

# Nonlinear mixed effects evaluation of Hamilton Depression Rating Score following combination treatment of presynaptic- and postsynaptic glutamate receptor inhibitors in bipolar depression patients

Jasper Stevens (1), Anantha Shekhar (2), Amit Anand (3), Robert Bies (1)

(1) Division of Clinical Pharmacology, Indiana School of Medicine, IN, USA

(2) Department of Psychiatry, Indiana School of Medicine, IN, USA

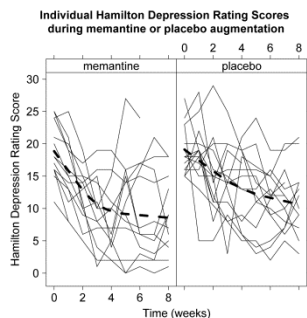
(3) Department of Psychiatry and Radiology, Indiana School of Medicine, IN, USA

## Introduction

Presynaptic- and postsynaptic glutamatergic modulation is associated with anti-depressant activity that takes several weeks to reach a maximal full effect [1]. Limiting mood elevating effects after single drug administration may be the result of compensatory synaptic processes [2, 3]. Therefore, using augmentation treatment with agents having presynaptic- and postsynaptic effects on the glutamatergic system (lamotrigine and memantine, respectively), **this study aims to evaluate the effect of augmentation therapy on the rate of change in mood elevation in patients with bipolar depression.**

## Methods

In a recent pilot study [4], 29 bipolar depression outpatients on a stable lamotrigine dose regimen received placebo or memantine (MMTN) pills daily (titrated up by 5 mg per week to 20 mg) in a randomized, double blind, parallel group, 8-week study. Patients were evaluated weekly using the 17-item Hamilton Depression Rating Score (HDRS) and all data were analyzed simultaneously.



**Figure 1.** Individual Hamilton Depression Rating Scores over time (solid lines), separated by memantine and placebo augmentation. The broken line represents the locally weighed polynomial regression per group.

In this study, linear-, exponential-, maximal effect-, Gompertz- and inverse Bateman functions were evaluated using a Bayesian approach population pharmacodynamic model framework (WinBUGS 1.4.3).

In these models, differences in parameters were examined across the memantine and placebo augmentation groups by estimating the parameter ( $\theta_i$ ) for both groups separately (eq.1).

$$Eq. 1; \theta_i = (trt_i - 1) \times \theta_{plac} + (2 - trt_i \times \theta_{MMTN})$$

As  $trt_i$  is the treatment for the  $i^{th}$  individual (1 = MMTN, 2 = placebo), this switch allows estimation of  $\theta_{MMTN}$  when MMTN is administered and estimation of  $\theta_{placebo}$  when placebo is administered.

- For model optimization- and comparison purposes, the Deviance Information Criterion (DIC) was used. With decreases in DIC, the model with one additional parameter was preferred over the parent model.

- History plots were qualified for lack of parameter correlation, and Gelman-Rubin-Brooks plots were created to investigate over-parameterization of the models.

- The shrink factor was considered acceptable when below 1.05 points at the end of the iterations.

- Models were internally qualified based on shape of the posterior parameter distributions as well as posterior- and posterior predictive goodness-of-fit of the HDRS data on individual- and population level.

## Results

A Gompertz function with a treatment switch on the parameter describing the speed of HDRS decline best described the data (eq.2, see for explanation of symbols Table 1).

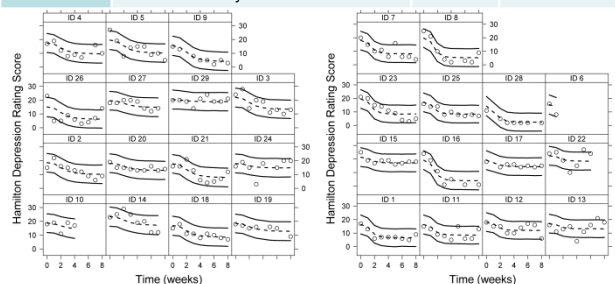
Between subject variability was identified on baseline HDRS and amplitude of score improvement.

## Results cont.

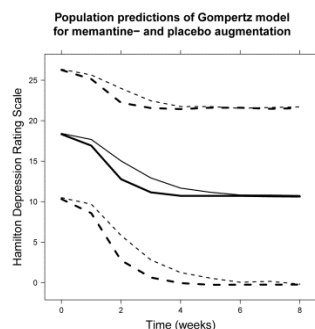
$$Eq. 2; HDRS(t) = s_0 - \alpha \times e^{-\beta \times e^{-\gamma \times t}}$$

**Table 1.** Posterior population parameter estimates

Parameter	Definition	Median	95% conf. interval
$s_0$	HDRS at t=0	18.4	16.6-20.6
$\alpha$	amplitude	7.7	5.6-10.8
$\beta$	Time to displacement	11.1	2.3-90.3
$\gamma_{MMTN}$	Speed of decline in memantine group	1.8	0.9-3.6
$\gamma_{placebo}$	Speed of decline in placebo group	1.2	0.5-3.5
$BSV_{s_0}$	Between subject variability $s_0$	2.9	1.5-4.4
$BSV_{\alpha}$	Between subject variability $\alpha$	4.3	2.7-6.5
$RV$	Residual variability	3.7	3.3-4.1



**Figure 2.** The median predictions (solid line) per individual (ID) over time for the memantine- (A) and placebo (B) augmented groups, with their 95% confidence intervals (broken lines). The open circles represent the observed Hamilton Depression Rating Scores.



**Figure 3.** The median population predictions (solid lines) of the final Gompertz model, with the 95% confidence intervals (broken lines) for the memantine- (bold lines) and placebo (fine lines) augmented groups.

Due to the intrinsic behavior of a Gompertz function, relapsing patterns in placebo response (IDs 11, 12, 13 and 22 in Fig 2) were not accurately described in the final model.

## Conclusion

**This pharmacodynamic approach identified an increased speed of response after memantine augmentation, compared to placebo augmentation in bipolar depression patients.**

## References

- [1] Cryan JF, O'Leary OF. Neuroscience. A glutamate pathway to faster-acting antidepressants? Science 2010; 329: 913-4.
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- [4] Anand A, Gunn, AD, Barkay G, Karne H, Nurnberger Jr, Mathew SJ, Ghosh S. Early antidepressant effect of memantine during augmentation of lamotrigine inadequate response in bipolar depression. Bipolar Disorders 2012;14-1:64-70.