NMDA Receptor Blocking Shown to Improve Functional Ability in Severe AD

While pharmacologic therapies for mild-to-moderate stage Alzheimer disease (AD) are currently available, agents for the treatment of more severe AD have yet to be approved. Glutamate, the primary excitatory brain neurotransmitter, normally regulates cell signaling by binding various postsynaptic receptors. However, glutamatergic overstimulation of the N-methyl-D-aspartate (NMDA) receptor may cause excitotoxicity, and has been implicated in the pathogenesis of neurodegenerative dosorders. If interception of this pathway can slow cell death, then introduction of an NMDA-receptor antagonist should be of therapeutic benefit. Based on this rationale, memantine, an uncompetitive NMDA receptor antagonist, was investigated for its treatment efficacy of late-stage AD.

In a double-blind, parallel-group study, 252 patients with moderate-to-severe AD were randomised to receive memantine 20mg daily or placebo for 28 weeks. Of these, 181 patients completed the study and were assessed at baseline, at mid-study and at the end of treatment (week 28). The primary efficacy variables were the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia (ADCS-ADLsev). The CIBIC-Plus quantifies overall changes in cognition, function and behaviour relative to baseline (increasing score signifies worsening disease). The ADCS-ADLsev is a questionnaire designed to determine a patient's ability to perform various activities of daily living, with lower scores indicating declining abilities.

Based on ADCS-ADLsev scores, at week 28 significantly less deterioration was observed in the treatment arm than in the placebo group (score decreases of 2.5 and 5.9 points, respectively). Bolstering this trend, the CIBIC-Plus ratings at week 28 were 4.4 for the memantine group, versus 4.7 for placebo. Subgroup analysis indicated that both patients with moderate and severe AD benefited from memantine over placebo for all outcome measures.

The results of this trial are promising and point towards therapeutic alternatives to anticholinergics. If memantine is, in fact, effective in lessening the severity of AD, there is reason to hope that it might be similarly capable of alleviating the pathogenesis of other neurological disorders in which NMDA receptor overstimulation has been implicated.

Source

Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333-41.