The Effects of Memantine Added to Cholinesterase Inhibitors on NPI Behavioral Domains: Pooled Post Hoc Analysis of 3 Randomized Controlled Trials in Patients With Moderate to Severe AD

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Objective: To assess the effect of memantine (MEM) and a cholinesterase inhibitor (ChEI) vs ChEI alone on four syndrome domains of the Neuropsychiatric Inventory (NPI).

Background: Neuropsychiatric symptoms negatively impact daily function and quality of life, hasten time to institutionalization, and increase overall healthcare costs. MEM significantly improved multiple domain scores of the NPI in patients with Alzheimer's disease (AD) compared with placebo (PBO).

Design/Methods: Data were pooled for participants with moderate to severe AD (baseline MMSE<20) from three, phase 3, randomized, double-blind, PBO-controlled 24-week trials (Tariot et al. *JAMA*, 2004; Porsteinsson et al. *Alzheimer Research*, 2008; Grossberg et al. *CNS Drugs*, 2013). The NPI has 12 items that were grouped into four syndrome domains: psychosis (agitation/aggression, hallucinations, delusions, irritability/lability), neurovegetative (aberrant motor behavior, nighttime behavior, appetite/eating change), frontal (disinhibition, euphoria/elation), and mood (anxiety, depression/dysphoria, apathy), based on previous analyses (Frisoni et al. *Dement Geriatr Cogn Disord*, 10:130-138, 1999). MEM/ChEI- and PBO/ChEI-treated participants were compared using an ANCOVA model estimating change from baseline at each time point.

Results: Of 1262 patients, 637 were treated with MEM/ChEIs and 625 with PBO/ChEIs (age [mean±SD]: 75.7±8.3 years; baseline MMSE: 11.5±3.5; baseline NPI total score: 14.9±14.6). For all syndrome domains, mean treatment differences favored MEM/ChEIs over PBO/ChEIs. For psychosis symptoms, MEM/ChEI-treated patients improved significantly compared with PBO/ChEI-treated patients at 12 (LSMD ‑1.167, *P*<0.0001) and 24 (LSMD -1.238, *P*<0.0001) weeks. Similarly, neurovegetative scores were significantly improved for MEM/ChEI vs PBO/ChEI-treated patients at 12 (LSMD -0.621, *P*=0.0103) and 24 (LSMD -0.583, *P*=0.0441) weeks. For frontal and mood symptoms, no significant LSMDs were observed at 12 or 24 weeks. No analyses showed PBO/ChEI to be superior to MEM/ChEI.

Conclusions: In patients with moderate to severe AD taking ChEIs, treatment with the combination of memantine and a ChEI was associated with significant benefit for psychosis and neurovegetative behavioral syndromes compared with ChEI alone.