

## **Study confirms benefit of combination therapy for Alzheimer's disease**

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Extended treatment with Alzheimer's disease drugs can significantly slow the rate at which the disorder advances, and combination therapy with two different classes of drugs is even better at helping patients maintain their ability to perform daily activities. Results from the first long-term study of the real-world use of Alzheimer's drugs, published by researchers from Massachusetts General Hospital in the July/September issue of *Alzheimer Disease and Associated Disorders*, support a level of effectiveness that may not be immediately apparent to patients or their family members.

"There has been the impression that these drugs only work for some patients and for a limited amount of time," says Alireza Atri, MD, PhD, of the MGH Department of Neurology, lead author of the current study. "One of the problems in judging these drugs has been that patients naturally continue to decline, which can make them think the drugs have stopped working. But our study, which has some unique strengths, indicates that treatment does have long-term benefit."

Two types of medications have received FDA approval for Alzheimer's treatment. Cholinesterase inhibitors have been available since the mid-1990s and act by inhibiting the breakdown of the neurotransmitter acetylcholine. The drug memantine, which received FDA approval in 2003, is the first of a second class of agents that modulate the actions of the amino acid glutamate and is often used in combination with cholinesterase inhibitors (CIs).



"Clinical trials that drug companies conduct for FDA approval only last six months and enroll patients according to very specific criteria," Atri explains. "Only large-population studies can really tell us how these drugs work for the full range of patients in real-life situations." The researchers were able to conduct such a study by analyzing data on patients treated at the MGH Memory Disorders Unit since 1990, including 144 who did not receive any pharmaceutical treatment, 122 treated with a CI alone and 116 who received both a CI and memantine. As part of their regular treatment, every six months patients received standardized assessments of both cognitive abilities and how well they carried out daily activities.

The results showed significant differences in the rate of symptom progression among all three groups – with the smallest level of decline in those receiving combination therapy. While there was an average of two and a half years' worth of data on the study participants, the researchers analyzed the information with a statistical model that predicted probable outcomes for up to four years. Although the model's projection of future benefits is conservative, it predicted that the longer patients kept receiving combination therapy, the smaller their rate of decline would become, suggesting that treatment might even protect brain cells from further damage, a possibility needing further investigation.

"Finding something that could actually modify the course of the disease is the Holy Grail of Alzheimer's treatment, but we really don't know if that is happening or what the mechanism behind these effects might be," Atri explains. "What we can say now is that providers should help patients understand that the benefits of these drugs are long term and may not be apparent in the first months of treatment. Even if a patient's symptoms get worse, that doesn't mean the drug isn't working, since the decline probably would have been much greater without therapy." Atri is an instructor in Neurology at Harvard Medical School (HMS) and associate director of the Center for Translational Cognitive



Neuroscience at the Veterans Administration Hospital in Bedford, Mass.

John Growdon, MD – director of the MGH Memory Disorders Unit, professor of Neurology at HMS, and senior author of the paper – explains, "The results of this study should change the way we treat patients with Alzheimer's disease. Cholinesterase inhibitors are approved for use in mild to moderate dementia, while memantine has been approved for advanced dementia. But it looks like there is an advantage in prescribing both drugs as initial treatment."

Source: Massachusetts General Hospital

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