketamine, long-term outcomes, real-world evidence