IMPORTANCE Epileptic activity associated with Alzheimer disease (AD) deserves increased attention because it has a harmful impact on these patients, can easily go unrecognized and untreated, and may reflect pathogenic processes that also contribute to other aspects of the illness. We report key features of AD-related seizures and epileptiform activity that are instructive for clinical practice and highlight similarities between AD and transgenic animal models of the disease.

OBJECTIVE To describe common clinical characteristics and treatment outcomes of patients with amnestic mild cognitive impairment (aMCI) or early AD who also have epilepsy or subclinical epileptiform activity.

DESIGN Retrospective observational study from 2007 to 2012.

SETTING Memory and Aging Center, University of California, San Francisco.

PATIENTS We studied 54 patients with a diagnosis of aMCI plus epilepsy (n = 12), AD plus epilepsy (n = 35), and AD plus subclinical epileptiform activity (n = 7).

MAIN OUTCOMES AND MEASURES Clinical and demographic data, electroencephalogram (EEG) readings, and treatment responses to antiepileptic medications.

RESULTS Patients with aMCI who had epilepsy presented with symptoms of cognitive decline 6.8 years earlier than patients with aMCI who did not have epilepsy (64.3 vs 71.1 years; P = .02). Patients with AD who had epilepsy presented with cognitive decline 5.5 years earlier than patients with AD who did not have epilepsy (64.8 vs 70.3 years; P = .001). Patients with AD who had subclinical epileptiform activity also had an early onset of cognitive decline (58.9 years). The timing of seizure onset in patients with aMCI and AD was nonuniform (P < .001), clustering near the onset of cognitive decline. Epilepsies were most often complex partial seizures (47%) and more than half were nonconvulsive (55%). Serial or extended EEG monitoring appeared to be more effective than routine EEG at detecting interictal and subclinical epileptiform activity. Epileptic foci were predominantly unilateral and temporal. Of the most commonly prescribed antiepileptics, treatment outcomes appeared to be better for lamotrigine and levetiracetam than for phenytoin.

CONCLUSIONS AND RELEVANCE Common clinical features of patients with aMCI- or AD-associated epilepsy at our center included early age at onset of cognitive decline, early incidence of seizures in the disease course, unilateral temporal epileptic foci detected by serial/extended EEG, transient cognitive dysfunction, and good seizure control and tolerability with lamotrigine and levetiracetam. Careful identification and treatment of epilepsy in such patients may improve their clinical course.
Alzheimer disease (AD) carries an increased risk of seizures. An estimated 10% to 22% of patients with AD develop unprovoked seizures, with higher rates in familial and early-onset cases. Patients with AD and seizure disorders have greater cognitive impairment, faster progression of symptoms, and more severe neuronal loss at autopsy than those without seizures. Because it is important to identify and treat these patients early, it is imperative to understand their characteristic clinical features.

In this group with AD and seizures, little is known about typical seizure semiology, diagnostic utility of electroencephalogram (EEG), common location of epileptogenic foci, seizure incidence relative to the onset of other neurodegenerative disease symptoms, and treatment responses to different antiepileptic medications. The goal of this report is to fill some of these knowledge gaps by describing epilepsies encountered in patients with mild AD and amnestic mild cognitive impairment (aMCI), a condition widely considered to be a harbinger or early stage of AD. Notably, more than half of the patients with aMCI and AD and comorbid epilepsy had only nonconvulsive seizures, which can easily go unrecognized.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents
All research subjects provided written informed consent before participating in protocols from which data were derived and were not required to reconsent for this analysis. This study was approved by the University of California, San Francisco Committee on Human Research.

Patient Selection
We searched the database of the Memory and Aging Center at the University of California, San Francisco for all patients who presented with cognitive decline between 2007 and 2012 and met the International Working Group research criteria for aMCI (n = 233) or National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association research criteria for probable AD (n = 1024). Eighty-eight percent of patients were seen in clinic, 5% in research, and 6% in clinic and research. Among these patients, we searched for patients with a clinical diagnosis of epilepsy or subclinical epileptiform activity. An epilepsy diagnosis required 2 or more unprovoked seizures or a first unprovoked seizure in the setting of a corroborating EEG showing epileptiform activity. We identified 17 patients with aMCI-epilepsy, none with aMCI-subclinical epileptiform activity (of 16 with EEG), 55 with AD-epilepsy, and 8 with AD-subclinical epileptiform activity (of 8 with EEG). We then excluded 1 patient with aMCI and 7 patients with AD who had seizure onset during childhood or early adulthood (before age 30 years). Of the remaining patients, we excluded those with other possible epilepsy risk factors including cortical stroke(s) (2 patients with aMCI, 4 patients with AD), cavernous hemangioma (1 patient with aMCI), meningioma (1 patient with aMCI, 1 patient with AD), suspected brain tumor (1 patient with AD), subdural hematoma (3 patients with AD), history of alcohol abuse (3 patients with AD), amyloid angiopathy (1 patient with AD), and enrollment in clinical treatment trials (1 patient with AD). None of the remaining patients had focal cortical dysplasia, head trauma with loss of consciousness more than 30 minutes, hydrocephalus, or substance abuse. Diagnoses were made by a multidisciplinary team consisting of behavioral neurologists, epileptologists, neuropsychologists, and psychiatrists, who performed extensive behavioral, neuropsychological, neurophysiological, and neuroimaging assessments. Seizures were classified and described according to their clinical features following the revised guidelines of the International League Against Epilepsy. Patients who had at least 1 seizure that involved limb shaking were classified as having convulsive seizures. Generalized seizures were defined as seizures rapidly involving both hemispheres with no clear or consistent focus. Focal seizures were subdivided into simple partial seizures, which involved no alteration in cognition or consciousness, and complex partial seizures, which involved dyscognitive symptoms.

We included 12 cases of aMCI-epilepsy, 35 cases of AD-epilepsy, and 7 cases of AD-subclinical epileptiform activity. Twelve patients with AD had an additional biomarker evaluation: 9 had fluorodeoxyglucose positron emission tomography, 3 of whom also had carbon 11-labeled Pittsburgh Compound B positron emission tomography amyloid imaging, and 3 had cerebrospinal fluid analysis for total tau, phosphorylated tau, and β-amyloid 1-42 peptide (Athena Diagnostics) levels. In all 12 cases, the biomarkers were supportive of an AD diagnosis. Apolipoprotein (apo) E genotyping was available for 11 patients with AD: 4 were homozygous E3/E3, 5 were E3/E4, and 2 were homozygous E4/E4. Two patients in the AD group came to autopsy and both met pathologic criteria for high-likelihood AD (National Institute on Aging–Reagan). A history of mild head trauma was reported in 21% of cases with epilepsy (2 patients with aMCI and 8 patients with AD). The date of onset of seizures was obtained by asking patients and caregivers when they noticed the first transient spells that were later characteristic of the patient’s epilepsy. The date of diagnosis of neurodegenerative disease was the first visit when all research criteria were fulfilled to establish the diagnosis of aMCI or probable AD. General cognitive functioning was assessed using the Mini-Mental State Examination. Scores range from 0 to 30, with higher scores denoting better performance. Only Mini-Mental State Examination scores obtained within 5 years of seizure onset were included in the analysis.
Clinical EEG recordings were obtained using a standard international 10-20 electrode placement. Recordings took place during routine 20-minute sessions unless otherwise stated in Table 1 or the eTable in Supplement. Epileptic foci were defined as the regions of maximum electronegativity, corresponding with scalp electrodes as follows: frontal (Fp1, Fp2, F3, F4), central frontal (Fz), central (C3, Cz, C4), central parietal (Pz), frontotemporal (F7, F8), temporal (T3, T4), posterior temporal (T5, T6), parietal (P3, P4), and occipital (O1, O2).

### Outcome Definition

Responses to antiepileptic drugs were assessed over a span of at least 3 months of continuous treatment and scored as follows: seizure free (no seizures at all), partial response (seizures reduced in severity or frequency), neutral (seizures were neither better nor worse), or paradoxical worsening (seizures increased in severity or frequency). These measurements were based on the observations of patients and their caregivers as recorded by physicians during clinic visits. Intolerance that necessitated discontinuation of a drug was reported with no restrictions on duration of treatment.

### Statistical Analyses

Differences between groups within the aMCI and AD cohorts were evaluated with the χ² test for sex, handedness, EEG type, and ratios of patients with early- (<65 years) vs late-onset (≥65 years) cognitive decline and the Mann-Whitney rank sum test for years of education and age at onset and age at diagnosis of aMCI or AD. The timing of seizure onset relative to the year of aMCI or AD onset was compared with a uniform distribution by the χ² test. Our a priori hypothesis was that this distribution would be uniform. The tolerability and responder ratios (partial response or seizure freedom) for different antiepileptic medications were assessed with the Fisher exact test for pairwise comparisons. All pairwise comparisons were 2-tailed and P < .05 was required to reject the null hypothesis. Statistical analyses were performed with SigmaPlot version 12.0 (Systat Software Inc).

### Results

Seizures and Epileptiform Activity Are Associated With an Earlier Age at Onset of Cognitive Decline

Clinical and demographic characteristics of the study groups are summarized in Table 2 and the eTable in Supplement. In the aMCI and AD cohorts, cognitive decline began roughly 5 to 7 years earlier in patients who developed epilepsy than in those without epilepsy (Table 2). Cognitive decline began before 65 years of age in 50% of aMCI-epilepsy cases compared with 21% of aMCI cases without epilepsy (P = .051) and in 51% of AD-epilepsy cases compared with 26% of AD cases without epilepsy (P = .002). Similarly, the diagnosis of aMCI or AD...
Seizures Occur Early in Relation to Cognitive Decline
Seizures in aMCI and AD generally began early in the disease course when patients had mild impairments on cognitive testing. The timing of new-onset seizures was nonuniform (P < .001) with clustering near the onset of cognitive decline (Figure 1A). Seizure onset preceded or coincided with the diagnosis of aMCI or AD in 83% (39 of 47) of patients (Figure 1B), and an epilepsy diagnosis preceded or coincided with the diagnosis of aMCI or AD in 51% (24 of 47) of patients. Scores on the Mini-Mental State Examination, which is a global test of cognition, nearest to the date of the first seizure were grouped near the upper end of the scale, indicating mild impairments (Figure 1C).

Seizure Semiology
The seizure type and semiology for each epilepsy case, along with the first nonepileptic symptoms of AD, are presented in Table 3 and the eTable in Supplement. The most common seizure type, occurring in 47% of cases (22 of 47), started locally and was associated with dyscognitive symptoms (complex partial seizures). Of the 22 cases with complex partial seizures, 7 developed bilateral convulsive seizures. Among the 25 remaining cases, 17 had apparent generalized seizures without clear focal or lateralizing symptoms and 8 presented with simple partial seizures.

Notably, 55% of the patients with aMCI or AD who had epilepsy (26 of 47) had only nonconvulsive seizures. Nonconvulsive symptoms included jamais vu, déjà vu, sensory phenomena (eg, metallic taste, burning smell, epigastric rising sensation, prickling, or chest warmth), psychic phenomena (eg, intense fear or dread), speech/behavioral arrest, aphasia, and amnestic spells. Five patients with epilepsy (3 with aMCI and 2 with AD) had pacemaker implantation after ictal bradycardia or asystole.

Epileptiform Activity Detection and Location
The EEG revealed epileptiform activity in 62% (24 of 39) of patients with aMCI or AD who were evaluated for seizures and
in 6% (7 of 113) of those without known seizures. The EEGs in nonepilepsy cases were obtained as part of a routine workup to rule out other causes of cognitive decline, which in some cases included vague reports of clinical fluctuations. None of the patients in this group were diagnosed with epilepsy. Across all patients, serial EEGs (≥2) or long-term video EEG monitoring (≥24 hours) appeared to be more effective at detecting epileptiform activity than routine EEG (Table 1). Sleep-deprived EEG was rarely performed.

Epileptic foci were predominantly unilateral and most commonly temporal, followed by frontotemporal, frontal, central, and generalized (Figure 2). Seventy-eight percent (7 of 9) of epileptiform EEGs in patients with aMCI or AD who had generalized seizures revealed a focal pattern. Epileptiform activity often occurred in brain regions supporting functions that were impaired clinically. Eighty-two percent (18 of 22) of cases with temporal/frontotemporal epileptic foci presented initially with memory impairments. Two patients with left frontal epileptic foci presented initially with aphasia; 1 of them is described in Figure 3.

**Response to Antiepileptic Treatment**
Clinical responses to commonly prescribed antiepileptic medications are provided in Table 4 and Table 5. The 4 medications prescribed most frequently as monotherapy were lamotrigine (n = 25), levetiracetam (n = 23), phenytoin (n = 9), and valproic acid (n = 11). Lamotrigine, levetiracetam, and valproic acid were all well tolerated, whereas phenytoin was poorly tolerated (22% tolerability; \( P < .05 \) vs lamotrigine, levetiracetam, and valproic acid). The antiepileptic efficacy of lamotrigine (53% seizure free; 41% partial responders) and levetiracetam (44% seizure free; 50% partial responders) was higher than that of phenytoin (17% seizure free; 33% partial responders) (\( P < .05 \)). Valproic acid administration provided

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**Table 3. Seizure Subtype, Semiology, and Nonepileptic Symptoms of Cognitive Decline for All Patients With aMCI-Epilepsy or AD-Epilepsy**

<table>
<thead>
<tr>
<th>Epilepsy Type</th>
<th>Sample Size</th>
<th>Semiology (No. of Patients)*</th>
<th>First Nonepileptic Symptoms of Cognitive Decline (No. of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple partial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>7</td>
<td>Jamais vu/déjà vu (4), psychic phenomena (2), sensory phenomena (4)</td>
<td>Apathy (1), memory (6)</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>Single-limb shaking (1)</td>
<td>Language (1)</td>
</tr>
<tr>
<td>Complex partial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>11</td>
<td>Altered consciousness (6), amnestic spells (1), confusion (2), psychic phenomena (4), sensory phenomena (7), speech arrest (2)</td>
<td>Language (1), memory (10)</td>
</tr>
<tr>
<td>Cb</td>
<td>11</td>
<td>Altered consciousness (3), amnestic spells (2), bilateral limb shaking (5), confusion (4), single-limb shaking (7), speech arrest (3)</td>
<td>Apathy (1), executive (1), language (1), memory (8)</td>
</tr>
<tr>
<td>Generalized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>7</td>
<td>Atonic/tonic (2), behavioral arrest (4), staring spells (1)</td>
<td>Language (2), memory (5)</td>
</tr>
<tr>
<td>C</td>
<td>10</td>
<td>Atonic (1), behavioral arrest (1), epileptic myoclonus (3), generalized tonic-clonic (6), staring spells (1)</td>
<td>Language (1), memory (9)</td>
</tr>
</tbody>
</table>

*Abbreviations: C, convulsive; NC, nonconvulsive.

*More than 1 semiology component may occur in the same patient.

*Includes seizures with secondary generalization.

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Of the 31 cases who had spikes or sharp waves on electroencephalogram, epileptiform activity was predominantly unilateral and most commonly temporal (8 left, 4 right, and 1 bitemporal), followed by frontotemporal (5 left and 4 right), frontal (2 left, 1 right, and 1 bifrontal), central (1 left central and 2 central frontal), and generalized (2). L indicates left, and R, right.

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**Figure 2. Distribution of Electroencephalogram Epileptiform Activity**
an intermediate level of seizure control (11% seizure free; 67% partial responders).

Discussion

Our findings indicate that epileptic activity may be more prevalent in the early stages of AD than was previously recognized. Several features of our study enabled us to capture patients who are often excluded from this type of investigation: (1) inclusion of patients with MCI, (2) allowing seizures to precede an MCI/AD diagnosis, (3) reporting of nonconvulsive seizures, and (4) use of nonroutine EEG. Epileptiform activity occurred most often in the temporal lobes, which harbor memory centers that are affected early and severely by AD, raising the possibility that it contributes to memory decline in these patients.

Our observation that seizures in patients with AD are associated with an earlier onset of cognitive decline is consistent with the literature. Our study extends these findings to patients with MCI. Seizures in AD are commonly reported in advanced cases and in such cases have been interpreted as a consequence of end-stage neuronal loss and gliosis. Although this supposition may or may not be true, seizure incidence appears to be independent of disease stage, and it can occur early or even coincide with the onset of cognitive decline, as our cohorts illustrate. Additionally, nonconvulsive seizures, which are more difficult to recognize than

Table 4. Efficacy of the Most Common AEDs Prescribed as Monotherapy

<table>
<thead>
<tr>
<th>AED</th>
<th>Sample Size</th>
<th>Dose Range, mg/d</th>
<th>Antiepileptic Efficacy, No./Total No. (%)</th>
<th>Total Responders, No./Total No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>17</td>
<td>50-600</td>
<td>0/17 (5.9)</td>
<td>9/17 (52.9)</td>
<td>.04 vs Phenytoin</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>16</td>
<td>250-3000</td>
<td>0/16 (6.3)</td>
<td>7/16 (43.8)</td>
<td>.046 vs Phenytoin</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>6</td>
<td>100-600</td>
<td>0/3 (50.0)</td>
<td>1/6 (16.7)</td>
<td>.04 vs Lamotrigine; .046 vs levetiracetam</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>9</td>
<td>250-1500</td>
<td>0/2 (22.2)</td>
<td>7/9 (77.8)</td>
<td>.33 vs Phenytoin</td>
</tr>
</tbody>
</table>

Abbreviation: AED, antiepileptic drug.

*Not including patients with only subclinical epileptiform activity or those who did not tolerate the AED for more than 3 months.

*Fisher exact test for each pairwise comparison of total responder ratios.
Table 5. Tolerability of the Most Common AEDs Prescribed as Monotherapy

<table>
<thead>
<tr>
<th>AED</th>
<th>Sample Size</th>
<th>Dose Range, mg/d</th>
<th>Tolerability, No./Total No. (%)</th>
<th>Adverse Effects (No. of Patients)*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>25</td>
<td>50-600</td>
<td>18/25 (72.0)</td>
<td>Aggressiveness (1), allergic rash (2), blurry vision (1), confusion (1), dizziness (1), fatigue (2), imbalance (2), tremor (2)</td>
<td>.02 vs Phenytoin</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>23</td>
<td>250-3000</td>
<td>18/23 (78.3)</td>
<td>Anxiety (1), confusion (2), diarrhea (1), dizziness (1), headache (1), incoordination (1), irritability (3), nausia (1)</td>
<td>.006 vs Phenytoin</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>9</td>
<td>100-600</td>
<td>2/9 (22.2)</td>
<td>Ataxia (3), cognitive worsening (3), delirium (1), dizziness (1), lethargy (2), low appetite (1), myoclonus (1), nausea (1), sedation (1), weakness (1)</td>
<td>.02 vs Lamotrigine; .006 vs levetiracetam; .02 vs valproic acid</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>11</td>
<td>250-1500</td>
<td>9/11 (81.8)</td>
<td>Cognitive worsening (1), delirium (1), hypertension (1), sedation (1), weight gain (1)</td>
<td>.02 vs Phenytoin</td>
</tr>
</tbody>
</table>

Abbreviation: AED, antiepileptic drug.

* More than 1 adverse effect was experienced by some patients.
† Fisher exact test for each pairwise comparison.

We also realize that patients with mMCI/AD and epilepsy can exhibit a spectrum of putative epileptic and nonepileptic cognitive symptoms that can be difficult or impossible to differentiate. In our cohorts, we attempted to distinguish “epileptic” cognitive symptoms from “nonepileptic” symptoms of AD by their abrupt onset and stereotyped nature (Table 3). In reality, though, some of the “nonepileptic” symptoms might result, at least in part, from chronic alterations caused by interictal epileptic activity, such as remodeling of hippocampal circuits.25,29 Fifth, patients with long-standing epilepsy may develop mesial temporal sclerosis, and we cannot rule out comorbid mesial temporal sclerosis in our cohorts. However, pure mesial temporal sclerosis is a very rare cause of dementia,30 and magnetic resonance imaging suspicion for mesial temporal sclerosis was lacking in all but 3 patients included in this study. Sixth, we had limited apoE genotyping in our cohorts, and we were unable to assess potential interactions between apoE, mild head trauma (present in 21% of epilepsy cases), epileptic activity, and AD, which others have reported.17,27,31

Within the limitations of a retrospective study, our findings are clinically instructive when placed in context of the current literature. Consistent with our observations, others have reported that treatment with levetiracetam or lamotrigine resulted in good seizure control and tolerability in patients with AD and epilepsy.32,33 In contrast, the sodium channel blockers phenytoin and carbamazepine, as well as phenobarbital and benzodiazepines, can worsen cognitive function in patients with AD.5,24 Of the 9 patients who were treated with phenytoin in our study, 6 reported worsening of cognitive or motor symptoms and only 3 had a reduction in seizure frequency (Table 4 and Table 5 and eTable in Supplement). Phenytoin also worsened cognition in patients with Down syndrome who had AD and seizures.34 Despite these findings, phenytoin may still be the antiepileptic drug most commonly used for patients with AD and epilepsy in clinical practice.5,33 Valproic acid has been investigated in AD clinical trials because of its possible neuroprotective properties and beneficial effects on agitation. However, patients treated with valproic acid (10-12 mg/kg/d) had a more rapid decline in brain atrophy36,37 and Mini-Mental State Examination scores37 than those treated...
Seizure/Epileptiform Activity in Alzheimer Disease

with placebo, making this drug less appealing for patients with AD and epilepsy.

Our observations also underscore similarities between AD and transgenic animal models of the disease. Human amyloid precursor protein (hAPP) transgenic mice, which simulate key aspects of AD, have epileptiform activity and nonconvulsive seizures.29 Epileptogenesis in this model appears to depend on the presence of tau and pathologically elevated levels of β-amyloid peptides in the brain and involve mechanisms that are at least partly distinct from those causing common seizure disorders.1,29,38-40 Phenytoin paradoxically exacerbates epileptiform activity, seizures, and cognitive deficits in hAPP mice.39 These detrimental effects of phenytoin and other sodium channel blockers may be due, at least in part, to an exacerbation of voltage-gated sodium channel deficits in inhibitory interneurons that were recently identified in both hAPP mice and humans with AD.39 In contrast, levetiracetam suppressed epileptiform activity in hAPP mice and improved learning and memory in this AD model11 as well as in age-impaired rats.42 Low-dose levetiracetam also suppressed hippocampal hyperactivation and improved cognitive performance in a hippocampus-dependent task in patients with aMCI.43 Although more randomized comparative clinical trials are needed, these previous studies, together with our observations, support the use of levetiracetam over phenytoin in the treatment of seizures in patients with AD, when clinically appropriate. Lamotrigine appears to be another reasonable choice. In our cohorts, both levetiracetam and lamotrigine were often effective at suppressing seizures, even at low doses. Although lamotrigine inhibits sodium channels, it preferentially inhibits activity-driven glutamate release from presynaptic terminals of excitatory neurons,44 which is reminiscent of levetiracetam effects.45

Conclusions

Our findings add to the mounting evidence that AD-related neural network hypersynchrony is an early and potentially treatable component of the disease.29,39-41,43,46-47 Features that should raise clinical suspicion for seizures in patients with aMCI or AD include cognitive decline at a relatively early age, transient stereotyped cognitive symptoms such as aphasia, amnestic spells, or déjà vu, and possibly a history of head trauma. Whether antiepileptic medications such as levetiracetam can improve cognition or disease course in these patients, and what doses are optimal, are critical questions that require further investigation.

REFERENCES