Evaluating the relationship among esketamine monotherapy efficacy and dissociation in patients with treatment-resistant depression

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SUBMISSION DETAILS

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Methodological Issue Being Addressed The evaluation of the relationship between esketamine antidepressant efficacy and reports of dissociation.

Introduction A new generation of antidepressants including esketamine, ketamine and psychedelics have unique side effects that can lead to functional unblinding that may confound the assessment of efficacy. For example, esketamine and ketamine can cause dissociation characterized by altered consciousness and feelings of floating (Ballard et al. 2020). A recent post-hoc analysis demonstrated there is no significant correlation between dissociative effects as measured by the Clinician-Administered Dissociation States Scale (CADSS) and antidepressive response to esketamine plus an oral antidepressant (Chen et al. 2022). It is of interest to explore the association of dissociation and esketamine monotherapy efficacy in treatment-resistant depression (TRD) population. This analysis assessed the relationship between rates of dissociation and antidepressant response to esketamine monotherapy using data from a recently completed phase 4 study.

Methods Data for this analysis were collected from a randomized, double-blind (DB), placebo-controlled study that evaluated the efficacy of 56 mg and 84 mg esketamine nasal spray as a monotherapy versus matching placebo nasal spray in adults with TRD. This post-hoc analysis examined the responder status of participants (response defined as ≥50% reduction from baseline in MADRS total score) at DB endpoint (Day 28) and reported treatment emergent adverse events (TEAE) of dissociation (defined as patient reported TEAE of dissociation during the DB phase) on dosing days during DB phase. To assess the relationship between dissociation and esketamine response, using Fischer exact test, we compared response rates at the DB endpoint in participants with and without reported TEAE of dissociation on treatment dosing days.

Results The overall study included 378 participants in the full efficacy analysis dataset and showed a twofold increase in the overall response rates for both esketamine dosing groups compared to the placebo group at the DB endpoint (Day 28). The response rate was 30.6%, 28.4% and 15.2% in the esketamine 56 mg, 84 mg and placebo group respectively. Data from the safety analysis set included 476 participants and showed TEAE reported dissociation was 21.9%, 26.4%, and 2.8% in the 56 mg and 84 mg esketamine groups and placebo group respectively. Our analysis shows similar response rates between participants with and without dissociation in esketamine groups at DB endpoint. The response rate for participants with and without dissociation was 31.6%

(6/19) vs 30.3% (20/66) for ESK 56 mg (p=1.000) and 30.4% (7/23) vs 27.8% (20/72) for ESK 84 mg (p=0.796). The placebo group response rate was 42.9% (3/7) in participants with dissociation and 14.2% (27/190) in participants without dissociation at the DB endpoint (p=0.073).

Conclusion These data suggest that dissociation does not account for the efficacy observed in participants receiving esketamine. These data are consistent with findings from Chen et al. 2022 which show there is no difference in responder rates among those with and without dissociation as assessed by the CADSS.

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Guidelines I have read and understand the Poster Guidelines

Disclosures All authors are employees of Johnson & Johnson.

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