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Levetiracetam in Alzheimer's Disease: Do Epileptologists Already Have the Cure?

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Effect of Levetiracetam on Cognition in Patients With Alzheimer Disease With and Without Epileptiform Activity: A Randomized Clinical Trial

Vossel K, Ranasinghe KG, Beagle AJ, et al. *JAMA Neurol.* 2021;78(11):1345-1354. doi:10.1001/jamaneurol.2021.3310.

Importance: Network hyperexcitability may contribute to cognitive dysfunction in patients with Alzheimer disease (AD). Objective: To determine the ability of the antiseizure drug levetiracetam to improve cognition in persons with AD. Design, setting, and participants: The Levetiracetam for Alzheimer's Disease–Associated Network Hyperexcitability (LEV-AD) study was a phase 2a randomized double-blinded placebo-controlled crossover clinical trial of 34 adults with AD that was conducted at the University of California, San Francisco, and the University of Minnesota, Twin Cities, between October 16, 2014, and July 21, 2020. Participants were adults 80 years and younger who had a Mini Mental State Examination score of 18 points or higher and/or a Clinical Dementia Rating score of less than 2 points. Screening included overnight video electroencephalography and a 1-hour resting magnetoencephalography examination. Interventions: Group A received placebo twice daily for 4 weeks followed by a 4-week washout period, then oral levetiracetam, 125 mg, twice daily for 4 weeks. Group B received treatment using the reverse sequence. Main outcomes and measures: The primary outcome was the ability of levetiracetam treatment to improve executive function (measured by the National Institutes of Health Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research [NIH-EXAMINER] composite score). Secondary outcomes were cognition (measured by the Stroop Color and Word Test [Stroop] interference naming subscale and the Alzheimer's Disease Assessment Scale—Cognitive Subscale) and disability. Exploratory outcomes included performance on a virtual route learning test and scores on cognitive and functional tests among participants with epileptiform activity. Results: Of 54 adults assessed for eligibility, 11 did not meet study criteria, and 9 declined to participate. A total of 34 adults (21 women [61.8%]; mean [SD] age, 62.3 [7.7] years) with AD were enrolled and randomized (17 participants to group A and 17 participants to group B). Thirteen participants (38.2%) were categorized as having epileptiform activity. In total, 28 participants (82.4%) completed the study, 10 of whom (35.7%) had epileptiform activity. Overall, treatment with levetiracetam did not change NIH-EXAMINER composite scores (mean difference vs placebo, .07 points; 95% CI, −.18 to .32 points; P = .55) or secondary measures. However, among participants with epileptiform activity, levetiracetam treatment improved performance on the Stroop interference naming subscale (net improvement vs placebo, 7.4 points; 95% CI, .2–14.7 points; P = .046) and the virtual route learning test (t = 2.36; Cohen f2 = .11; P = .02). There were no treatment discontinuations because of adverse events. Conclusions and relevance: In this randomized clinical trial, levetiracetam was well tolerated and, although it did not improve the primary outcome, in prespecified analysis, levetiracetam improved performance on spatial memory and executive function tasks in patients with AD and epileptiform activity. These exploratory findings warrant further assessment of antiseizure approaches in AD.

Commentary

Alzheimer's disease (AD), one of the most common neurological disorders, has remained a frustratingly difficult disorder to treat despite decades of advancements in diagnosis. There is an urgent need for therapeutics given its projected increase in prevalence with the aging of the US population, and the

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financial burden on societies and health care systems. For example, the health care and services related costs in 2022 are estimated to be $321 billion.[1]

Network dysfunction and hyperexcitability has been identified as a feature of AD[2] and manifests itself electrophysiologically as epileptiform abnormalities (EA) on EEG or Magnetic Encephalogram (MEG) and clinically as seizures. In cross-sectional studies of AD, prolonged EEG monitoring has identified epileptiform abnormalities in 22% of patients with EEG alone[3] and up to 42% when combining EEG and MEG.[4] The presence of EAs has been associated with a more aggressive disease course with rapid decline in executive function and the mini mental status exam.[4] The logical next step was to examine the impact of treating EAs with an antiseizure medication to determine whether this would affect disease course. We finally have a randomized control trial to help us answer this question; The Levetiracetam for Alzheimer's Disease–Associated Network Hyperexcitability (LEV-AD) study. Low dose levetiracetam was chosen given its favorable effects in animal models of AD[5] and in a functional MRI-based study of reducing hippocampal hyperactivity in amnestic mild cognitive impairment.[6] Levetiracetam was also an appealing intervention given its wide-spread clinical use and relatively low cost compared to the other biologics currently being studied.

In the LEV-AD trial, 34 subjects with AD were randomized to receive placebo or levetiracetam 125 mg twice a day for 4 weeks, followed by a 4-week wash out, and then a cross over to levetiracetam or placebo for another 4 weeks depending on what they received during the first phase of the study. Although the initial aim was to recruit only subjects younger than 70 with a history of seizures or EAs, the criteria had to be broadened to improve recruitment and subjects with or without EAs were now included. Subjects had an overnight EEG followed by a 1-hour M/EEG the next day. Cognitive assessments included the National Institutes of Health Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (NIH-EXAMINER) which consists of a battery of tests measuring executive functions, Stroop color and word test, the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog), and a virtual route learning test. Several caregiver measures were also assessed. The 1-hour M/EEG and cognitive battery was repeated during each study visit. Overall, the drug was well tolerated with no discontinuations due to adverse side effects.

The primary outcome of the study, the NIH-EXAMINER composite score was negative, so were the secondary cognitive and questionnaire outcomes, and the outcome of EA suppression. However, a prespecified subset analysis in subjects with EAs (13/34) showed an improvement on the learning rates in the visual route learning test and the Stroop interference naming subscale. There were differences between the two study sites with only the UCSF participants benefiting from the drug likely because of the 56% prevalence of EA in the cohort.

The study represents an important and essential step in identifying whether antiseizure medications have a role in treating AD. It was clearly difficult to recruit for this labor-intensive study. Future studies will need to take that into account and will likely need to plan for remote assessments in case pandemic restrictions arise again. The other challenge is identifying the patients who might benefit the most from the intervention. This is not a trivial matter as EA in AD, when they occur, are not frequent, their morphology not as robust, and even a panel of board certified epileptologists might disagree on whether a waveform is truly epileptiform or not.[3] Is a patient with an "equivocal" sharp wave as likely to benefit as a patient with frequent, robust or periodic sharp waves or subclinical seizures? It is also worth considering whether we should include subjects with temporal rhythmic delta activity or unilateral small sharp spikes. We also need to explore the effect of spike laterality on the outcomes of interest and will need larger sample sizes to do so. It seems EEG-identified EAs tend to be left sided in most cases and perhaps more sensitive verbal memory measures might be needed. Other neurophysiological tools such as transcranial magnetic stimulation might also provide neurophysiological evidence of network hyperexcitability and can increase the pool of patients who could benefit. Perhaps more sophisticated quantitative EEG measures will also be useful in the future. We are likely underestimating the true burden of EA and seizures by relying solely on surface based studies.[7]

Importantly, based on the data from the trial, a future trial restricted to AD patients with EA would only require 20 participants to show a difference on the NIH-EXAMINER and 60 for the ADAS-Cog.

The other challenge is identifying clinically meaningful outcome measures in AD. This is an issue that remains unresolved in the field.[8] Although the findings in the LEV-AD subgroup analysis were statistically significant, it is unclear if they met the threshold of clinical significance with no apparent changes noted by the subject's caregivers based on their questionnaire responses. Will levetiracetam prolong someone's ability to drive given the improvement seen on the visual route learning test?

Patients with AD have frequent neuropsychiatric comorbidities and exposure to levetiracetam may exacerbate their symptoms. This should be considered when assessing the risks and benefits of the intervention. Based on the trial, a 4-week course was well tolerated but it is unclear if that will remain the case with prolonged daily exposure.

There are several other ongoing trials exploring the role of antiseizure medications in AD that will advance the field further. Ultimately, what will be needed is a large multicenter trial with longer follow up to determine whether levetiracetam affects disease course and outcomes and will become an AD treatment option for some patients. Until then, we will have to anxiously wait for more evidence, and grapple with the dilemma of whether to treat EAs in AD when and if we find them.

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