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Commentary

Putting the Brakes on Accelerated Cognitive Decline in Alzheimer's Disease with Epileptic Activity

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Abstract. Epileptic activity is known to exacerbate Alzheimer's disease (AD) pathology and worsen disease course. However, few studies have assessed whether treating epileptic activity with antiseizure drugs (ASDs) can improve patient outcomes. The current study by Hautecloque-Raysz et al. shows that patients with prodromal AD and epilepsy (epAD) fare well with ASD treatment, achieving seizure control in a large majority of cases using low dosage ASDs in monotherapy. Compared to slowly progressing AD patients without epilepsy, treated epAD patients experienced a similarly slow cognitive decline. These results suggest that ASDs that suppress seizures can improve outcomes in AD patients with epileptic activity.

Keywords: Alzheimer's disease, antiseizure drugs, epilepsy, epileptic activity, mild cognitive impairment

Epileptic activity in Alzheimer's disease (AD) is increasingly recognized as an important condition to detect and treat early due its exacerbation of AD pathophysiology and contribution to disease progression. Several studies have shown that epileptic activity (epilepsy or subclinical epileptiform activity) occurs early and often in AD and is associated with a more rapid cognitive decline [1–4] and greater neuropathology [5]. In a phase IIa clinical trial, we found that treatment with low doses of levetiracetam over four weeks can improve spatial memory and executive function in AD patients with detectable epileptic activity [6]. However, more studies are needed to guide clinical practice for epileptic activity in AD, both in detection and treatment. Outcomes of treatment with different antiseizure drugs (ASDs) with a range of dosages for epileptic activity in AD need to be systematically assessed.

The current study by Hautecloque-Raysz et al. [7] provides a useful longitudinal assessment of the outcome of treatment with ASDs in epileptic prodromal AD (epAD) cases (i.e., patients with epilepsy and mild cognitive impairment due to AD). The investigators studied the effects of ASDs on AD symptoms over the course of four to five years. The comparison group was patients with prodromal AD without epilepsy. Ninety percent of epAD patients had seizure reduction of greater than 50%, and all but one of these responders were effectively treated with monotherapy. These results are consistent with previous findings [8, 9]. The top three ASDs used were lamotrigine, lacosamide, and benzodiazepines. Levetiracetam was often withdrawn due to adverse events related to mood and behavior. Brivaracetam might have been a useful alternative to levetiracetam

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in such cases, as it has been associated with lower rates of behavioral adverse events [10, 11], but it is not as widely available or prescribed. In long-term follow up, both the epAD group treated with ASDs and the AD comparison group declined at a very slow rate (less than one point a year on the Mini-Mental State Examination), with no differences in rate of decline between groups. There were minor and unavoidable limitations, most notably lack of a control group with AD and untreated seizures. Additionally, distinguishing epAD from non-epileptic prodromal AD is inherently difficult, as seizure presentations in AD can be subtle and scalp electrode recordings can miss seizures and epileptiform activity.

When considered in the context of currently knowledge that epilepsy, when untreated, is associated with faster cognitive decline in AD [3], the results from Hautecloque-Raysz et al. support a potential disease modification by ASDs in epAD cases by preventing their more rapid decline (Fig. 1). Figure 1 superimposes results from the current study on our previous findings that patients with AD and subclinical epileptic activity (AD-Epi+) have accelerated cognitive decline compared to those without epileptic activity (AD-Epi-) [1]. Although the patients in the study by Hautecloque-Raysz et al. differed from those in our study by being older (diagnosed in 70 s versus 60 s), having different levels of education (11-12 years versus 16 years), and presenting with overt seizures rather than subclinical epileptic activity, it is intriguing to consider that ASDs could slow disease progression in AD patients with detectible epileptic activity. Preclinical models support the concept that certain ASDs that treat AD-associated epileptic activity can modify and improve brain structure and function. ASDs that chronically suppress epileptic activity can remodel hippocampal circuits to improve synaptic plasticity [12]. Moreover, Fu et al. showed that levetiracetam treatment over two weeks normalizes seizure-associated alterations in hippocampal neurogenesis and improves spatial discrimination in a transgenic mouse model of AD [13]. Similar beneficial effects could be happening in epAD patients who are treated chronically with ASDs.

ASDs with different mechanisms of action had similar efficacy in treating seizures associated with AD, even though much of the research focus has been on the SV2A mechanisms of action (levetiracetam). Notably, the study included only epAD patients who stayed on ASDs continuously over three or more years, which resulted in a focus on ASDs that were best tolerated. It is helpful to know that lacosamide

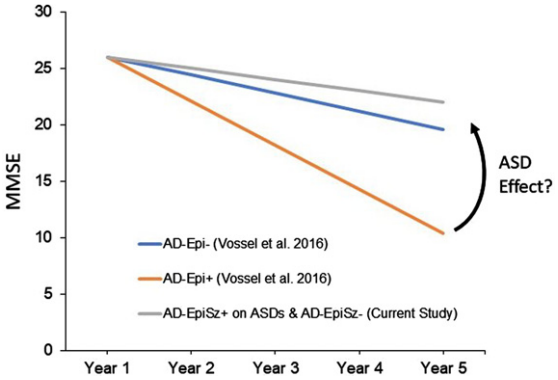

Fig. 1. Potential disease modification with treatment of antiseizure drugs (ASD) in patients with Alzheimer's disease (AD) and epileptic activity. In a previous study by Vossel et al. [1], AD patients with subclinical epileptic activity, detected by overnight EEG and/or 1-h magnetoencephalography recordings, had a faster decline in their Mini-Mental State Examination (MMSE) scores (AD-Epi+, 3.9 points/year) than AD patients without detectable epileptic activity (AD-Epi-, 1.6 points/year). In the current study by Hautecloque-Raysz et al. [7], patients with prodromal AD and epileptic seizures (AD-EpiSz+) treated with ASDs had a slow cognitive decline of one MMSE point a year, which was similar to the slow rate of decline in prodromal AD patients without epilepsy in their study (AD-EpiSz-), as well as the slow rate of decline in the AD-Epi- group in Vossel et al. These studies indicate that epileptic activity worsens cognitive decline in AD and that ASDs can slow progression in AD patients with detectible epileptic activity.

was efficacious without cognitive side effects in the epAD group as there is not much literature about this medication in AD. It is somewhat surprising that benzodiazepines did not worsen cognitive decline in the epAD group, but this may reflect that the beneficial effects of suppressing seizures counters the cognitive side effects of benzodiazepines.

The study by Hautecloque-Raysz et al., along with others on this topic, adds to precision medicine approaches in AD by showing that prodromal AD patients with detectable epileptic activity are excellent candidates for treatment with newer generation ASDs, which often suppress seizures at low doses and in monotherapy and can slow cognitive decline to match that of slowly progressing AD patients without epileptic activity. Investigators can build on these findings by determining which ASDs and what dosages are most useful to effectively treat epileptic activity associated with AD and their effects on cognitive and functional outcomes. Large populations studies, such as real-world data platforms utilizing electronic health records, pharmacy data, and other sources, will create more inclusive and broader databases to address these important questions. These studies will have extensive clinical utility, as an

estimated 60% of AD patients or more experience seizures or subclinical epileptiform activity.

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CONFLICT OF INTEREST

The author has no conflict of interest to report.

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