The spectrum of epileptic activity in Alzheimer's disease

Keith A Vossel, Maria Carmela Tartaglia, Haakon B Nygaard, Adam Z Zeman, Bruce L Miller

From the Memory and Aging Center, Department of Neurology, University of California, San Francisco, CA, USA (Keith A Vossel MD, MSc and Bruce L Miller MD); Department of Neurology, University of Toronto, ON, Canada (Maria C Tartaglia, MD); Division of Neurology, University of British Columbia, Vancouver, BC, Canada (Haakon B Nygaard, MD, PhD); and Cognitive Neurology Research Group, University of Exeter Medical School, UK (Adam Zeman, DM, FRCP).

Correspondence to: Dr. Keith A Vossel, Memory and Aging Center, Department of Neurology, University of California, San Francisco, Sandler Neurosciences Center, 675 Nelson Rising Lane, Suite 190, San Francisco, CA 94158, USA, kvossel@memory.ucsf.edu

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ABSTRACT

Epileptic activity associated with Alzheimer's disease (AD) has important therapeutic implications due to its early occurrence and potential contributions to pathogenesis. In clinical practice, seizures in AD patients can easily go unrecognized because they are commonly non-motor and overlap symptomatically with other features of the disease. Seizures in AD may hasten cognitive decline, highlighting the importance of their early recognition and treatment. Recent evidence indicates that subclinical epileptiform activity in AD, detected by extended neurophysiological monitoring, also associates with accelerated cognitive symptoms. Treating clinical seizures in AD with select antiseizure drugs (ASDs), in low doses, is well tolerated and can improve symptoms and quality of life. Moreover, preclinical studies in animal models of AD suggest that certain classes of ASDs that reduce network hyperexcitability could have disease modifying properties. These ASDs target distinct mechanisms of epileptogenesis involving amyloid-β peptides and the tau protein. Clinical trials targeting network hyperexcitability in AD will address many important questions that have emerged from these preclinical investigations.

INTRODUCTION

Transient worsening of cognitive symptoms occurs commonly among patients with Alzheimer's disease (AD), sometimes raising the possibility of underlying epilepsy. Caregivers may report that the patient seems to "check out" for periods of time or appears more confused than usual on some days compared to others. Such symptoms warrant attention as new evidence indicates that seizures and network hyperexcitability can occur in the early stages of AD and contribute to cognitive decline.[1-5] Treatment options with antiseizure drugs (ASDs) are plentiful, but choosing whether to treat seizures and finding the best ASD for an individual with AD can be difficult. Even more challenging is whether to treat subclinical epileptiform activity, the occurrence of epileptiform activity in the absence of clinical seizures. This review will provide an update on current views about mechanisms and therapeutic implications of AD-associated epilepsy and epileptiform activity and guidance on the approach to evaluating and treating patients with AD and suspected seizures.

PREVALENCE OF SEIZURES IN ALZHEIMER'S DISEASE

The increased incidence of seizures in AD, in relation to older populations without dementia, has been known since Alois Alzheimer's earliest patient descriptions. Initial studies focused on seizures in AD patients at later stages of disease, many of whom were institutionalized. With new evidence of seizures and epileptiform activity in transgenic animal models of AD, occurring prior to amyloid-β plaque deposition, closer attention has been paid to seizures occurring in early stages of dementia.[2,3] Epidemiological studies have revealed that unprovoked seizures occur in 10-22% of AD patients, but reports vary widely and rates as high as 64% have been observed in cohorts that were closely monitored through all stages of disease.[6] Overall, seizures occur with higher

incidence in AD than non-AD dementias, but studies have not looked beyond this level of distinction.[7] Myoclonus, which in AD is generally considered to be due to cortical hyperexcitability, is also common in AD with a prevalence of 7–10% and a cumulative risk as high as 80% by late stages of disease.[8,9] In atypical presentations of AD that include more neocortical involvement, myoclonus rates may be higher. For instance, a myoclonus rate of 22% was reported in a cohort of patients with corticobasal syndrome who had AD pathology at autopsy.[10]

For unclear reasons, seizures and myoclonus occur more commonly in younger AD patients.[2,7] In a study of 198 patients with early-onset AD, defined as age-at-onset <65 years, seizures were reported in 45% and myoclonus in 36%; presence of myoclonus increased seizure risk by 7.7 fold.[11] The inverse relationship between seizure risk and age in AD contrasts with the age-associated increase in seizures in the general population, which is likely secondary to increases in vascular disease and other morbidities. A possible explanation for higher seizure risk in younger AD patients is that they have unique risk factors such as altered expression of genes that regulate neural network activity in comparison to older AD patients. Alternatively, seizures could hasten onset of cognitive decline in AD and thereby associate with earlier disease presentations.

Genes linked to AD have been implicated in aberrant network activity. Individuals with Down syndrome, due to an additional copy of chromosome 21 which contains the *APP* gene, often develop AD in their 40s to 60s. In an eight-year prospective evaluation, those with Down syndrome and AD had a seizure risk of 84%.[12] In those who carry *APP*, *PSEN1*, or *PSEN2* genetic mutations or *APP* duplications linked to autosomal dominant AD, risk for seizures and myoclonus is also high, with seizure rates of 28% (range 15–67%, highest in carriers of *APP* duplications),[13] and myoclonus rates of 27% (range 9–31%, highest in *PSEN1* mutation carriers).[13]

Importantly, seizures may hasten cognitive decline when they occur in AD patients.[14,15] In a case-control study of ten institutionalized patients with advanced AD, patients with new-onset seizures had faster declines in language assessment scores over 12 months compared to a severity-matched group of patients without seizures.[14] Moreover, seizures and myoclonus have been variably associated with reduced survival in AD.[11,16]

TEMPORAL AND PATHOLOGICAL RELATIONSHIPS BETWEEN EPILEPSY AND ALZHEIMER'S DISEASE

The common co-morbidity of seizures and AD raises questions of cause versus consequence. Does long-standing epilepsy increase the risk of developing AD or do pathological changes in the AD brain set the stage for seizure initiation? Epidemiological studies would suggest that both mechanisms are possible, although the latter scenario appears more likely. From epilepsy studies, those with longstanding seizure disorders have a slightly increased risk of developing dementia, but this trend does not reach statistical significance unless seizures begin within ten years of AD diagnosis.[17] Dementia-based studies that followed patients prior to their dementia diagnosis also suggest that in some cases seizures can be a harbinger of AD or begin concurrently with onset of cognitive decline.[2,3,17] Seizures that precede onset of cognitive decline may reflect the epileptogenic potential of amyloid-β, which begins to accumulate more than ten years prior to clinical signs of dementia.[18]

Interestingly, temporal lobe epilepsy (TLE) and AD share several pathological and neuroimaging features. In a series of 101 nondemented patients (ages 30–61 years) with chronic TLE who underwent temporal lobectomy, ten specimens had amyloid-β plaques.[19] Although plaques were positively correlated with age, the age-related incidence of plaques was greater in

patients with TLE than in control cases. In a postmortem analysis, chronic epilepsy was associated with increased tau neurofibrillary tangles (NFTs) at mid-Braak stages in patients aged 40–65.[20] A recent clinicopathological study on tissue resected for refractory TLE revealed hyperphospohorylated tau in 94% of excised tissue samples, and the level of tau pathology was associated with greater decline in verbal learning, recall, and language scores over one year after temporal lobe resection.[21] Other pathological features common to AD and epilepsy include hippocampal sclerosis[22] and depletion of the calcium-binding protein calbindin-D_{28K} in the dentate gyrus, indicating chronic over-excitation of this region.[5,23] Finally, from a neuroimaging perspective, during functional MRI (fMRI), patients with TLE, absence epilepsy, and AD have reduced resting-state activity and functional connectivity within the default mode network, a cortical network that is most active during conscious rest, suggesting shared regions of network dysfunction.[24]

SUBCLINICAL AND INTERICTAL EPILEPTIFORM ACTIVITY IN ALZHEIMER'S DISEASE

Epileptiform activity is defined as paroxysmal sharp waveforms (spikes and sharp waves) on electroencephalogram (EEG), lasting 20 to 200 ms, that disrupt background activity and have an associated subsequent slow wave. Such activity is labeled interictal epileptiform activity when it is detected in patients with seizures, and subclinical epileptiform activity when detected in patients without known seizures. The sensitivity of scalp EEG recordings to detecting epileptiform activity depends highly on the type of EEG protocol that is used. Importantly, estimates of epileptiform activity in AD are limited by use of noninvasive scalp recordings, a limitation that does not exist in animal models in which subdural or depth electrodes are commonly used. Consistent with

studies of seizures in older adults, routine EEG detects interictal epileptiform activity in about a third of patients with mild cognitive impairment (MCI) or dementia and comorbid seizures.[2-4] The sensitivity of EEG increases with extended recordings that capture sleep states or serial EEGs.[2]

While EEG can provide clarity in the evaluation of AD patients with suspected seizures, limited information is available about the utility of EEG in patients without suspected seizures. Estimates of subclinical epileptiform activity in AD vary widely. In a study that used 30-min EEGs and kept patients awake with eyes closed during monitoring, only 2% of AD patients were noted to have subclinical epileptiform activity.[25] AD patients with epileptiform activity were significantly younger than those without such activity (mean age ± standard deviation, 63 ± 10 vs. 71 ± 9, respectively), consistent with their increased risk for seizures. In a study that used various EEG protocols and included patients with amnestic MCI and AD, subclinical epileptiform activity was detected in 6% of patients.[2] In these investigations, limited longitudinal information on effects of seizures or epileptiform activity on clinical progression was provided. Motivated by findings from animal studies, a recent, prospective observational study reported on the incidence of subclinical epileptiform activity in AD and its potential impact on cognitive decline. This investigation evaluated a relatively young cohort of AD participants without a history of seizures (mean age 62) and age-matched controls with a combination of 24-hour long-term monitoring with video EEG (LTM-EEG) and a 1-hour magnetoencephalography exam (MEG) with simultaneous EEG.[1] Subclinical epileptiform activity was detected in 42.4% of AD patients, a four-fold increase over age-matched controls. Ninety percent of epileptiform discharges in AD patients occurred during sleep. AD patients with epileptiform activity did not differ clinically from those without such activity at the time of monitoring. However, over time, patients with subclinical epileptiform activity showed faster decline on the Mini-Mental State Examination (MMSE) and in executive

function. These results suggest that subclinical epileptiform activity may be more common in AD than previously recognized, and raise the possibility that it may accelerate cognitive decline, either directly or by association with unrecognized silent seizures.

Based on these observations, patients with AD who should be evaluated carefully for epileptiform activity and possible silent seizures include those with 1) fluctuations in cognition, 2) rapidly progressive decline, 3) very early-onset of AD (e.g., onset in 50s), and 4) myoclonus given the co-occurrence of myoclonus and seizures.[11] A major determinant of an EEG's sensitivity to detecting epileptiform activity in AD is whether patients sleep during the exam.[1] Therefore, extended EEGs or MEGs of 1–2 hours during a time when patients can sleep would be most informative.

The most common electrodes in which epileptiform activity is detected in AD are those that surround frontotemporal and temporal brain regions,[2-4] and such activity is often multifocal reflecting the diffuse networks that are affected.[4,26] Since the temporal lobes are the most common regions of epileptiform activity in older adults with seizures, the location of epileptiform activity does not help distinguish whether seizures are secondary to AD, other causes, or idiopathic.

CURRENT TREATMENT APPROACHES

A number of factors must be considered when deciding to treat seizures in patients with AD including age, comorbidities, drug interactions, cognitive and noncognitive side effects, and optimal dosage. In those who have epileptiform activity but no witnessed seizures the decision of whether to treat with ASDs is controversial, and should be based on the clinician's judgment on whether 'silent' seizures could be contributing to cognitive symptoms (e.g., cognitive fluctuations or confusion upon waking). Empiric treatment with ASDs is not recommended for patients without

clinical or electrographical signs of network hyperexcitability. Such decisions will be guided by future clinical trials targeting network hyperexcitability in AD. The exact mechanism of action of most ASDs is unknown, and mechanisms may differ depending on the dosage used. Because of the current lack of randomized, double-blind clinical trials specifically addressing AD-associated seizures, therapeutic choices should be guided by other studies of ASDs in older adults with or without dementia (table 1).

Levetiracetam and lamotrigine have the strongest evidence supporting their use to treat seizures associated with AD. Notably, both ASDs can reduce excessive glutamate release from excitatory neurons, which is relevant to mechanisms of epileptogenesis in AD (panel 1).[27,28] Belcastro et al. conducted a prospective, open-label, observational study of levetiracetam 1000–1500 mg/day for ≥1 year in 25 patients with advanced AD and epilepsy.[29] Sixteen percent of participants discontinued the medication due to intolerable side effects, and 72% were seizure-free for at least one year. Cumbo et al. conducted a prospective, randomized, three-arm parallel-group, case-control study of levetiracetam 500–2000 mg/day, lamotrigine 25–100 mg/day, and phenobarbital 50–100 mg/day in 95 patients with AD and epilepsy (mean age 72) and 68 age-matched AD control patients without epilepsy who did not receive ASDs.[26] Treatment consisted of a 4-week dose adjustment period followed by a 12-month dose evaluation period. Levetiracetam and lamotrigine caused fewer adverse events than phenobarbital, which caused somnolence in 30% of patients. Seventeen percent of patients on phenobarbital withdrew because of adverse effects. The three ASDs had equivalent effects on seizure reduction (responder rates: levetiracetam 71%, lamotrigine 59%, and phenobarbital 64%). Levetiracetam and lamotrigine treatment resulted in better cognitive outcomes than phenobarbital, and lamotrigine improved mood. AD-epilepsy patients on levetiracetam had improved performance on MMSE and ADAS-cog, similar to the AD

control patients without epilepsy. An early but very small prospective, double-blind crossover trial of 150 and 300 mg of lamotrigine for AD patients without epilepsy demonstrated that 300 mg of lamotrigine was associated with improved performance on recognition and naming tasks as well as depression after 8 weeks.[30]

In the Veterans Administration Cooperative Study, Rowan et al. conducted a randomized, double-blind, parallel trial comparing the relative tolerability and efficacy of gabapentin 1,500 mg/day, lamotrigine 150 mg/day, and carbamazepine 600 mg/day for 12 months in a cohort of 593 older adults (mean age 72) with new-onset epilepsy.[31] Notably, 35% of participants had MCI and 66% had vascular disease. Overall, patients tolerated lamotrigine and gabapentin better than carbamazepine. Seizure control was similar among all three ASDs, and more than half of participants remained seizure free after 12 months.

A multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy of valproic acid 10–12 mg/kg/day, given over two years, to treat agitation in 313 patients with moderate AD without epilepsy.[32,33] Valproic acid treatment did not reduce incidence of agitation or psychosis and was associated with higher rates of somnolence, gait disturbance, tremor, diarrhea, and weakness. Valproic acid treatment was also associated with an accelerated loss of brain volume and faster decline in MMSE over one year. These results should dissuade use of valproic acid, at least at the dosages used in this trial, as a first-line therapy for AD patients with epilepsy.

Evidence for using phenytoin in patients with AD is mostly limited to observational studies that report variability in phenytoin's efficacy in seizure treatment as well as neurological side effects, including ataxia, delirium, sedation, and accelerated cognitive decline.[2,34,35] Phenytoin paradoxically exacerbates seizures in the hAPP-J20 mouse model,[36] but not in APP/PS1 mice.[37]

Deleterious effects of phenytoin on seizures, as well as cognition, in hAPP-J20 mice may be related to depletions of Nav1.1 in parvalbumin-positive interneurons in parietal cortex; a change also observed in the AD brain.[36] Blocking Nav1.1 activity with phenytoin could exacerbate cortical excitability by reducing activity of Nav1.1-containing interneurons and disinhibiting neighboring pyramidal neurons. Lamotrigine also inhibits sodium channels, but it has a higher potency for inhibiting release of glutamate than of GABA, which distinguishes it from phenytoin.[28] In a noteworthy observation, individuals with Down syndrome who develop epilepsy early in life tolerate phenytoin well, but those who develop AD and epilepsy later in life have deleterious cognitive side effects when taking phenytoin.[35]

Benzodiazepines should be used as a last resort to treat seizures associated with AD. Although they are highly effective at suppressing seizures and myoclonus, they can induce delirium, and their sudden discontinuation (e.g., when forgetting to take the medication) can induce withdrawal seizures, even in people without epilepsy. Further, chronic benzodiazepine use has been associated with increased risk of AD.[38] Topiramate reduces behavioral deficits in animal models of AD;[39] however, cognitive side effects, such as word-finding difficulty and reduced concentration span, make it less appealing as a treatment for patients with AD. Other ASDs such as oxcarbazepine and lacosamide are being used successfully as monotherapy to treat seizures in older adults, but limited data are available for their use in patients with AD. Patients on carbamazepine or oxcarbazepine should have sodium levels monitored regularly, as these ASDs can cause hyponatremia, particularly with advanced age.

Importantly, some symptomatic treatments for AD have been associated with an increased risk of seizure. In particular, the antidepressant buproprion and typical neuroleptics can decrease the seizure threshold. Acetylcholinesterase inhibitors, the mainstay of current symptomatic treatments,

likely has neutral effects on seizure risk. A randomized-controlled study of donepezil in epilepsy did not reveal an increased frequency of seizures.[40] Memantine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, has been reported to have both pro- and antiseizure effects in animal models.[41]

Overall, most seizures associated with AD are responsive to ASD monotherapy, often at low doses, which is preferred in an older population.[2-4,26] Whether low-dose levetiracetam (125 mg b.i.d.), which improved hippocampal-based memory performance in patients with MCI,[42] is also effective at suppressing AD-associated seizures and epileptiform activity is unclear, but treatment with low-dose levetiracetam deserves consideration from a cognitive standpoint, particularly in AD patients in whom seizures are mild or infrequent and who have no history of status epilepticus. Levetiracetam should be used with caution in patients with advanced dementia and behavioral disturbances because it can exacerbate agitation.

Many ASDs, particularly enzyme-inducing ASDs such as carbamazepine, phenytoin, and phenobarbital, are associated with decreased bone density. Therefore, long-term use of ASDs in older patients should be accompanied by routine examination of bone mineral density and supplementation with calcium, vitamin D, and other therapies as needed.

SEIZURES AND EPILEPTIFORM ACTIVITY AND COGNITION

Acute versus chronic effects of epileptiform activity in AD. In AD patients in whom epileptiform activity is detected, potential acute and chronic effects of such activity on cognitive functions should be considered. In both rodent models and patients with interictal epileptiform discharges in the hippocampus, epileptiform events disrupt short-term memory retrieval.[43] These studies are carried out using depth electrodes in patients with refractory seizures. However, such invasive

testing is rarely performed in AD patients, and the exact extent and acute cognitive effects of hippocampal epileptiform discharges in the AD population is unknown.

In addition to transient effects on cognition, epileptiform activity over time results in inhibitory compensatory changes in brain networks to prevent propagation of seizures. While such changes can limit overall network hyperexcitability, they can have deleterious consequences for neural plasticity, particularly in the hippocampus.[5,44] In animal models of AD, diverse interventions that suppress epileptiform activity, including genetic ablation of tau and cellular prion protein (in APP/PS1 transgenic mice), and treatment with certain ASDs, reduce synaptic and cognitive deficits.[39,45-49] Suppression of epileptiform activity acutely with ASDs does not improve cognitive function in such mouse models, whereas prolonged treatment over three weeks or longer improves both synaptic function and cognition.[39,46-48] These data support the view that deleterious effects of epileptiform activity on cognition in AD occur more through chronic remodeling of neuronal circuits than through abrupt disruptions of network functions.[5,44] Interestingly, in AD patients with epilepsy, epileptiform activity is often lateralized to brain regions that are most impaired clinically.[2] Such activity could either be a surrogate marker of a more aggressive form of disease, or it could represent a level of network hyperexcitability that contributes causally to cognitive decline. Clinical trials with ASDs and related strategies will address this essential question.

Transient epileptic amnesia/epileptic amnesic syndrome versus AD-associated epilepsy. Neurodegenerative dementia is not the only possible cause of new-onset seizures in older adults in association with interictal memory impairment. When underlying brain lesions and other classical seizure risk factors are ruled out, many such patients fall into one of two categories: 1) transient epileptic amnesia (TEA)/epileptic amnesic syndrome and 2) AD-associated epilepsy. At presentation, these conditions may overlap in some aspects, but they also have many distinguishing

characteristics, as listed in panel 2. Transient amnesia refers to discrete episodes of mixed anterograde and retrograde memory loss followed by return to baseline, and it can occur in both conditions. Patients presenting with non-degenerative TEA are typically middle-aged males who report recurrent amnestic attacks, lasting 30 to 60 minutes, often occurring upon awakening.[50] There may be other, more familiar seizure manifestations, especially olfactory hallucinations which occur in 42% of patients with TEA.[50] The epileptic amnesic syndrome, a term coined by Galassi,[51] overlaps substantially with TEA, but also allows for subtle, non-amnestic, temporal lobe seizures, giving rise, for example, to episodes of déjà vu or brief complex partial seizures. Between seizures patients with TEA function well cognitively although they often report a distinctive loss of memory for personal events (autobiographical memory), such as holidays or the birth of a child, that may stretch back to decades prior to the onset of seizures. In contrast, they have preserved semantic, or factual, memory for events that occurred over the same time period. They also commonly report forgetting newly learned information over days to weeks (accelerated long-term forgetting), as well as difficulties navigating. Patients with TEA perform normally or near-normally on standardized bedside neuropsychological tests but show accelerated long-term forgetting, often associated with a patchy autobiographical amnesia for salient remote events.[52] The amnesic seizures usually cease promptly with antiseizure treatment, and the interictal memory problems stabilize or improve. The brief duration of amnesia, recurrence, and interictal cognitive changes distinguish TEA from transient global amnesia, a syndrome of profound anterograde amnesia lasting 4 to 10 hours often occurring after stressful events or exercise and rarely recurring.[50]

Patients who develop seizures in association with AD may also report amnestic attacks. However, a broader variety of seizure types, in relation to TEA, occur in AD reflecting the diffuse

brain regions involved. Between seizures, patients with symptoms of AD have a progressive decline in multiple cognitive domains, and these deficits are reflected in their performance on bedside neuropsychological tests. Long-term memories for personal and factual events are relatively preserved. EEG can reveal frontotemporal or temporal epileptiform activity in both TEA and AD-associated epilepsy, but AD biomarkers (MRI, amyloid-PET, and CSF amyloid-β, tau, and phospho-tau levels) can help distinguish the two syndromes, particularly in younger patients, in whom positive biomarkers are more likely due to AD than age-related changes.[53]

NETWORK HYPEREXCITABILITY AS A BIOMARKER IN ALZHEIMER'S DISEASE

In addition to epileptic activity, other neuroimaging and neurophysiological markers of network hyperexcitability are evident in early stages of AD. In patients with MCI due to AD, task-based fMRI studies have demonstrated increased hippocampal activation during memory encoding.[54] While such activity could be conceptualized as compensatory recruitment of neural reserves to meet cognitive demands within compromised brain regions, recent evidence indicates that, in AD, hyperactivation of hippocampus and related regions during encoding is inefficient and may contribute to AD pathogenesis.[54,55] The degree of hippocampal hyperactivation in patients with MCI due to AD predicts future cognitive decline.[54] Furthermore, suppressing hippocampal dentate gyrus/CA3 hyperactivation with the ASD levetiracetam in patients with amnestic MCI also improves their performance on a hippocampal-based pattern-separation task.[42] Interestingly, 125 mg b.i.d. of levetiracetam was more effective than 250 mg b.i.d. at normalizing fMRI changes and improving memory function in these patients.[42] Since fMRI is an indirect measure of neuronal activity, the relationship between hippocampal hyperactivation detected by fMRI and epileptiform activity detected by EEG is unknown.

Regions outside of the hippocampus also show excess network activity and synchrony in early stages of AD. For instance, patients with MCI or mild AD, and cognitively normal people with PET evidence for amyloid-β deposition have aberrant activity in the default network, including the precuneus and posterior cingulate cortex, indicated by failure to deactivate this network during memory encoding.[56] In addition, resting-state MEG has demonstrated network hypersynchronization across multiple frequency bands in fronto-parietal and interhemispheric networks in patients with amnestic MCI.[57]

The projected temporal relationship of such network alterations to amyloid-β and tau deposition in the brain is shown in figure 1.[18,58] This graph illustrates an intriguing relationship between amyloid-β plaques and tau NFTs showing a critical period of time during MCI stages in which hippocampal hyperactivation associates with an increase in NFT deposition while amyloid plaque deposition begins to plateau.[54] Importantly, brain deposits of amyloid-β and tau are not as tightly linked with cognitive dysfunction as soluble assemblies of these proteins in animal models of AD. Since we currently have no noninvasive means of measuring soluble protein assemblies in the brain, as opposed to insoluble protein deposits, functional imaging and neurophysiological recordings may become critical pharmacodynamic biomarkers of the functional effects of these disease proteins, both for protein lowering approaches and other network stabilizing strategies.

SEIZURE SEMIOLOGY AND MECHANISMS OF EPILEPTOGENESIS IN ALZHEIMER'S DISEASE

The predominant seizure subtype in AD is non-motor complex partial seizures (table 2).[2-4,34] Some aspects of these spells can overlap with more chronic cognitive features of AD, but they can often be distinguished as epileptic events by their recurrent and stereotyped nature and supported by

epileptiform activity on EEG. Such episodes can include amnestic spells, déjà vu or jamais vu, speech arrest, staring spells, psychic phenomena (e.g., fear or euphoria) or sensory phenomena (e.g., metallic taste or rising epigastric sensation). Many of these are symptoms of focal hippocampal seizures. Seizures can induce tachycardia, bradycardia, or even asystole requiring pacemaker implantation, possibly due to involvement of insular cortical regions that influence sympathetic and parasympathetic output to the heart via the amygdala and hypothalamus.[2]

Seizures in animal models of Alzheimer's disease. Animal models of AD typically feature overexpression of human amyloid precursor protein (hAPP) and/or presenilin 1 (PS1) with genetic mutations that are linked to familial AD. Similar to humans, transgenic mouse models of AD exhibit a variety of seizure types.[5,23,59] The majority of electrographic seizures in such mice have little to no motor manifestation, with the exception of APP/PS1 mice which have more frequent motor seizures.[5,23,49]

Evidence from these models suggests that epileptogenesis in AD occurs through mechanisms that, in many ways, are distinct from mechanisms derived from epilepsy models (panel 1). The initiator of many of these mechanisms is oligomeric species of amyloid-β peptide. This hypothesis is supported by the high prevalence of seizures in patients with familial AD genetic mutations that result in increased production of amyloid-β;[13] however, the relative contributions of amyloid-β, hAPP, and other hAPP metabolites to network hyperexcitability is not entirely clear.[23,59,60] The tau protein appears to have an enabling role for epileptogenesis in AD. Interestingly, endogenous tau levels modulate seizure susceptibility. Levels of wild-type tau, which can vary naturally or experimentally, correlate with neuronal and network excitability in a dose-dependent manner in both AD and non-AD epilepsy models.[45,61-63] Additionally, transgenic mice overexpressing human wild-type tau or tau with an A152T mutation, which confers higher risk of AD and other

tauopathies, have epileptiform activity and higher seizure susceptibility than nontransgenic mice.[64] The A152T mutation in tau induces higher levels of network hyperexcitability than does wild-type tau, possibly because the A152T substitution increases production or decreases clearance of the tau protein.[64] Excess tau may, in turn, stimulate presynaptic glutamate release.[65] Notably, amyloid-β at low levels can also enhance synaptic transmission, whereas at higher levels it can suppress synaptic activity.[66] Under scenarios of amyloid-β induced synaptic suppression, epileptogenesis could be initiated by inhibition of selectively vulnerable neurons within circuits. For instance, impaired cortical inputs to the reticular thalamic nucleus may lead to aberrant corticothalamic activity, which is associated with non-motor seizures.[67]. Emerging evidence indicates increased neuronal activity increases both amyloid-β and tau secretion; thus recurrent epileptic activity in AD could establish a vicious cycle augmenting the aberrant aggregation and spread of these disease proteins.[68,69] Apolipoprotein E4 also contributes to hippocampal over-excitation in animal models by causing tau-dependent decrease in GABAergic interneurons in the hilus of the dentate gyrus.[70,71]

CONCLUSIONS AND FUTURE DIRECTIONS

Patients with MCI and AD are prone to seizures, as well as silent forms of aberrant network activity, which are associated with more rapid cognitive decline. Evidence for detrimental network hyperexcitability in the early stages of AD raises new therapeutic opportunities for antiepileptic strategies that could complement or enhance existing approaches and potentially modify disease progression. Besides seizures, no clear guidelines exist for treating clinically silent forms of aberrant network activity in AD. As we have learned from other medical conditions such as hypertension and diabetes, recognizing presymptomatic and subclinical forms of disease is

imperative for protecting against future organ damage. Clinical trials are required to establish the benefits and risks of treating network hyperexcitability in AD. The optimal degree to which excessive brain activity and network synchrony in AD can be suppressed without compromising network activity that subserves normal cognitive functions is unknown. Therefore, early phase clinical trials will benefit from adaptive designs such as those that include multiple treatment dosage arms initially and direct more participants into the most efficacious treatment arm in later stages.

Several trials are ongoing or soon to be initiated (table 3). A phase 2a study of levetiracetam for AD-associated network hyperexcitability (LEV-AD, NCT02002819) is underway, and AgeneBio announced an NIH and privately sponsored multicenter phase III clinical trial of levetiracetam to treat amnestic MCI due to AD, scheduled to begin in 2017. In the LEV-AD trial, participants are prescreened for seizures and/or epileptiform activity with overnight video LTM-EEG and 1-hour MEG/EEG exams to identify those with and without epileptiform activity prior to trial entry. Given the associations of such activity with cognitive decline, having neurophysiological measures at trial entry may be important to ensure balance and precision in future studies, regardless of the therapeutic target.

In addition to ASDs, diverse therapies have been shown to suppress aberrant network activity in animal models of AD, as listed in table 3. Reducing the tau protein is one such strategy that has broad antiepileptic effects, both in animal models of AD and of epilepsy.[45,61-63] In addition to these therapies, neuromodulatory approaches, such as deep brain stimulation (DBS), transcranial magnetic stimulation, and vagus nerve stimulation are being developed to improve cognitive function in AD and also show capacity to treat seizures.[72,73] Such approaches offer the advantage of precisely targeting zones of hyperexcitability and dysfunction, but also need to consider

potential adverse effects of stimulating the circuits involved. For instance, DBS of anterior thalamus effectively treats seizures but carries the risk of behavioral and mood changes.[74]

In conclusion, AD patients with seizures have accelerated cognitive decline and might stand to benefit from antiepileptic strategies; network hyperexcitability, more generally, offers a possible target for treatment in AD. Prolonged neurophysiological monitoring is often required to detect epileptiform activity in AD patients, and the precise extent of pathological network hyperactivity in AD is unknown. Clinical trials using ASDs and related strategies will address the efficacy of assessing and treating aberrant network activity in AD and determine whether subgroups with seizures, silent neurophysiological abnormalities, or broader populations could benefit from network stabilizing strategies.

SEARCH STRATEGY AND SELECTION CRITERIA

We selected references by reviewing the authors' personal files and by searching PubMed for manuscripts published in English prior to November 2016, with the term "Alzheimer's disease" and assorted combinations of the following terms: "epilepsy", "seizures", "epileptiform activity", "network hyperexcitability", "antiepileptic drugs", "antiseizure drugs", "anticonvulsants", "Down syndrome", "trisomy 21", "dementia", "neurodegenerative disease", "early-onset", "presenilin 1', "presenilin 2", and "amyloid precursor protein". We reviewed reference lists within original articles and review articles for additional references. We determined the final reference list on the basis of originality and relevance to the scope of this Personal View. We focused on manuscripts published in the past eight years, but also included older publications of high merit or originality. Additional information about current clinical trials was obtained from www.clinicaltrials.gov.

CONTRIBUTORS

KAV developed the manuscript concept and structure. All authors contributed to the literature review and preparation of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Panel 1: Proposed mechanisms of epileptogenesis in Alzheimer's disease

1. Extrasynaptic glutamate spillover due to impaired glial or neuronal glutamate transporters.[75,76]
2. Tau-induced enhancement of presynaptic glutamate release.[65]
3. Reduced axonal and dendritic transport of cargoes that regulate neuronal excitability.[77-79]
4. Altered trafficking and surface expression of postsynaptic AMPA and NMDA receptors.[49,80]
5. Altered levels of voltage-gated ion channels in the brain.[36,81,82]
6. Fyn-mediated alterations in NMDA activity.[45,49,61,83]
7. Selective impairment of GABAergic interneurons in hippocampus and parietal cortex.[36,70,76,84-86]
8. Shortened dendrites lowering threshold for action potential generation.[87]
9. Impaired cortical input to reticular thalamic nucleus and subsequent disinhibition of thalamic relay nuclei and their cortical and limbic targets.[67]
10. Increases in cholinergic tone prior to degeneration of cholinergic pathways.[88]

Panel 2: Main features of non-degenerative transient epileptic amnesia and AD-associated epilepsy.

	Non-degenerative transient epileptic amnesia	**MCI/AD-associated epilepsy**
Mean age at onset of seizures	62 – 69 years	62 – 74 years
Sex distribution	More common in males	Equally common in males and females
Seizure semiology – most common features	Amnestic spells often upon waking (100%), olfactory hallucinations (42%), automatisms (36%), GTC (4%)	Automatisms (31%), sensory or psychic phenomena (22%), speech or behavioral arrest (13–39%), déjà vu or jamais vu (5–8%), amnestic spells (4-54%), staring spells (3%), GTC (15–40%)
Interictal cognitive complaints	Autobiographical memory loss, accelerated forgetting over days to weeks, topographical memory loss	Short-term memory loss, word-finding difficulty, difficulty with multitasking and calculations, visuospatial impairments
Neuropsychological testing	Normal/near-normal performance on standardized neuropsychological testing; impairments in recall of verbal and visual information at extended delays (> 30 min); loss of autobiographical memories for events extending decades prior to onset of seizures.	Impairments in multiple cognitive domains on standardized neuropsychological testing including learning and recall of verbal and visual information, executive function, language abilities, and visuospatial function.
EEG epileptiform foci – predominant locations	Temporal or frontotemporal	Temporal, frontotemporal, or frontal
Brain MRI	Normal (group studies suggest subtle atrophy in limbic structures)	Grey matter atrophy in medial temporal lobes and/or posterior cortical regions
AD molecular biomarkers*	Probably negative (not systematically studied)	Positive
Response of seizures to ASDs	Good	Good

*PET measures of brain amyloid-β deposition or cerebrospinal fluid measures of amyloid-β, tau, and phosphorylated tau levels. These tests are less accurate in determining likelihood of AD in people over 80 years old.[89]

Key references: Butler et al. (2007);[50] Cretin et al. (2016);[3] Muhlert et al. (2010);[52] Rao et al. (2009);[34] Sarkis et al. (2016);[4] and Vossel et al. (2013)[2]

Table 1: Commonly prescribed antiseizure drugs for older adults with cognitive impairment.

ASD	Dosage (mg/day)	Tolerability	Efficacy	Cog. side effects?	Other potential adverse effects*	Other uses
LEV	250–2,000	Excellent	Excellent	No	Aggression, asthenia, dizziness, fatigue, headache, irritability, nausea	Treatment of myoclonus
LTG	25–500	Excellent	Excellent	No	Asthenia, ataxia, blurred vision diarrhea, diplopia, dizziness, hypersensitivity reaction, incoordination, insomnia, nausea, rash, somnolence, Stevens-Johnson syndrome, tremor	Mood stabilization
GBP	300–1,500	Good	Good	Possible	Ataxia, dizziness, fatigue, nystagmus, nausea, peripheral edema, somnolence, weight gain	Treatment of insomnia, peripheral neuropathy, postherpetic neuralgia, and migraine prophylaxis
CBZ	600	Fair	Good	Yes	Agranulocytosis, asthenia, ataxia, blurred vision, cardiac dysrhythmia, constipation, decreased bone density, dizziness, hepatotoxicity, hypersensitivity reaction, hyponatremia, nausea, rash, somnolence, xerostomia	Mood stabilization, treatment of trigeminal neuralgia
VPA	250–1000	Fair	Good	Yes	Alopecia, asthenia, ataxia, constipation, diarrhea, diplopia, dizziness, gait disturbance, headache, hepatotoxicity, indigestion, nausea, nervousness,	Mood stabilization, migraine prophylaxis,

					nystagmus, peripheral edema, rash, somnolence, tinnitus, tremor, weakness, weight gain	treatment of myoclonus
PHT	200–300	Poor	Good	Yes	Ataxia, constipation, decreased bone density, dizziness, dysarthria, gingival hyperplasia, hepatotoxicity, hypersensitivity reaction, incoordination, lethargy, muscle hypotonia, nausea, nervousness, nystagmus, sedation/drowsiness	None
PB	50–100	Poor	Excellent	Yes	Asthenia, barbiturate withdrawal, decreased bone density, hypersensitivity reaction, somnolence, syncope	Long-term sedation

ASD=antiseizure drug. CBZ=carbamazepine. GBP=gabapentin. LEV=levetiracetam. LTG=lamotrigine. PB=phenobarbital. PHT=phenytoin. VPA=valproic acid.

Key references: Belcastro et al. (2007);[29] Cretin et al. (2016);[3] Cumbo and Ligori (2010);[26] Fleisher et al. (2011);[33] Rowan et al. (2005);[31] Tariot et al. (2011);[32] Tsiouris et al. (2002);[35] and Vossel et al. (2013)[2]

* Partial list that includes more common side effects and serious side effects

Table 2: Observational studies of patients with mild cognitive impairment or dementia (predominantly AD) and co-morbid epilepsy

Study	Diagnoses (n)	Mean age at first seizure	Mean age at onset of cognitive decline	Mean age at diagnosis of degenerative disease	Seizure types	Epileptiform EEG (protocol)	Epileptic foci - major regions
Cretin et al. (2016)[3]	MCI due to AD (13)	63	66	70	CPS (62%) SPS (23%) GTC (15%)	23% (routine 20-min EEGs)	Temporal (L>R)
Rao et al. (2009)*[34]	MCI (10), AD (9), vascular dementia (6), DLB (5)	62†	71	Not provided	CPS (72%) GTC (39%) SPS (13%) Atypical absence (3%) Myoclonic (8%) Unknown (3%)	38% (unspecified EEG protocols)	Unilateral or bilateral temporal
Sarkis et al. (2016)[4]	AD (64)‡, AD-vascular (4), DLB (4) ,bvFTD (3), vascular dementia (1), nfvPPA (1)	74	68	72	CPS (53%) GTC (40%) SPS (7%)	36% (routine, serial, and extended EEGs)	Frontal or temporal
Vossel et al. (2013)[2]	aMCI (12), AD (35)	67	65	68	CPS (47%) Generalized (36%) SPS (17%)	62% (routine, serial, and extended EEGs)	Frontal or temporal (L>R)

AD=Alzheimer's disease. aMCI=amnestic MCI. DLB=dementia with Lewy bodies. bvFTD=behavioral variant frontotemporal dementia. MCI=mild cognitive impairment. nfvPPA=nonfluent variant primary progressive aphasia. CPS=complex partial seizures. GTC=generalized tonic-clonic seizures. SPS=simple partial seizures.

* Included 14 patients with structural lesions on MRI.

† Included longstanding seizure disorders.

‡ Included possible AD (13%), probable AD (65%), and autopsy-proven AD (5%).

Table 3: Therapies that could suppress AD-associated network hyperexcitability and excitotoxicity in preclinical and clinical trials

Class	Therapy	Proposed mechanism(s)	Stages of investigation for MCI/AD
Antiseizure drugs	Levetiracetam	Binds SV2A and prevents synaptic vesicle release,[27] increases glutamate transporter expression[90]	Preclinical;[39,46] prospective case-control;[26] phase 2 (NCT02002819);[42] and phase 3 (AgeneBio)
	Brivaracetam	Binds SV2A with higher affinity than levetiracetam[91]	Preclinical[47]
	Lamotrigine	Inhibits Na^+ channel activity; more potent at inhibiting glutamate release than other ASDs in class[28]	Preclinical;[48] prospective case-control[26]
	Topiramate	Inhibits GSK-3β activation and histone deacetylase activity,[39] inhibits Na^+ and Ca^{2+} channels, enhances $GABA_A$ receptor function, blocks AMPA and kainate receptors	Preclinical[39]
Antineoplastic	Bexarotene	Retinoid X receptor agonist, alters gene expression	Preclinical[92]
Cell-replacement therapies	GABAergic interneurons derived from stem cells	Increase local GABAergic interneuron populations (e.g., somatostatin-positive interneurons in hilus of dentate gyrus)	Preclinical[71]
Dietary	Ketogenic diet	Increases mitochondrial biogenesis and oxidative phosphorylation, and enhances GABA levels[93]	Phase 2 (NCT02551419, NCT02709356, and NCT00142805);[94] interventional placebo-controlled, single blind (NCT02521818); phase 4 (NCT00777010)
	Taurine	Activates GABA receptors[95]	Preclinical[96]
Gene therapy	Enhancing Nav1.1 expression	Improves function of parvalbumin-positive interneurons	Preclinical[36]

Kinase inhibitors	Src family kinase inhibitor	Suppresses Fyn kinase-associated phosphorylation of Tyr-1472 in NR2B subunit of NMDA receptors[83]	Phase 1 (AZD0530, Saracatinib, completed);[97] phase 2 (Saracatinib, NCT02167256)
	Tyrosine kinase inhibitor	Reduction in mast cell-mediated inflammation through c-Kit inhibition; Src family kinase inhibition, including Fyn kinase[98]	Phase 2 (Masitinib, completed);[98] and phase 3 (Masitinib, NCT01872598)
Tau reduction	Salsalate	Inhibits tau acetylation, which enhances tau turnover[99]	Preclinical (phase 1 for progressive supranuclear palsy (NCT02422485))
	Anti-sense oligonucleotides	Reduces tau mRNA levels[63]	Preclinical
	Methylene blue	Inhibits Hsp70 enzymatic activity[100]	Phase 2 (NCT02380573)

AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid. ASD=antiseizure drug. GABA=gamma-amino-butyric acid. GSK-3β= glycogen synthase kinase 3β. NMDA= N-methyl-D-aspartate. SV2A= synaptic vesicle protein 2A

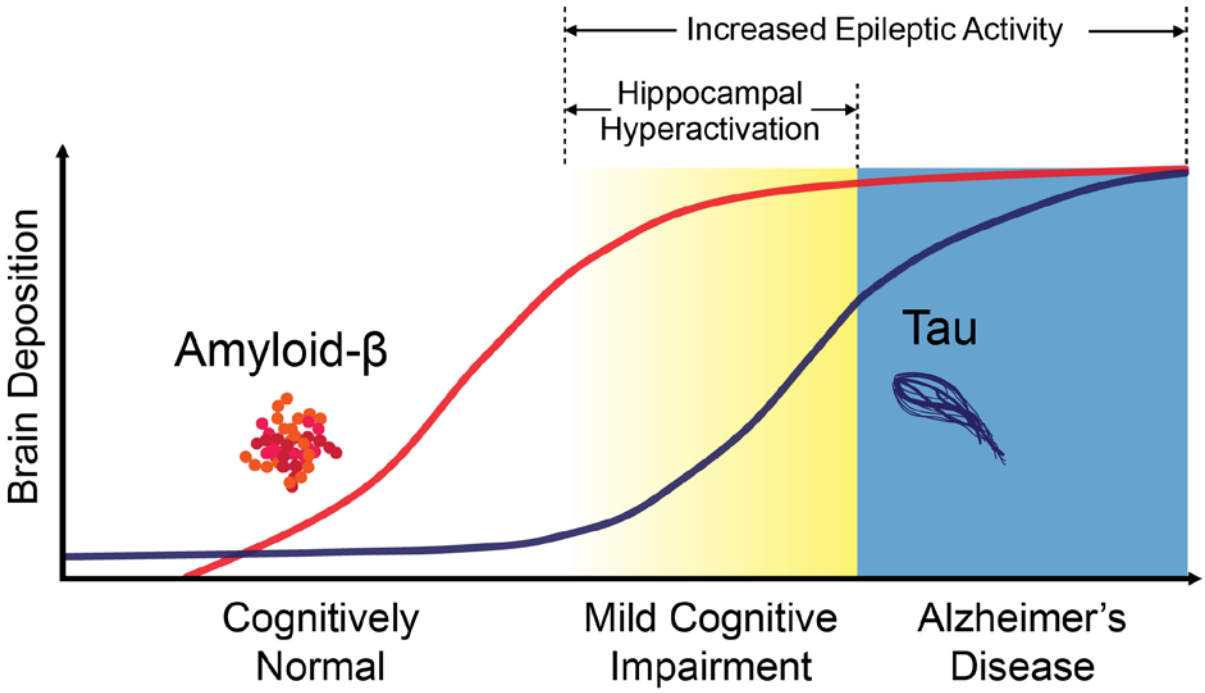

Figure 1: Proposed temporal associations between total brain amyloid-β (plaques) and tau (neurofibrillary tangles) deposition, hippocampal hyperactivation, and network hypersynchony, which can manifest as epileptiform activity and seizures throughout the course of Alzheimer' disease.[2,18,42,54,58]

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