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

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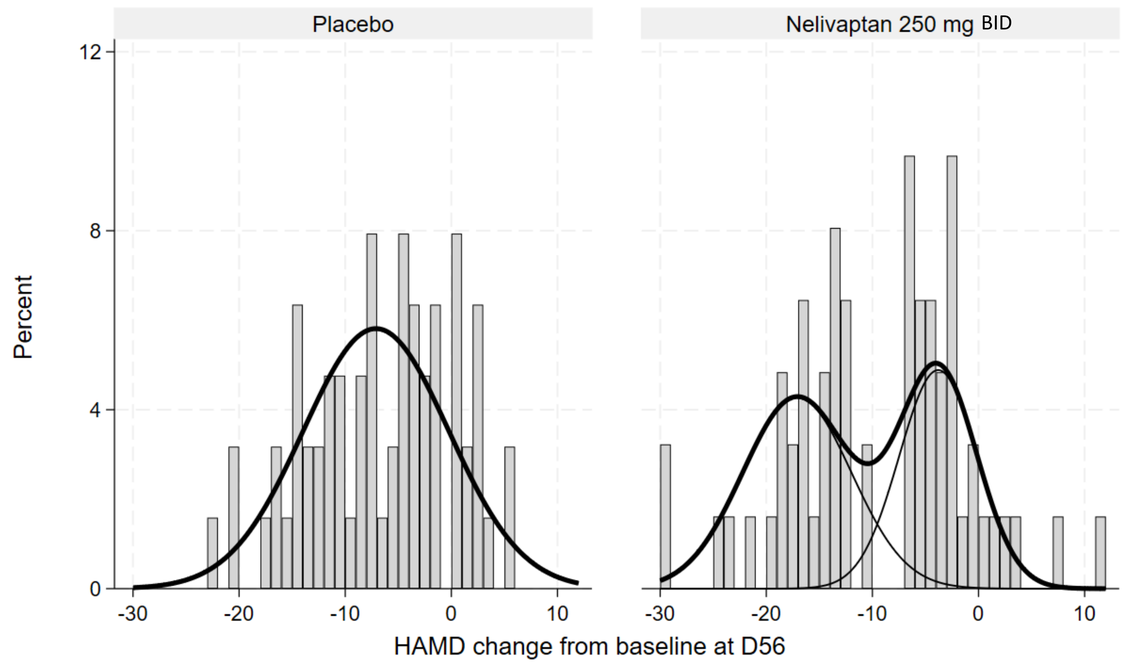
Response has a bimodal distribution in the active arm, but not in the placebo arm.



Objective

- Treatment heterogeneity in depression trials are pointing towards underlying biological mechanisms—such as HPA-axis dysfunction.
- Posthoc analysis of data from a large phase II trial in depression (NCT00358631) patients was performed, testing the efficacy and safety of nelivaptan 250 mg BID.
- Hypothesis: Response in active arm is a compound of multiple (normal-) distributions.

Methods

- Finite mixture models with one, two or three classes were calculated.
- Model fit is rated with AIC and BIC in terms of the likelihood and the number of model parameters (the lower the better).
- BIC penalizes model complexity in relation to the sample size more than AIC.

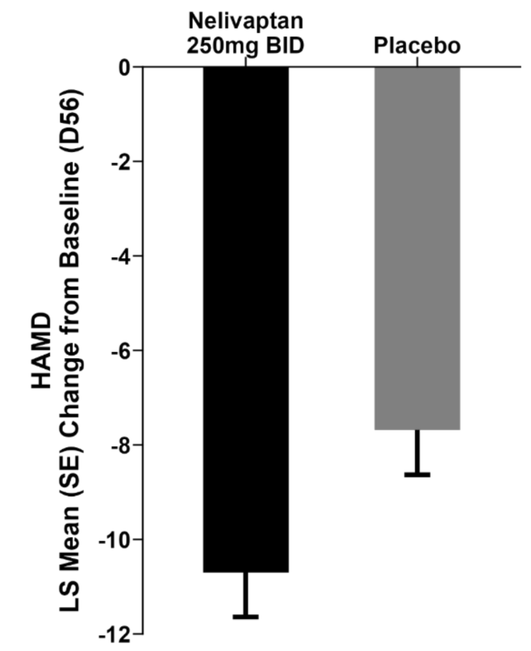


Fig. 1.: LS mean change from baseline in HAM-D17 on Day 56 in Nelivaptan (10.7, SE 0.94) compared to placebo (-7.7, SE 0.95); p=0.0244

Results

- Bimodal distribution of response was observed in the active arm, but not in the placebo arm.
- Average mean change of -17.1 and -3.9 in high- and low-responder subgroups were present in the active arm, versus mean change of -7.1 in placebo.
- Distribution of groups is not associated with age or sex.

	Nelivaptan			Placebo		
Model	**N**	**AIC**	**BIC**	**N**	**AIC**	**BIC**
1 group	62	443	451	63	425	433
2 groups	62	437	452	63	425	440
3 groups	62	438	461	63	425	449

Table 1: Goodness of fit from different Gaussian mixture models. AIC = Akaike information criteria, BIC = Bayesian information criteria

	Class 1	Class 2
Fraction of patients	55%	45%
Mean	-17.1	-3.9
SE	0.96	1.58

Table 2: Finite Mixture Model with 2 groups for responders and non-responders within the active treatment arm

Conclusions

- Heterogeneous treatment responses require more precise medication.
- The recently finalized OLIVE trial (EudraCT number: 2022-002757-26) addresses this directly, testing nelivaptan efficacy in conjunction with a genetic companion diagnostic tool designed to predict vasopressin V1b receptor signaling disturbances.

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References
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Disclosures
CzE, DG, MM, LA, CS, BMM, and HE are employed by or consultants to HMNC Brain Health and may hold stock options.

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