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Article

Mechanisms Involved in Epileptogenesis in Alzheimer's Disease and Their Therapeutic Implications

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Abstract: Epilepsy and Alzheimer's disease (AD) incidence increase with age. There are reciprocal relationships between epilepsy and AD. Epilepsy is a risk factor for AD and, in turn, AD is an independent risk factor for developing epilepsy in old age and abnormal AD biomarkers in PET and or CSF are frequently found in late onset epilepsies of unknown etiology. Accordingly, epilepsy and AD share pathophysiological processes including neuronal hyperexcitability and an early excitatory-inhibitory dysregulation leading to dysfunction in the inhibitory GABAergic and excitatory glutamatergic systems. Moreover, both β-amyloid and tau protein aggregates, the anatomopathological hallmarks of AD, have proepileptic effects. Finally, these aggregates have been found in the resection material of refractory temporal lobe epilepsies suggesting that epilepsy leads to amyloid and tau aggregates.

Some epileptic syndromes, such as medial temporal lobe epilepsy share structural and functional neuroimaging findings with AD, leading to overlapping symptomatology such as episodic memory deficits and toxic synergistic effects. In this respect, the existence of epileptiform activity and electroclinical seizures in AD appears to accelerate progression of cognitive decline and the presence of cognitive decline is much more prevalent in epileptic patients than in elderly without epilepsy. Notwithstanding their clinical significance, the diagnosis of clinical seizures in AD is a challenge. Most are focal and manifest with altered level of consciousness without motor symptoms, and are often interpreted as cognitive fluctuations. Finally, despite the frequent association of epilepsy and AD dementia, there is a lack of clinical trials to guide the use of antiseizure medications (ASM). There is also a potential role for ASMs to be used as disease-modifying drugs in AD.

Keywords: seizures; epilepsy; Alzheimer's disease; antiseizure medications; hyperexcitability

1. Introduction:

Alzheimer's disease (AD) is the most common neurodegenerative disorder and leading cause of dementia, accounting for over 60-70% of dementia cases [1]. Epilepsy is the third most frequent neurological condition in the elderly after cerebrovascular pathology and neurodegenerative dementias [2]. AD dementia and epilepsy frequently coexist, and there are reciprocal relationships between

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the two diseases. AD is an independent risk factor for epilepsy with an increased risk ranging from 2 to 10 times compared to age-matched healthy controls [3,4,13–16,5–12]. Conversely, epilepsy, specially late-onset epilepsy of unknown etiology (no cause identified after completing etiological study), has been described as risk factor for the development of AD [5,9,17–20]. In addition AD and epilepsy share several risk factors including advanced age, cardiovascular risk factors and damage to the cerebral vasculature, history of brain traumatic injury and the presence of the ε4 allele of the APOE gene [17,21]. Importantly, both β-amyloid and tau protein aggregates have proepileptic effects [9,22–24] and conversely, these defining anatomopathologic hallmarks of AD have been described in surgical material from refractory mesial temporal lobe epilepsies [25].

There are also shared pathophysiological processes in the two diseases. Both present a dysregulation of the excitatory-inhibitory tone presumably caused by alterations in the glutamatergic (excitatory) and GABAergic (inhibitory) systems. AD and epilepsy, especially some epileptic syndromes such as medial temporal lobe epilepsy, predominantly target similar brain regions (CA1, subiculum and entorhinal cortex) [26,27], leading to an overlapping symptoms such as episodic memory deficits and alterations in similar large-scale networks, especially the default neural network [26,27]. Therefore, a detailed electroclinical characterization of both AD-associated epilepsy and late-onset epilepsy of unknown etiology (LOEU) may facilitate early diagnoses.

Our objectives are to review the epidemiology, etiopathogenic mechanisms and risk factors and as well as clinical overlap between symptomatic AD and epilepsy. We also review available evidence to guide the use of anti-seizure medications (ASM) in AD and the rationale of ASM potentially AD disease-modifying treatments.

2. Methodology

We performed a literature review January 24th 2022 using PubMed and Web of Science (WOS), combining the Mesh Terms "Alzheimer Disease", "Epilepsy", "Seizures" and "Anticonvulsionants"(Figure 1). We did not apply any time restriction, and we included original articles and review articles with data from human subjects (exclusion of papers in animals only) written in English, Spanish or French. We selected articles with abstracts available in PubMed or WOS. After reading the titles and abstracts, those papers that met eligibility criteria were selected for full-text revision. Those papers specifically dealing with epilepsy and Alzheimer's disease and antiseizure medications potential benefits beyond its antiepileptic effect were included for this review.

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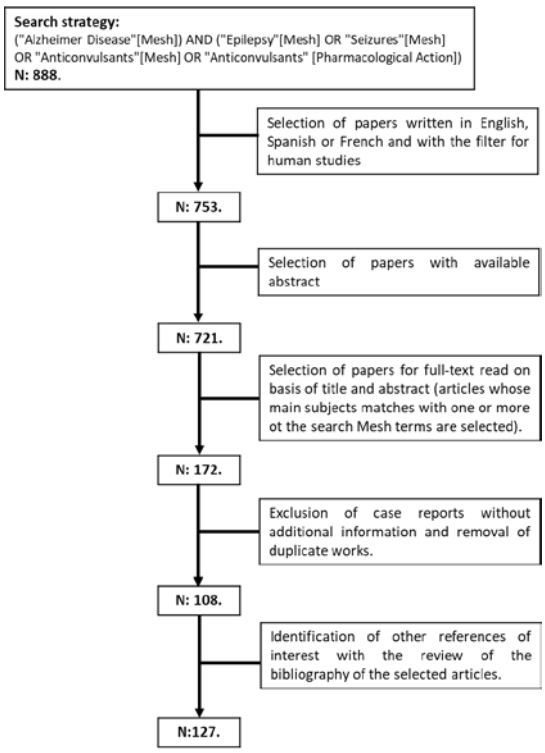

Figure 1. Flowchart of research strategy.

3. Epilepsy in Alzheimer's disease

The prevalence of epilepsy in sporadic preclinical, prodromal and AD dementia is higher than in healthy age-matched controls [7,10,28,29]. Genetically determined AD (autosomal dominant AD –ADAD- and Down syndrome-associated AD -DSAD-) are at particularly high risk: Down syndrome > *APP* > *PSEN2* > *PSEN1* mutations [9,29–34]. Interestingly, in agreement with the ultrahigh risk in DSAD, those ADAD patients with amyloid precursor protein (*APP*) gene duplications (57%) have a higher risk than those with presenilin 1 (*PSEN1*) (37%) and presenilin 2 (*PSEN2*) mutations (31%) [29,35–38]. In the specific case of *PSEN1*, those mutations that occur before codon 200 have been associated with a higher risk for epilepsy [39,40]. In subjects with Down syndrome and AD, the risk of developing epilepsy ranges from 46 to 84%, and a specific type of epilepsy called late-onset myoclonic epilepsy has been described [30,33].

Table 1. summarizes the sociodemographic and clinical risk factors for the development of epilepsy in AD as well as the comorbidities increasing the risk of epilepsy [4,5,45–54,8,14,22,26,41–44]. It is noteworthy that although the risk of epileptic seizures seems to increase with disease severity, the risk is already increased in prodromal and preclinical stages of the disease [20,31].

Suggested risk factors of epilepsy in AD
Sociodemographic:
Male sex.
Earlier onset of symptoms (both in sporadic and autosomal dominant AD).
Clinical and anatomic features:
Longer disease duration (in years).
Disease severity.
Greater involvement of precuneus and a parietal-dominant atrophy pattern.
Chronic use of antipsychotics.
Comorbidities increasing the risk of epilepsy:
Cerebrovascular pathology (mainly with when there is cortical involvement).
Brain traumatic injury.

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Table 1. Summary of identified risk factors for development of epilepsy in context of Alzheimer's disease.

The semiology of seizures varies among the different forms of AD. In sporadic AD the most frequent type are focal epileptic seizures presenting with altered level of consciousness without motor symptoms (55-70%) [10,14,41,51,55–57]. Other symptoms include episodes of amnestic spells, *déjà vu* or *jamais vu*, speech arrest, staring spells and unexplained emotions or sensory phenomena. All this symptomatology is often erroneously interpreted as cognitive fluctuations, which are frequent in sporadic AD [41,58]. In ADAD seizure semiology is more varied, and more frequently have a motor component in the form of focal seizures and/or bilateral tonic-clonic and myoclonic seizures [32,38,40,43,44,47,59]. Finally, in DSAD the most frequent seizures are bilateral tonic-clonic and myoclonic seizures [30,33].

The identification of epilepsy in AD is, therefore, difficult [41,58]. In this context, a routine electroencephalogram (EEG) at symptomatic AD diagnosis might be advisable, especially in genetically determined AD. The EEG should, nonetheless, be interpreted as a supportive diagnostic tool, always assessed in the clinical context of the patient (more value to the semiology of the seizures than to the findings of a specific recording), since the absence of interictal epileptiform discharges (IEDs) does not exclude epileptiform etiology and the existence of IEDs not necessarily imply that the patient has epileptic seizures. Multiple non-epileptiform, unspecific (diffuse slowing and triphasic waves), and ictal and interictal epileptiform abnormalities (sharp waves, spikes, spike-waves and polyspike-waves) are detected in the surface EEG of subjects with AD with or without previous epilepsy diagnosis [5,60]. Indeed, the presence of IEDs are more frequent (up to 4 times) in subjects with AD with respect to age-matched healthy controls [41,50,56,61–63]. The presence of IEDs, however, do translate a higher risk for clinical seizures. In subjects with AD and epilepsy IEDs are twice more frequent than AD dementia patients without epilepsy. The diagnostic yield is, however, suboptimal [10,12,14,23,36,49,64–66]. The low diagnostic performance of surface EEG seems to be related to the focal character and preferential temporal localization (with lower representation in surface EEG) of IEDs in AD [9,22,41]. In this respect, some IEDs confer more risk. High frequency IEDs of right temporal location during wakefulness and during REM sleep are associated with higher risk of developing seizures [65]. Another factor contributing to the lower diagnostic performance is the fact that EEG is routinely performed during wakefulness. IEDs are more frequent during sleep, especially in the N2 phases [10,31,41,60,62,67]. Finally, patients with AD with or without epilepsy do frequently show EEG rhythm abnormalities. In this respect, the use of quantitative EEG in AD has also shown an increase in delta and theta frequency range and a decrease in alpha and beta power with respect to controls [5,60].

Epilepsy in the context of AD has an impact on both AD biology and clinical course [68]. The presence of electroclinical seizures seems to accelerate the progression of cognitive multidomain impairment (memory, executive and visuospatial functions) and may contribute to more rapid loss of functional autonomy [4,11,73,74,36,62,63,67,69–72]. Similar impact of IEDs in the absence of observed clinical seizures in AD has also been reported in recent years [67,72], especially if IEDs occur in the left temporal location [72] and during the slow wave sleep phase [65], a brain region and a sleep phase that are essential for memory consolidation.

4. Late onset epilepsy

The risk of developing epilepsy increases with age, being 2 to 6 times higher after 55 years of age than in young adults [18]. Late-onset epilepsy is defined

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when the onset occurs after age 55 years [18,20,75]. The risk, nevertheless, continues to increase even after this age, with a reported incidence of untriggered seizures of 80.8 cases/100.000 inhabitants/year at age 60 compared to 135-175 cases/100.000 inhabitants/year at age 80 [76–78].

Multiple causes of late-onset epilepsy have been described (Figure 2). The majority of them in relation with acquired cerebral damage, most frequently cerebral vascular damage [16,20,79,80]. But in recent years there has been an increasing appreciation of the importance of neurodegenerative diseases, especially AD [20,81] as the underlying cause. It is important to note that despite the improvement in diagnostic tools, up to 20-33% of cases remains unknown (late onset epilepsy of unknown etiology or LOEU) [2,16,20,82,83]. Men are at higher risk for late onset epilepsy, LOEU and the epilepsy associated with AD [20]. Another risk factor for late-onset epilepsy is the ε4 allele of APOE, which in turn is the major genetic risk factor for sporadic AD [18,80].

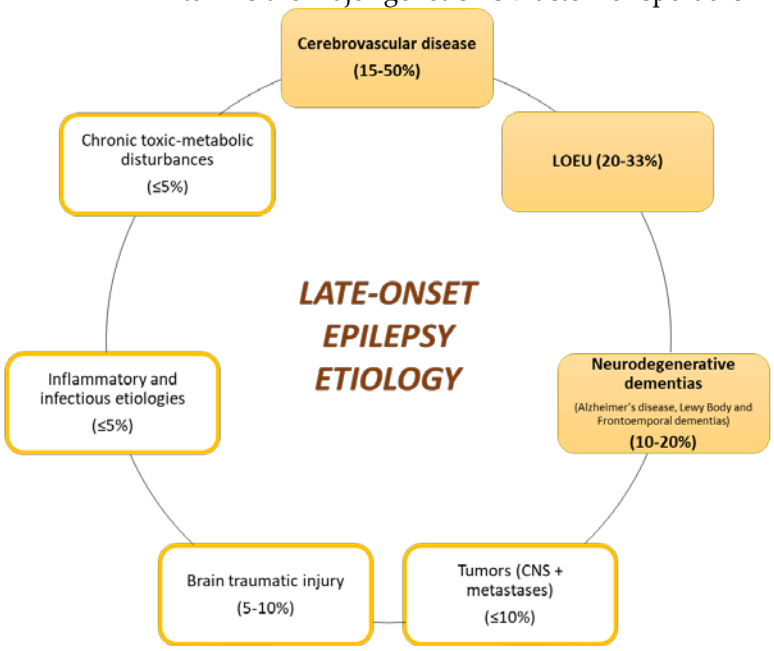

Figure 2. Identified causes of late-onset epilepsy. Cerebrovascular diseases, Late onset epilepsy of unknown etiology (LOEU) and neurodegenerative dementias are the most prevalent etiologies. .

In late-onset epilepsies the semiology of seizures is very variable and is related to the location of the underlying brain damage origin of the ictal activity. The most frequent clinical seizures (in approximately 66%) are focal with altered level of consciousness without motor symptoms [2,16]. The low frequency of motor symptoms and the high frequency of altered level of consciousness of in late onset epilepsy makes early identification of these episodes difficult [16]. The EEG is not sensitive enough address this diagnostic challenge as approximately only 29% of routine EEGs in subjects with late-onset epilepsy have IEDs [83].

Cognitive impairment is a common finding in epilepsy, including late-onset epilepsy [20,84]. Indeed, multiple studies support a higher prevalence of mild cognitive impairment (MCI) in late-onset epilepsy (40-55%) [75,85] and in temporal lobe epilepsies (TLE) in which prevalence is up 60% [84]. The amount of temporomedial IEDs and hippocampal onset seizures correlate with progressive episodic memory decline in TLE [20,78,86]. In turn, up to 50% of LOEU patients have frequent multidomain, dysexecutive-predominant MCI with frequent involvement of visuospatial functions [9,87]. Whether the MCI described in the context of LOEU is a consequence of the presence of electroclinical seizures and IEDs or instead reflects the existence of a previously undiagnosed neurodegenerative dementia is not yet fully resolved and the two

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options are not mutually exclusive. Changes in cerebrospinal fluid (CSF) AD biomarkers, particularly reductions in Aβ1-42 have been recently reported in LOEU patients, mainly but no exclusively, in those patients with MCI [22]. In the same line, progression to dementia in LOEU patients might be as high as 22% after 10 years of follow-up, especially in those with MCI and reduced Aβ1-42 levels at LOEU diagnosis [22].

5. Epileptogenic mechanisms in Alzheimer's disease:

Multiple mechanisms involved in the increased risk of epilepsy in AD have been described. These mechanisms are linked to neurotransmitters involved in excitatory-inhibitory balance (glutamate, GABA, acetylcholine and noradrenaline), alterations of ion channels, changes in neuronal networks, anatomophatological hallmarks of AD (amyloid and tau), neuroinflammation and genetic risk factors. All these mechanisms lead to a state of neuronal hyperexcitability.

Neuronal hyperexcitability is a physiological process associated with aging but it is exacerbated in AD [49,67]. This neuronal hyperexcitability in AD starts in the dentate gyrus, spreads to the hippocampus and finally affects the rest of the brain [23,38].

Excitatory-inhibitory imbalance:

The excitatory-inhibitory balance and synapse homeostasis are essential for normal brain function. Minimal changes in these processes increase the probability of epileptic seizures and cognitive impairment [23,49,88] and, in AD, both these processes are affected [23,49].

Role of neurotransmitters in epiletogenesis:

The main excitatory neurotransmitter in the central nervous system (CNS) is glutamate and the main inhibitory neurotransmitter is GABA. Both are altered in AD and epilepsy [23,49] (Table 2).

		Neurotransmitters (NT)			
		Glutamate	**GABA**	**Noradrenaline**	**Acetylcholine**
Effect in excitatory-inhibitory balance		Excitatory	Inhibitory	Inhibitory	Excitatory
Pro or antiepileptic effect		Proepileptic	Antiepileptic	Antiepileptic	Proepileptic
NT tone	**Both in AD and epilepsy**	Increased	Decreased	Decreased	Early compensatory increase before decreasing
Mechanisms involved in NT disturbance	**Both in AD and epilepsy**	Lower levels of glutamate transporter (GLT-1) and glutaminase (GS)	Reductions of GABA-mediated inhibition and activity of glutamate decarboxylase	Not clearly established	Cholinergic dysfunction in TLE and AD
	In AD	Extrasynaptic N-methyl-D-aspartate receptor (NMDAR) activation	Selective loss of GABAergic inhibitory neurons, reduction of GABA concentrations in	Reduction of noradrenergic neurons in the locus ceruleus	Deficit of cholinergic neurons in the nucleus basalis of Meynert

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		temporal lobe and number of GABAergic terminals close to amyloid plaques		
Abnormal hypersynchronization of neuronal networks in AD	Yes	Yes	Yes	Yes
Relationship with AD anatomipathological hallmarks (amyloid and tau)	Promotes formation of amyloid plaques and tau hyperphosphorylation	Not clearly established	Not clearly established	Not clearly established

Table 2. Summary of reported disruption of neurotransmitters (NT) in Alzheimer's disease (AD) and epilepsy.

The increased glutamatergic tone has been linked to glutamate-glutamine cycle disturbances, which lead to increased extracellular glutamate and decreased GABA levels [36,88,89]. In AD animal models the glutamatergic N-methyl-D-aspartate receptors (AMPARs) activation increases beta-secretase activity, promotes the formation of amyloid plaques [90–92], tau hyperphosphorylation [11] and cell death [88]. GABAergic dysfunction has gained increasing attention in recent years. In this respect, a significant reduction in GABA concentration in the temporal lobe, selective reduction of GABAergic inhibitory interneurons and a reduction of GABAergic terminals, especially in the areas closest to amyloid plaques, have all been reported in animal models [23,85,93,94]. This decreased GABAergic tone [12] leads to abnormal cortical hypersynchronization and could also decrease neuro and synaptogenesis [93,94].

Other neurotransmitters such as acetylcholine and noradrenaline in epilepsy and AD, also influence neuronal hyperexcitability, but their role seems to be of lesser magnitude than that of glutamate and GABA. A compensatory increase in cholinergic tone in relation to neurodegeneration in the nucleus basalis of Meynert has been linked in AD animal models to neuronal hyperexcitability and to subclinical epileptiform activity [11,19,36]. Noradrenaline has antiepileptic effects in animal models. The early degeneration of noradrenergic neurons in the locus ceruleus in AD impedes the compensatory increase in noradrenaline levels in the hyperexcited hippocampus [19,36].

Ion channel disruptions:

AD impacts the number and function of voltage-dependent sodium (Na^+), calcium (Ca^+) and potassium (K^+) ion channels [11]. These ion channels contribute both to the generation and maintenance of epileptic seizures and AD pathophysiology as they can also increase glutamate-mediated excitotoxicity and neuronal hyperexcitability [90–92]. Intracellular calcium, in particular, must be tightly regulated for the excitatory-inhibitory balance. Both AD and epilepsy impair intracellular calcium regulation [38,40]. Interestingly, beta-secretase 1 (BACE 1), which is hyperexpresed in AD, is able to modulate the expression and the functionality of voltage-dependent potassium channels[19,22,85,95]. In addition, in animal models of AD an increased level of L-type calcium channels (essential for synchronous calcium oscillations), overexpression of voltage-dependent sodium channel Nav 1.6 [22] and decreased in the sodium channel Nav 1.1 levels in GABAergic interneurons, all of them previously related to different epileptic syndromes, have been related to increased hyperexcitability in the context of AD [92,93,95]. In turn, altered expression and/or function of voltage-dependent ion channels, a reduction of the calbindin protein responsible

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for intracellular calcium transport in the dentate gyrus has also been demonstrated in animal models of AD, and this reduced expression has also been associated with reduced seizure threshold and increased difficulties in memory consolidation [22,96].

Network dysfunction:

Neural network dysfunction plays an important role in AD [34,39,97]. This network dysfunction can be assessed with functional MRI and quantitative EEG [34], it is present decades before the onset of symptoms [24] and has been linked to cognitive deficits. Normal neuronal synchrony, which is closely linked to neural network integrity, is essential for the creation of oscillatory brain rhythms, rhythmic fluctuations of electrical activity and is the basis of various cognitive functions, including memory [24]. AD is associated with an early disruption of gamma oscillations [41,60], synaptic dysfunction and synaptic depression [24].

Amyloid and tau promote hyperexcitability and facilitates epileptogenesis:

There is growing evidence of the potential proepileptic role of amyloid and tau [4,39].

Amyloid (Aβ):

Aβ, which begins to accumulate 20 years before symptom onset, has been linked with hyperexcitability [39], synaptic dysfunction and neuronal death [67]. Fibrillar or oligomeric forms of Aβ (pre-plaques stages) contribute more than amyloid plaques to neuronal hyperexcitability in cortical and hippocampal neurons, a change in slow-wave oscillations, and increase IEDs and network hypersinchrony [9,23,28,36,49,89,98].

The mechanisms through which Aβ soluble have these effects include an increase in the glutamatergic [22,38,88] tone, a reduction in GABAergic activity [36,43,88], a dysregulation of the activity of voltage-dependent ion channels (which induce spontaneous action potentials [22]) and an increase in proinflammatory cytokines [88] (Figure 3), which also favor epileptogenicity. Of note, neuronal hyperexcitability increases the deposition and propagation of amyloid and tau protein, leading to a feed forward cycle [9,28,31,32,39,49,67]. In this respect, IEDs, even in the absence of anatomopathological hallmarks of AD, can promote Aβ deposition. Childhood onset epilepsy (before the age of 5 years) is associates with increased amyloid PET uptake in the sixth decade of life when compared to age-matched controls [93].

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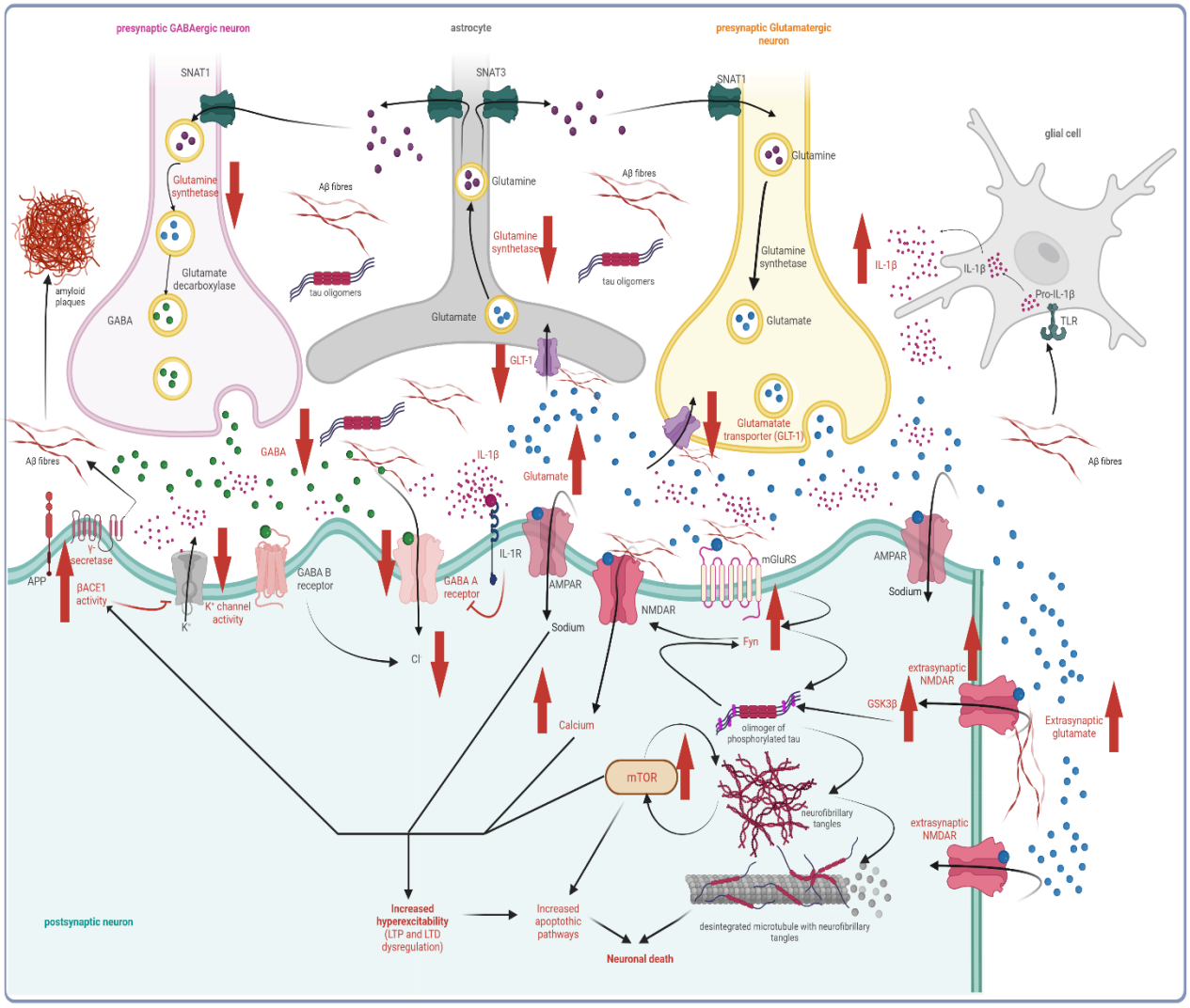

Figure 3. Possible mechanisms involved in the proexcitatory and proepileptic role of soluble forms of amyloid (Aβ) and tau protein. LTP: long term potentiation; LTD: long term depression; TLR: toll like receptor; GSK3β: Glycogen synthase kinase 3 beta. Created by biorender.com.

Tau:

Tau protein regulates the stability and dynamics of the cytoskeleton of neurons. Phosphorylation of tau is necessary for its correct functioning, but hyperphosphorylation can lead to loss of functionality, eventually leading to altered axonal transport, synaptic loss and finally neuronal death [9]. Intracelullar deposits of hyperphosphorylated tau have been found in brain traumatic injury, epilepsy and AD [8,93].

Neurofibrillary tangles at autopsy load has been associated with neuronal hyperexcitability and risk of epilepsy [11,36,39,55,99]. Similarly, patients with AD and epilepsy have higher CSF tau levels than those without epilepsy [36,99]. Finally, tau soluble forms, prior to formation of neurofibrillary tangles, are also able to increase the glutamatergic tone and to induce neuronal network reorganization, increasing the amount of IEDs and electroclinical seizures in animal models of AD [11,17,19,22,41,56,89] (Figure 3).

Other mechanisms:

Neuroinflammation:

Neuroinflammation occurs early in AD, even before the deposition of amyloid plaques. It is also present in some type of epilepsies including TLE

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[22,100]. Both in AD and epilepsy, astrogliosis and microgliosis (activation and proliferation of astrocytes and microglia) alter the glutamate-glutamine cycle. In particular, astrocytes and glial cells secrete proinflammatory cytokines (IL-6, IL-1β and TNF-α) that can modulate the release of glutamate and modify its postsynaptic reuptake [22,26,36,88]. They also reduce GABA signaling [22].

mTOR:

From early preclinical stages of AD, mTOR, serine/threonine kinase expressed in multiple cell types, is involved in the generation of Aβ42 and its washout, tau protein synthesis and in the endoplasmatic reticulum stress [92]. Both in TLE and AD an hyperactivation of mTOR has been reported [85].

Apolipoprotein (APOE):

The APOE ε4 allele is the most important genetic risk factor for sporadic AD, and also is a risk factor for post-traumatic epilepsy [26,101]. APOE ε4 allele is related in AD to increased impairment and reduction of GABArgic interneurons and is believed to favor a decreased inhibitory tone [26,38,43]. In addition, the APOE ε4 haplotype can also influence the clinical phenotype of TLE. Carriers have an earlier onset of seizures, increased risk of postictal confusion, longer standing seizures, lower probability of seizure control with ASM and higher verbal and memory deficits [19]. Of note, cognitively normal adults APOE ε4 allele carriers have more frequent IEDs (sharp waves in hyperventilation) compared to non-carriers [26,43].

6. Antiseizure medications (ASM) in Alzheimer's Disease:

Treating epileptic seizures in AD:

In context of symptomatic AD, there is a 70% risk of seizure recurrence after a first episode. Therefore, indefinite treatment with ASM is advisable after a first untriggered seizure [4,13,102] in symptomatic AD patients. The response to treatment is, however, good with 72-80% of patients without seizures after a year in monotherapy [4,13,16,58,102–105]. Despite this good response to treatment in clinical series, there are no double-blind, placebo-controlled clinical trials to support the use of one ASM over another in AD-related epilepsy [106,107]. Levetiracetam and lamotrigine, broad-spectrum ASM are the most widely recommended drugs due to a better security profile compared to other ASM [41,68,104,105,108–111]. Lacosamide and brivaracetam have been proposed as potential alterative ASMs in epilepsy in AD, but results supporting their use are still preliminary [76,108] (Table 3).

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	SV2A ligands		Na⁺ channel blockers			Multiple mechanisms		Ca⁺ channel blockers	AMPAR blocker
	Levetiracetam (LEV)	**Brivaracetam (BVT)**	**Lamotrigine (LTG)**	**Lacosamide (LCS)**	**"Zepines" (CBZ, OXC, ESL)**	**Valproic acid (VPA)**	**Zonisamide (ZNS) and Topiramate (TPM)**	**Pregabalin (PGB) and Gabapentin (GBP)**	**Perampanel (PER)**
Mechanism of action	- Bind SV2A. - Blocks AMPA and NMDAR (reduce release of glutamate). - Induce GABA potentiation. - Effect on glycine or kainic-acid currents.	- Bind SV2A (20-fold higher affinity compared to LEV). - Minor block on NMDAR.	- Blocks voltage-dependent sodium channels.	- Blocks voltage-dependent sodium channels (enhancing slow inactivation).	- Blocks voltage-dependent sodium channels.	- GABA potentiation. - Blocks T-type calcium channels, sodium channels and NMDAR.	- GABA potentiation (only TPM). - Blocks AMPAR (only TPM), T-type calcium channels (only ZNS) and voltage-dependent sodium channels.	- Blocks voltage-dependent calcium channels.	- AMPA glutamate receptor antagonist.
Spectrum of efficacy	- Broad-spectrum. Including antimyoclonic effect.	- Focal seizures. - Preclinical models: broad spectrum efficacy.	- Broad-spectrum.	- Focal seizures.	- Focal seizures.	- Broad-spectrum.	- Broad-spectrum.	- Focal seizures.	- Focal seizures, generalized seizures (only as adjunctive therapy), useful for myoclonic seizures.
Experience in AD	- First-line treatment.	- Well tolerated.	- First-line treatment. - Less sedative	- Well tolerated. - Alternati	- Not consider as first or second	- Not consider as first or	- Not consider as first or	- Not consider as first or second	- Possible alternative treatment,

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	- Safety and absence of interactions.	- Less irritability than LEV. - Alternative for LEV or LTG.	and few cognitive adverse effects.	ve for LEV or LTG.	line treatment.	second line treatment.	second line treatment.	line treatment.	study data are lacking. - No data on cognitive side effects.
Potential limitations and risks in AD	- Dose-dependent somnolence and irritability. - % 10-15 stop due to neuropsychiatric side effects.	- Irritability but with lower frequency compared to LEV.	- Unsteadiness. - Onset insomnia. - May exacerbate myoclonic seizures.	- Unsteadiness (less frequent than others Na+ blockers). - May exacerbate myoclonic seizures.	- Cognitive impairment related with decreased cholinergic tone (less frequent with ESL). - Unsteadiness.	- Encephalopathy, hyperammonemia. - May induce cognitive impairment and/or motor worsening (tremor).	- Cognitive adverse effects (less frequent with ZNS).	- Less effective. - Cognitive slowing. - Dizziness.	- Dizziness. - Aggression and hostility (special caution if neuropsychiatric symptoms with LEV).

Table 3: Recommendations for the use of antiseizure medications (ASM) in Alzheimer's disease (AD) based in scientific evidence and clinical practice experience. Na^+: sodium, CBZ: carbamazepine, OXC: oxcarbazepine, ESL: eslicarbazepine, Ca^+: calcium; NMDAR: N-Methyl-D-Aspartate receptor.

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Impact of AD treatments on seizure occurrence and control:

Table 4 summarizes the data on the effect of the most frequently used drug classes in symptomatic AD patients. There is no data to support neither to discontinue or not to initiate acetylcholinesterase inhibitors in subjects with AD and personal history of seizures [112,113]. There is insufficient information to make the statement in the case of memantine [112]. Selective serotonin reuptake inhibitors or mirtazapine are preferred over others antidepressants. There is more data relating antipsychotics and worse seizure control [113], but if required, second generation antipsychotics (especially quetiapine and risperidone) should be the first option in AD [112,113].

Acetylcholinesterase inhibitors: Neutral.
Memantine: Controversy (both anti and proepileptic effect reported).
Antipsychotics:
Quetiapine and risperidone: Neutral or low impact in seizure threshold.
Clozapine, chlorpromazine, and haloperidol: moderate impact in decreasing seizure threshold.
Antidepressants:
Selective serotonin reuptake inhibitors: Neutral.
Tricyclic antidepressants: Low to moderate impact in decreasing seizure threshold.
Bupropion: Low to moderate impact in decreasing seizure threshold.

Table 4: Impact on seizure threshold of frequently used symptomatic treatments in AD.

1. Antiseizure medications (ASM) as possible Alzheimer's disease modifying treatments:

The presence of neuronal hyperexcitability, synaptic dysfunction, IEDs and electroclinical seizures are phenomena described from the preclinical stages of AD. As we have discussed, their presence, in turn, promotes the deposition and propagation of amyloid and tau protein. ASMs, in addition to reducing the frequency of IEDs and electroclinical seizures, could also help reestablish the excitatory-inhibitory balance and normalize synaptic function, potentially influencing disease progression in AD.

SV2A ligands (Levetiracetam -LEV- and Brivaracetam -BVT-):

Multiple potential benefits of LEV have been described in animal models supporting its possible role as a modifying treatment for AD biology: 1) reduces glutamate release and glutamate-mediated excitotoxicity [14,58,113,114], favoring synaptic function recovery and reducing neuronal death [9]; 2) restores mitochondrial dysfunction [105,115]; 3) promotes neurogenesis and modifies positively the hippocampal remodeling [105,115] and 4) decreases Aβ42 cortical levels and amyloid plaque burden [98]. Also in animal models, clinical benefits in AD with the use of LEV have been reported: improvement of learning and memory deficits [105] and spatial discrimination tasks [109] (Table 5).

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		ANIMAL MODELS AND CELL CULTURES											HUMANS		
		Fibrillar and amyloid plaque deposition	Tau deposition and/or hyperphosphorylation	Glutamate extracelular levels	GABA extracelular levels	Noradrenaline levels	Neural death	Neurogenesis and/or hipocampal remodeling	Mitochondrial dysfunction	mTOR signaling	Histone deacetylase inhibition	Cognitive function improvement	Neuronal hipocampal hyperactivity	Global cognitive improvement	Memory improvement
SV2A ligands	**LEV**	-	-	-			-	+	-			+	-	+	+
	BVT			-								+			
Na^+ channel blockers	**LTG**	-		-			-	+		-		+		+	+
	LCS	-	-								+	+			
	CBZ	-		-		+									
Ca^+ channel blockers	**GBP**	-													
Multiple mechanisms of action	**VPA**	-	-	-	+		-	+			+				
	ZNS/GBP	-	-	-	+						+				

Table 5: Summary of potential clinical and biological benefits as AD disease modifying treatments of different ASM both from animal models and cell cultures and humans. "+" signs refers to an increase or to a positive response while "–" refers to a decrease or negative response. Na: sodium; Ca: calcium; LEV: levetiracetam; BVT: brivaracetam; LTG: lamotrigine; LCS: lacosamide; CBZ: carbamazepine; GBP: gabapentin; VPA: valproic acid; TPM: topiramate; ZNS: zonisamide.

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The promising results obtained in animal models have led to several clinical trials in humans proposing the use of LEV at low doses as a treatment to modify the clinical and biological course of AD. These are the most important findings in humans: 1) suppresses neural hyperactivity in CA3 hippocampus region and dentate gyrus [9,41]; 2) normalizes the oscillation of rhythmic activity assessed by quantitative EEG [116]; and 3) improves cognitive functions globally assessed by MMSE and ADAS-Cog [9,41] and specially spatial memory and executive dysfunction in AD patients with IEDs [110]. Future clinical trial protocols for the use of LEV in AD aim to jointly evaluate the improvement of EEG abnormalities and clinical improvement (cognitive, behavioral and functional) in relation to low-dose LEV administration [111].

Preliminary data from animal models suggest similar results with the use BVT: 1) modifies the sensitivity of synaptic vesicles to calcium and reduces the glutamate release and glutamate-mediated excitotoxicity [89]; 2) reduces the frequency of electroclinical seizures and IEDs [23,106], and 3) improvement of memory dysfunction [23].

Sodium channel blockers:

Lamotrigine (LTG) has shown in animal models its potential to slow the biology and clinical progression of AD: 1) reduces the glutamate release from excitatory neurons [14,23,41,58,113]; 2) decreases expression of BACE1 [117]; 3) inhibits mTOR signaling [117]; 4) attenuates selective CA1 hippocampal neuronal loss, upregulates anti-apoptotic protein Bcl-2 and stimulates neurogenesis in the granule cell layer of dentate gyrus [118]; 5) reduces amyloid plaque density [73] and 6) improves executive dysfunction [119]. In turn, there is anecdotal evidence in humans showing an improvement in naming and recognition tasks and depression scales scores in AD patients treated with low-moderate doses of LTG [23,41] (Table 5).

Lacosamide (LCS), potential alternative for LTG, has also preliminary data from animal models showing: 1) inhibition of Aβ induced hyperphosphorylation of tau and 2) inhibition of histone deacetylase, which regulates the expression of important genes for learning and memory processes improving their dysfunctions [120].

Carbamazepine (CBZ), currently not of first or second choice treatment for epilepsy in AD, has also beneficial effect in the biological progression of AD in animal models: 1) reduces glutamate-mediated excitotoxicity [118]; 2) increases noradrenergic tone [121] and 3) decreases the burden of amyloid plaques [9].

Calcium channel blockers:

From animal models there is information that suggest the capacity of gabapentin (GBP) to reduce 1) Aβ-induced toxicity [118,122] and 2) neuronal hyperexcitability in context of AD [123] (Table 5).

ASM with multiple mechanisms:

Valproic acid (VPA) is a broad-spectrum ASM currently not indicated in AD-related epilepsy due to its suboptimal cognitive and motor security profile. It has, however, also shown evidence in animal models and cell cultures to: 1) reduce the amount of Aβ oligomers and neuritic plaques [73,124]; 2) inhibit the activity of GSK-3β and thus the amount of hyperphosphorylated tau [124,125]; 3) reduce neuronal loss activating the antiapoptotic protein Bcl-2 and promotes neurogenesis by its histone deacetylase inhibitor capacity [126]; 4) stimulate GABAergic neuron differentiation and 5) reduce glial differentiation [118,126,127]. Only one study including LOEU patients suggested improvement of verbal fluency, but not other cognitive domains with the use of VPA [9] (Table 5).

Animal models have also suggested the potential biological benefit on AD progression for topiramate (TPM) which: 1) stimulates $GABA_A$ receptor function [108]; 2) blocks AMPA receptors; 3) acts as histone deacetylase and 4) inhibits GSK-3β reducing the amount of hyperphosphorylated tau [23]. Similar benefits for ZNS has also been suggested [118].

7. Conclusions:

The excitatory-inhibitory imbalance in AD not only leads to an increased risk of epileptiform activity and electroclinical seizures, but also plays a key role in the progression of AD pathophysiology. ASMs could potentially not only ameliorate clinical and subclinical epileptiform activity, but also potentially modify the natural progression of the disease. Clinical trials to guide the use of ADM in AD-associated epilepsy and to evaluate the impact of ASM on AD biomarkers and cognitive decline may represent a new therapeutic strategy to prevent and treat AD.

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