

Precision Psychiatry in MDD: Finite Mixture Modeling of Nelivaptan Response Suggests Distinct Responder Classes

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SUBMISSION DETAILS

Methodological Issue Being Addressed Central nervous system (CNS) trials often overlook treatment response heterogeneity by relying on conventional analyses that assume uniform efficacy across patient populations. This is a critical limitation in disorders like Major Depressive Disorder (MDD), where underlying biological mechanisms—such as HPA-axis dysfunction—are present in only a subset of patients. For compounds like the vasopressin V1b receptor antagonist nelivaptan, which targets this pathway, conventional mean-based analyses may mask efficacy in biologically relevant subgroups. To address this, we applied Finite Mixture Modeling (FMM), a statistical approach that estimates latent subgroups within response data. FMM allows for the detection of distinct response profiles—such as responders and non-responders—based on outcome distributions, providing a novel and clinically meaningful method for evaluating efficacy in stratified populations.

Introduction The aim of this study is to assess whether nelivaptan's antidepressant efficacy in MDD is confined to a biologically specific subgroup of patients. By applying statistical modeling techniques to reanalyze Phase 2 trial data, showing significant efficacy of nelivaptan compared to placebo, we sought to uncover latent subpopulations that may respond differentially to treatment, thereby supporting a precision psychiatry approach to patient stratification and drug development.

Methods Data from the placebo-controlled Phase 2 trial NCT00358631 were reanalyzed, focusing on MDD patients in the intent-to-treat population with available HAM-D17 scores at day 56 (nelivaptan 250 mg BID: $n = 62$; placebo: $n = 63$). FMM was used to model the distribution of changes in HAM-D17 scores from baseline, allowing for identification of latent subgroups within each treatment arm. Models with one, two, and three Gaussian components were compared using Akaike (AIC) and Bayesian Information Criteria (BIC). Covariate analysis tested associations between subgroup and baseline HAM-D17 score, age, and sex.

Results The placebo group exhibited a unimodal response distribution (mean HAM-D17 change: -7.06). In contrast, the nelivaptan group demonstrated a bimodal distribution, consisting of a high-responder subgroup (mean change: -17.14) and a low-responder subgroup (mean change: -3.85), with subgroup proportions of 55% and 45%, respectively. The two-class model provided the best fit in the nelivaptan arm based on AIC and was nearly equivalent to the one-class model under BIC. Baseline HAM-D17 score was significantly associated with improvement in the high-responder group ($p < 0.001$), but no associations were found with age or sex.

Conclusions These findings indicate heterogeneity in response to nelivaptan in MDD, consistent with the possibility of biologically meaningful subgroups. While no biological markers were used in

this analysis, future work incorporating HPA-axis measures will be needed to test this hypothesis. The presence of a bimodal distribution in the active treatment arm—but not in the placebo arm—underscores the value of modeling latent heterogeneity in antidepressant trials. Future studies should incorporate biological measures of HPA-axis function to validate subgroup membership. The ongoing OLIVE trial, which includes a genetic companion diagnostic, aims to test this hypothesis and could pave the way for precision psychiatry in depression treatment.

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