## Treatment of Alzheimer disease with an AMPA potentiator

Chappell et al. found that an AMPA potentiator had no cognitive benefit in patients with mild to moderate AD. The authors point out that the dose tested was limited by animal toxicology although a comparable dose in animals did provide a cognitive benefit.

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## Are null findings informative? A clinical trial of AMPA modulation and AD

Commentary by Raj C. Shah, MD; and David A. Bennett, MD

Translational research advances basic science discoveries from the bench to the bedside to improve public health via disease prevention and treatment. In Alzheimer disease (AD), different model systems have been developed to identify therapeutic targets. Long-term potentiation (LTP) is one such model used to study memory function at a cellular level. In LTP, brief periods of intense synaptic activation increase the strength of the synaptic response over time. AMPA-type glutamate receptors are required to generate LTP and positive AMPA receptor modulators have been developed which increase LTP. These modulators enhance AMPA receptor-mediated responses in the hippocampus and reverse age-associated memory deficits in rats.

Based on preclinical findings and human phase I studies, Chappell et al. conducted an 11-week, phase II randomized controlled trial of LY451395, a positive AMPA modulator. The study had 70% power to detect at least a 1.7-point difference on a cognitive measure widely used in AD clinical trials. More than 90% of participants completed the study, which is quite good for AD clinical trials. Unfortunately, the study failed to demonstrate cognitive benefit on the primary outcome measure, although behavior on a secondary outcome measure did improve.

The null finding of this well designed, well conducted, and appropriately analyzed study with a balanced discussion provides fairly conclusive evidence that LY451395 at the tested doses does not improve cognition. Other positive AMPA receptor modulators that can be tolerated at higher doses may have possible benefit. It is also possible that this novel drug class may be useful for the treatment of behavior changes common in AD. Further work is needed in this area.

The information gained from this study will inform future clinical trials involving AMPA modulation for both cognitive and behavior outcome measures. Peer-reviewed publication of clinical trial findings is an essential element for advancing translational research in AD. Even null findings advance the field, when well conducted.

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