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Alzheimers' Disease and Epilepsy: A Literature Review

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Abstract

Context: The incidence of Alzheimer's disease and epilepsy increases with age and it is possible that they are interlinked.
Evidence Acquisition: Medline literature search before April 2016.
Results: In general, all authors agree that seizures, especially partial simplex or complex, can appear at any stage of the disease with greater frequency in the later stages or in younger subjects with familial Alzheimer's disease. Seizures are often unrecognized by standard electroencephalograms but using prolonged recordings are recorded in more than 60% of the subjects. Some associated diseases, especially vascular complications or therapies, can help the appearance of the seizures. According to some authors, amyloid-β peptide or some metabolites trigger intermittent aberrant excitatory neuronal activity in the cortex and hippocampus.
Conclusions: In Alzheimer's disease, the seizures are frequent also in the early stages and can worsen the cognitive impairments. The national institute of neurological and communicative diseases and stroke/alzheimer's disease and related disorders association (NINCDS-ADRDA) criteria state that the appearance of seizures at the onset or at very early stages of the Alzheimer's disease is unlikely, but in light of the current knowledge, this statement needs to be modified.

Keywords: Alzheimer's Disease, Dementia, Epilepsy, Seizure

1. Context

Alzheimer 's disease (AD) and isolated or recurrent seizures, i.e. epilepsy, are two common neurologic disorders whose incidence increases with age. It is possible that they appear concurrently in the same subject causing at times serious difficulties in diagnosis and illness management, and also raising questions as to the nature of their association, e.g. fortuitous or causally interlinked. The aim of this research was to review the literature in search of a possible link between these two diseases.

2. Evidence Acquisition

Medline literature until July 2016 was scanned using epilepsy, seizures, Alzheimer's disease, dementia and mild cognitive impairment, as key-words. When epilepsy was identified, the search was narrowed using electroencephalographic discharges, epileptiform activity and models of Alzheimer's disease. Other studies were identified by reviewing relevant bibliography quoted in the original papers. Clinical studies were included if they could meet these fundamental criteria: 1, AD diagnosis according to the NINCDS- ADRDA criteria (1); including patients with dementias other than AD when sufficient data on the AD were provided; 2, minimum sample of twenty subjects; and 3, use of standardized instruments of evaluation.

3. Results

3.1. Clinical and Electroencephalographic Findings

Alzheimer himself reported seizures in the late course of the disease of his second patient (2). However, it was only in the 1950s when a few small series drew attention to the high frequency of seizures in patients affected by AD (3, 4); from the 1980s, researches on the subject became relatively more frequent and the series became larger. Except for a few cases (5), early work on seizures only considered the later stages of the disease (6-11). However, from the 1990s, seizures were also referred in the early stages (12-18), in mild cognitive impairment (MCI) (17) and as early symptoms of AD (19, 20). Irizarry and Coll (21) examined 3078 subjects with AD and without history of seizures: the overall incidence of seizures was 484 per 100000 individuals/year; a higher percentage than the incidence found in other elderly population samples. Sherzai and Coll (22) claimed that AD patients were about three times more likely to have seizures and patients in younger age groups tend to have higher odds of having seizures. Also Cheng and Coll (23) reported that the incidence of seizures was doubled in AD patients compared to non-demented subjects and in their series the increment of age was significantly associated with higher occurrence of seizures. In the dominantly inherited AD, Zarea and Coll (24) reported seizures in the 47.7 of the patients after a mean follow-up of 8.4 years. The average time between the onset of the

cognitive decline and the first seizure was 5.8 years but in four patients the seizure was the first sign of the disease. In summary, today all authors agree that seizures can appear at any stage of the disease and that greater frequencies are found in the later stages or in younger subjects with familial AD. Also the seizure' frequency varies between series, ranging from a minimum of 3.5% of the patients (17) to a maximum of 64% (7). These disparities are likely related to the different populations examined: in older studies the patients were in advanced stages of dementia whereas in more recent studies the patients were chosen from all stages of the disease. The typology of reported seizures also changes with time: older studies mainly report tonic-clonic seizures (8-10, 14) whereas more recent studies consider focal seizures with or without impairment of consciousness with similar or even greater frequency, ranging from 47% to 92% (16, 17, 25). Inconsistencies between different series are also related to methodological problems: most studies are retrospective and it is sometimes difficult to distinguish an epileptic seizure from a convulsive syncope on the basis of medical records. Focal seizures without impairment of consciousness are even more difficult to recognize because aggression, wandering or inattentiveness can be easily misdiagnosed as signs of dementia. The epileptic amnesic syndrome is very difficult to recognize because the syndrome typically begins in the late-middle or old age and AD can coexist (19, 20) (see later). The routine Electroencephalograms (EEG) are seldom more useful: they usually register focal or generalized slowing whereas epileptiform activity is infrequent. In 21 patients with epileptic events, Scarmeas et al. (14) observed epileptiform activity in 16% of the EEG and Rao (15) in 38% while Bernardi et al. (16) observed spike-waves in 35.7% of their epileptic patients. Vossel et al. (17) refer instead a greater frequency of epileptic foci defined as regions of maximum electronegativity: in 62% of the patients evaluated for seizures and in 6% of those without known seizures they were predominantly unilateral and most commonly temporal. This greater frequency is due to the use of serial EEG or long-term video EEG. In some subjects epileptiform discharges are recorded in absence of clinical seizures. In the series of Amatniek et al. (12) focal epileptiform activity was found to be predictive of seizures; in a wide series (26) including 510 patients with AD and 225 with MCI focal epileptiform activity mainly temporal was recorded in 2% of the patients respectively; the same percentage of electroencephalographic anomalies was found in patients with other dementias or with subjective complaints; one AD patient and one with vascular dementia developed seizures after two years. In Vossel et al.'s series (17) epileptiform foci were recorded in 6% of patients without know seizures; however the Authors do not indicate whether some patients displayed seizure over time.

3.2. Possible Risk Factors for Seizures, Therapy, and Prognosis

Typically, the AD is a disease of the old age so it is not unusual to be associated with diseases or therapies that can help the appearance of seizures. Cerebral vascular lesions are common in the AD with frequency of seizures found to be 5.6/1.000 person-years in the AD and 7.5/1.000 person-years in vascular dementia (18). When availables, pathology (3-5, 7-11, 14) or neuroimaging (16, 17) ruled-out vascular lesions serious enough to cause seizures. The importance of the microbleeds is still under debate: they are encountered in the 4.8% of the AD patients (25, 27-29) and only in the 0.7% of the general population (30) and are related to transient focal neurological episodes that can resemble transient ischemic attacks, seizures or migraine crisis. Some Authors understand the Apolipoprotein $\varepsilon 4$ as a risk factor for seizures: Ponomareva et al. (31) show epileptiform activity during hyperventilation in first-order relatives of patients with early-onset AD. The same Authors refer the appearance under hyperventilation of synchronous high-voltage delta, theta activity and sharp-waves together with decrease in alpha and increase in delta and theta activity in Apolipoprotein $\varepsilon 4$ carriers without signs of dementia (32). Even if Lhetovirta et al. (33) did not find any difference in the seizures' frequency according to the Apolipoprotein $\varepsilon 4$ genotype, some Authors related Apolipoprotein $\varepsilon 4$ to refractory seizures (34). Some Authors claimed a drop in the epileptic threshold due to use of acetylcholinesterase inhibitors, memantine, antidepressants or neuroleptic drugs (35-38). In the study of Fisher et al. (39) donepezil was administered to epileptic patients complaining about their memory: two patients experienced an increase in the frequency of the seizures. But in a similar work (40) the use of donepezil was not associated with increased seizure frequency or severity. In the wide series of Irizarry and Coll. (21) the use of antipsychotic drugs was a risk factor for new-onset seizures whereas this finding is not confirmed in other series (14, 16). In the population study of Bell et al. (41) the annual prevalence of antiepileptic drugs use was 5% among persons with AD compared to 3.4% among persons without AD; these data indirectly confirm the high prevalence of seizures in the AD and particularly in younger patients. The main finding of this study was the prevalent use of the older antiepileptic drugs, mainly valproic acid and carbamazepine. There are only few series reporting therapies and their efficacy. In the series of Rao et al. (15) the most commonly used drugs are phenytoin and valproic acid causing at least a 95% reduction of seizures frequency in 79% of the patients.

However, Fleischer et al. reported that chronic use of valproate enhances cognitive decline (42). In the series of Vossel et al. (17) the mostly used drugs are lamotrigine and levetiracetam; the Authors underline their greater efficacy and lighter side-effects. The efficacy of levetiracetam is confirmed in a prospectic study of 25 patients with advanced AD and new-onset seizures: 72% of patients were seizure-free for at least one year but 16% discontinued the drug because of the side-effects and 4% were unresponsive (43). Cumbo and Ligori (44) compared leviteracetam, phenobarbital and lamotrigine in 95 AD patients. There were no significant differences in efficacy but phenobarbital produced persistent negative cognitive effects whereas levetiracetam was associated with improved cognitive performance and lamotrigine with a better effect on mood. Few Authors tried to evaluate whether the appearance of seizures could have a prognostic value, obtaining contradictory results. According to Volicer et al. (11), the patients' condition suddenly worsened after seizures; however according to Samson et al. (45) seizures could not be associated with mortality.

3.3. Putative Links between AD and Epilepsy

Clinically the clearest link between the AD and epilepsy shows in the familial AD mainly if due to a mutation in the presenilin 1 gene. The phenotype is variable: pyramidal and extrapyramidal signs, cerebellar ataxia, myoclonus and seizures may add to dementia (www. Molgen.vib-na.be/ADmutations). The seizures sometimes appear in the late curse of the disease but can also precede cognitive symptoms for several years (24, 46). The data of Vossel et al. (17) confirm seizures' frequency also in the early stages of sporadic AD and even in the MCI. Researchers' attention was directed to the temporal lobe epilepsy (TLE) because these patients often refer of memory impairments (47) or depression (48) similarly to patients with AD and because experimental works in animals (see later). A link between the AD and epilepsy was also confirmed in pathological studies: Thom et al. (49) showed a significant increase in Braak stages III and IV in middle-aged subjects with chronic drug-resistant epilepsy. However, the same authors noticed that the Braak stage was low in over half of the patients with cognitive decline, thus suggesting that other factors contribute to such cognitive decline. Animal models of the AD confirm the link with seizures; in this field the most important work is that of Palop et al. (50), which found spontaneous non-convulsive seizure activity in cortical and hippocampal networks in all transgenic mice with high levels of amyloid-β peptide. The authors believe that the amyloid-β peptide triggers intermittent aberrant excitatory neuronal activity in the cortex and hippocampus resulting in a remodelling of inhibitory circuits and increased inhibition of the granule cells. In their view the cognitive deficit results from the combination of neuronal over-excitation and the subsequent development of compensatory inhibitory mechanisms. Such results were confirmed by several authors (51-53). For a long time, it has been know that interictal spikes cause cognitive impairments (54); using a rodent model in a behaviour task, Kleen et al. (55) showed that hippocampal spikes were also associated with dramatic alterations in both response latency and accuracy. It is possible that modification of neuronal excitability is not directly related to amyloid-β but instead it is related to certain metabolites, for example, high levels of amyloid precursor protein intracellular domain alters membrane stability (52). Another example is the observation that altered processing of voltage-gated sodium channels may contribute to aberrant neuronal activity and cognitive deficits in mice (56). Also the tau protein exerts important effects on the neuronal excitability: in transgenic mice reduction of the tau increased resistance to pentylenetetrazole-induced seizures (57). The AD and TLE are similar yet they also have some differences: preeminent deficit in the remote memory and in the long-term forgetting and temporal sclerosis are frequently are different in TLE when compared to AD (58). In AD the GABAergic neurons are spared and no recurrent sprouting of excitatory collateral mossy fibers onto GABAergic basket cells is found (50). Another difference is that in AD the more damaged neurons are in the layer II of the entorhinal cortex (59) whereas in TLE the more damaged neurons are in layer III (60). However, according to Scharfman (61), AD and TLE likely show similarities in the neurobiological mechanisms and the comparison of these two diseases may identify novel opportunities for mechanistic insight and therapeutic strategies. According to the hypothesis that seizures can worsen cognitive deficits, the use of antiepileptic drugs was suggested. Valproic acid administered to subjects with moderate AD for 24 months was ineffective in slowing cognitive and functional impairment or in slowing the emergence of agitation (62). Sodium valproate and levetiracetam at low doses improved memory in aged rats (63) and also potentiators of γ-amino-butyric acid and GABAa α5 receptors improved performances in aged rats (64). Devi et al. (65) confirmed that pre-training administration of levetiracetam ameliorates memory impairment in aged mice, but not in transgenic mice, whereas Cumbo and Ligori (44) observed improved cognitive performances in AD subjects treated with levetiracetam and better mood in those treated whit lamotrigine whereas patients treated with phenobarbital showed cognitive side effects.

4. Discussion

For a long time, seizures in AD were thought to be due to neuronal damage and gliosis and typical of the late stages of the disease. Only recently, was reported their appearance in the early stages of AD or even before the appearance of cognitive impairments. Because seizures are often focal and because there are some similarities between patients affected by AD and patients affected by TLE, attention has been drawn to the temporal lobe and relevant questions have been put forward. First of all, the true frequency of the seizures was investigated. Actually non-convulsive seizures seem more frequent in AD but are difficult to recognize clinically especially in confused patients and it is well-know that temporal seizures are often unrecognised by the standard Electroencephalogram (EEG). Interestingly, both Minkiviciene in mice (51) and Vossel in humans (17) recorded anomalies in more than 60% of their subjects using prolonged recording, a much greater percentage than that reported using standard recording techniques. According to the data of Palop et al. (50) the epileptiform discharges are the rule, at least in mice. The question is of practical importance because some authors (21, 24) have reported an association between seizures and rapid progression of cognitive decline; this is a matter for future studies. The second question is why seizures appear. It seems reasonable to suppose that these two diseases have a common mechanism responsible for similar symptoms such as depression, seizures and cognitive impairment. To a certain extent, AD and TLE remain different both clinically and pathologically; at this stage, it is therefore not possible to refuse the alternative hypothesis that similar symptoms appear simply because the same cerebral region is affected by both diseases. In support of this hypothesis, it must be noted that seizures were recorded also in other dementias and particularly in vascular dementia (18). It remains well-recognized that seizures cause cognitive impairment; it is therefore logical to investigate whether antiepileptic drugs can slow the process. Works in this direction are very few: in old animals antiepileptic drugs seem to improve the cognitive performances; however in general animal models of AD and in humans these drugs are ineffective. The improved knowledge of the mechanisms responsible for neuronal hyperexcitability may lead to more selective and effective drugs. Finally, it should be noted that the NINCS-ADRDA criteria (1) take into account only cognitive impairments, thus leaving out several non-cognitive symptoms that can also appear in the early stages and can be precocious signs of the disease (66). According to the NINCS-ADRDA criteria seizures at the onset or very early in the course of the illness make the diagnosis uncertain or unlikely. However, this statement dates back to 1984 whereas more recent studies both in animals (Palop 2007, Minkieviciene 2009, Vog 2011, Yan 2012) and humans (Vossel 2013, Zarea 2016) showed a greater frequency. Studies on humans are few but if confirmed this statement needs to be modified.

Footnote

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References

1. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;**34**(7):939–44. [PubMed: 6610841].
2. Alzheimer A, Forstl H, Levy R. On certain peculiar diseases of old age. *Hist Psychiatry.* 1991;**2**(5 Pt 1):71–101. [PubMed: 11622845].
3. Sjogren T, Sjogren H, Lindgren AG. Morbus Alzheimer and morbus Pick; a genetic, clinical and patho-anatomical study. *Acta Psychiatr Neurol Scand Suppl.* 1952;**82**:1–152. [PubMed: 13171126].
4. Letemendia F, Pampiglione G. Clinical and electroencephalographic observations in Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 1958;**21**(3):167–72. [PubMed: 13576166].
5. Hauser WA, Morris ML, Heston LL, Anderson VE. Seizures and myoclonus in patients with Alzheimer's disease. *Neurology.* 1986;**36**(9):1226–30. [PubMed: 3092131].
6. Sulkava R. Alzheimer's disease and senile dementia of Alzheimer type. A comparative study. *Acta Neurol Scand.* 1982;**65**(6):636–50. [PubMed: 7113668].
7. Risse SC, Lampe TH, Bird TD, Nochlin D, Sumi SM, Keenan T, et al. Myoclonus, seizures, and paratonia in Alzheimer disease. *Alzheimer Dis Assoc Disord.* 1990;**4**(4):217–25. [PubMed: 2264979].
8. Romanelli MF, Morris JC, Ashkin K, Coben LA. Advanced Alzheimer's disease is a risk factor for late-onset seizures. *Arch Neurol.* 1990;**47**(8):847–50. [PubMed: 2375689].
9. Forstl H, Burns A, Levy R, Cairns N, Luthert P, Lantos P. Neurologic signs in Alzheimer's disease. Results of a prospective clinical and neuropathologic study. *Arch Neurol.* 1992;**49**(10):1038–42. [PubMed: 1417511].
10. Mendez MF, Catanzaro P, Doss RC, A. Rguello R , Frey W2. Seizures in Alzheimer's disease: clinicopathologic study. *J Geriatr Psychiatry Neurol.* 1994;**7**(4):230–3. [PubMed: 7826492].
11. Volicer L, Smith S, Volicer BJ. Effect of seizures on progression of dementia of the Alzheimer type. *Dementia.* 1995;**6**(5):258–63. [PubMed: 8528372].
12. Amatniek JC, Hauser WA, DelCastillo-Castaneda C, Jacobs DM, Marder K, Bell K, et al. Incidence and predictors of seizures in patients with Alzheimer's disease. *Epilepsia.* 2006;**47**(5):867–72. doi: 10.1111/j.1528-1167.2006.00554.x. [PubMed: 16686651].
13. Lozsadi DA, Larner AJ. Prevalence and causes of seizures at the time of diagnosis of probable Alzheimer's disease. *Dement Geriatr Cogn Disord.* 2006;**22**(2):121–4. doi: 10.1159/000093664. [PubMed: 16733353].
14. Scarmeas N, Honig LS, Choi H, Cantero J, Brandt J, Blacker D, et al. Seizures in Alzheimer disease: who, when, and how common?. *Arch Neurol.* 2009;**66**(8):992–7. doi: 10.1001/archneurol.2009.130. [PubMed: 19667221].
15. Rao SC, Dove G, Cascino GD, Petersen RC. Recurrent seizures in patients with dementia: frequency, seizure types, and

treatment outcome. *Epilepsy Behav.* 2009;**14**(1):118–20. doi: 10.1016/j.yebeh.2008.08.012. [PubMed: 18782632].
16. Bernardi S, Scaldaferri N, Vanacore N, Trebbastoni A, Francia A, D'Amico A, et al. Seizures in Alzheimer's disease: a retrospective study of a cohort of outpatients. *Epileptic Disord.* 2010;**12**(1):16–21. doi: 10.1684/epd.2010.0290. [PubMed: 20172846].
17. Vossel KA, Beagle AJ, Rabinovici GD, Shu H, Lee SE, Naasan G, et al. Seizures and epileptiform activity in the early stages of Alzheimer disease. *JAMA Neurol.* 2013;**70**(9):1158–66. doi: 10.1001/jamaneurol.2013.136. [PubMed: 23835471].
18. Imfeld P, Bodmer M, Schuerch M, Jick SS, Meier CR. Seizures in patients with Alzheimer's disease or vascular dementia: a population-based nested case-control analysis. *Epilepsia.* 2013;**54**(4):700–7. doi: 10.1111/epi.12045. [PubMed: 23215680].
19. Picco A, Archetti S, Ferrara M, Arnaldi D, Piccini A, Serrati C, et al. Seizures can precede cognitive symptoms in late-onset Alzheimer's disease. *J Alzheimers Dis.* 2011;**27**(4):737–42. doi: 10.3233/JAD-2011-110896. [PubMed: 21876255].
20. Cretin B, Blanc F, Gaultier C, Sellal F. Epileptic Amnesic Syndrome revealing Alzheimer's disease. *Epilepsy Res.* 2012;**102**(3):206–9. doi: 10.1016/j.eplepsyres.2012.08.002. [PubMed: 22959716].
21. Irizarry MC, Jin S, He F, Emond JA, Raman R, Thomas RG, et al. Incidence of new-onset seizures in mild to moderate Alzheimer disease. *Arch Neurol.* 2012;**69**(3):368–72. doi: 10.1001/archneurol.2011.830. [PubMed: 22410444].
22. Sherzai D, Losey T, Vega S, Sherzai A. Seizures and dementia in the elderly: Nationwide Inpatient Sample 1999-2008. *Epilepsy Behav.* 2014;**36**:53–6. doi: 10.1016/j.yebeh.2014.04.015. [PubMed: 24857809].
23. Cheng CH, Liu CJ, Ou SM, Yeh CM, Chen TJ, Lin YY, et al. Incidence and risk of seizures in Alzheimer's disease: A nationwide population-based cohort study. *Epilepsy Res.* 2015;**115**:63–6. doi: 10.1016/j.eplepsyres.2015.05.009. [PubMed: 26220378].
24. Zarea A, Charbonnier C, Rovelet-Lecrux A, Nicolas G, Rousseau S, Borden A, et al. Seizures in dominantly inherited Alzheimer disease. *Neurology.* 2016;**87**(9):912–9. doi: 10.1212/WNL.0000000000003048. [PubMed: 27466472].
25. Liedorp M, Stam CJ, van der Flier WM, Pijnenburg YA, Scheltens P. Prevalence and clinical significance of epileptiform EEG discharges in a large memory clinic cohort. *Dement Geriatr Cogn Disord.* 2010;**29**(5):432–7. doi: 10.1159/000278620. [PubMed: 20502017].
26. Hesdorffer DC, Hauser WA, Annegers JF, Kokmen E, Rocca WA. Dementia and adult-onset unprovoked seizures. *Neurology.* 1996;**46**(3):727–30. [PubMed: 8618673].
27. Yarchoan M, Xie SX, Kling MA, Toledo JB, Wolk DA, Lee EB, et al. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. *Brain.* 2012;**135**(Pt 12):3749–56. doi: 10.1093/brain/aws271. [PubMed: 23204143].
28. Wollenweber FA, Buerger K, Mueller C, Ertl-Wagner B, Malik R, Dichgans M, et al. Prevalence of cortical superficial siderosis in patients with cognitive impairment. *J Neurol.* 2014;**261**(2):277–82. doi: 10.1007/s00415-013-7181-y. [PubMed: 24221645].
29. Zonneveld HI, Goos JD, Wattjes MP, Prins ND, Scheltens P, van der Flier WM, et al. Prevalence of cortical superficial siderosis in a memory clinic population. *Neurology.* 2014;**82**(8):698–704. doi: 10.1212/WNL.0000000000000150. [PubMed: 24477113].
30. Vernooij MW, Ikram MA, Hofman A, Krestin GP, Breteler MM, van der Lugt A. Superficial siderosis in the general population. *Neurology.* 2009;**73**(3):202–5. doi: 10.1212/WNL.0b013e3181ae7c5e. [PubMed: 19620607].
31. Ponomareva NV, Selesneva ND, Jarikov GA. EEG alterations in subjects at high familial risk for Alzheimer's disease. *Neuropsychobiology.* 2003;**48**(3):152–9. [PubMed: 14586166].
32. Ponomareva NV, Korovaitseva GI, Rogaev EI. EEG alterations in non-demented individuals related to apolipoprotein E genotype and to risk of Alzheimer disease. *Neurobiol Aging.* 2008;**29**(6):819–27. doi: 10.1016/j.neurobiolaging.2006.12.019. [PubMed: 17293007].
33. Lehtovirta M, Soininen H, Helisalmi S, Mannermaa A, Helkala EL, Hartikainen P, et al. Clinical and neuropsychological characteristics in familial and sporadic Alzheimer's disease: relation to apolipoprotein E polymorphism. *Neurology.* 1996;**46**(2):413–9. [PubMed: 8614504].
34. Sporis D, Sertic J, Henigsberg N, Mahovic D, Bogdanovic N, Babic T. Association of refractory complex partial seizures with a polymorphism of ApoE genotype. *J Cell Mol Med.* 2005;**9**(3):698–703. [PubMed: 16202217].
35. Babic T, Zurak N. Convulsions induced by donepezil. *J Neurol Neurosurg Psychiatry.* 1999;**66**(3):410. [PubMed: 10084551].
36. Peltz G, Pacific DM, Noviasky JA, Shatla A, Mehalic T. Seizures associated with memantine use. *Am J Health Syst Pharm.* 2005;**62**(4):420–1. [PubMed: 15745897].
37. Cardamone L, Salzberg MR, Koe AS, Ozturk E, O'Brien TJ, Jones NC. Chronic antidepressant treatment accelerates kindling epileptogenesis in rats. *Neurobiol Dis.* 2014;**63**:194–200. doi: 10.1016/j.nbd.2013.11.020. [PubMed: 24321434].
38. Eyal S, Rasaby S, Ekstein D. Concomitant therapy in people with epilepsy: potential drug-drug interactions and patient awareness. *Epilepsy Behav.* 2014;**31**:369–76. doi: 10.1016/j.yebeh.2013.09.041. [PubMed: 24211058].
39. Fisher RS, Bortz JJ, Blum DE, Duncan B, Burke H. A pilot study of donepezil for memory problems in epilepsy. *Epilepsy Behav.* 2001;**2**(4):330–4. doi: 10.1006/ebeh.2001.0221. [PubMed: 12609209].
40. Hamberger MJ, Palmese CA, Scarmeas N, Weintraub D, Choi H, Hirsch LJ. A randomized, double-blind, placebo-controlled trial of donepezil to improve memory in epilepsy. *Epilepsia.* 2007;**48**(7):1283–91. doi: 10.1111/j.1528-1167.2007.01114.x. [PubMed: 17484756].
41. Bell JS, Lonnroos E, Koivisto AM, Lavikainen P, Laitinen ML, Soininen H, et al. Use of antiepileptic drugs among community-dwelling persons with Alzheimer's disease in Finland. *J Alzheimers Dis.* 2011;**26**(2):231–7. doi: 10.3233/JAD-2011-110200. [PubMed: 21593561].
42. Fleisher AS, Truran D, Mai JT, Langbaum JB, Aisen PS, Cummings JL, et al. Chronic divalproex sodium use and brain atrophy in Alzheimer disease. *Neurology.* 2011;**77**(13):1263–71. doi: 10.1212/WNL.0b013e318230a16c. [PubMed: 21917762].
43. Belcastro V, Costa C, Galletti F, Pisani F, Calabresi P, Parnetti L. Levetiracetam monotherapy in Alzheimer patients with late-onset seizures: a prospective observational study. *Eur J Neurol.* 2007;**14**(10):1176–8. doi: 10.1111/j.1468-1331.2007.01907.x. [PubMed: 17880574].
44. Cumbo E, Ligori LD. Levetiracetam, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer's disease. *Epilepsy Behav.* 2010;**17**(4):461–6. doi: 10.1016/j.yebeh.2010.01.015. [PubMed: 20188634].
45. Samson WN, van Duijn CM, Hop WC, Hofman A. Clinical features and mortality in patients with early-onset Alzheimer's disease. *Eur Neurol.* 1996;**36**(2):103–6. [PubMed: 8654478].
46. Borroni B, Pilotto A, Bonvicini C, Archetti S, Alberici A, Lupi A, et al. Atypical presentation of a novel Presenilin 1 R377W mutation: sporadic, late-onset Alzheimer disease with epilepsy and frontotemporal atrophy. *Neurol Sci.* 2012;**33**(2):375–8. doi: 10.1007/s10072-011-0714-1. [PubMed: 21822699].
47. Helmstaedter C, Kurthen M. Memory and epilepsy: characteristics, course, and influence of drugs and surgery. *Curr Opin Neurol.* 2001;**14**(2):211–6. [PubMed: 11262738].
48. Hoppe C, Elger CE. Depression in epilepsy: a critical review from a clinical perspective. *Nat Rev Neurol.* 2011;**7**(8):462–72. doi: 10.1038/nrneurol.2011.104. [PubMed: 21750525].
49. Thom M, Liu JY, Thompson P, Phadke R, Narkiewicz M, Martinian L, et al. Neurofibrillary tangle pathology and Braak staging in chronic epilepsy in relation to traumatic brain injury and hippocampal sclerosis: a post-mortem study. *Brain.* 2011;**134**(Pt 10):2969–81. doi: 10.1093/brain/awr209. [PubMed: 21903728].
50. Palop JJ, Chin J, Roberson ED, Wang J, Thwin MT, Bien-Ly N, et al. Aber-

rant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. *Neuron.* 2007;**55**(5):697–711. doi: 10.1016/j.neuron.2007.07.025. [PubMed: 17785178].
51. Minkeviciene R, Rheims S, Dobszay MB, Zilberter M, Hartikainen J, Fulop L, et al. Amyloid beta-induced neuronal hyperexcitability triggers progressive epilepsy. *J Neurosci.* 2009;**29**(11):3453–62. doi: 10.1523/JNEUROSCI.5215-08.2009. [PubMed: 19295151].
52. Vogt DL, Thomas D, Galvan V, Bredesen DE, Lamb BT, Pimplikar SW. Abnormal neuronal networks and seizure susceptibility in mice overexpressing the APP intracellular domain. *Neurobiol Aging.* 2011;**32**(9):1725–9. doi: 10.1016/j.neurobiolaging.2009.09.002. [PubMed: 19828212].
53. Yan XX, Cai Y, Shelton J, Deng SH, Luo XG, Oddo S, et al. Chronic temporal lobe epilepsy is associated with enhanced Alzheimer-like neuropathology in 3xTg-AD mice. *PLoS One.* 2012;**7**(11):48782. doi: 10.1371/journal.pone.0048782. [PubMed: 23155407].
54. Holmes GL, Lenck-Santini PP. Role of interictal epileptiform abnormalities in cognitive impairment. *Epilepsy Behav.* 2006;**8**(3):504–15. doi: 10.1016/j.yebeh.2005.11.014. [PubMed: 16540376].
55. Kleen JK, Scott RC, Holmes GL, Lenck-Santini PP. Hippocampal interictal spikes disrupt cognition in rats. *Ann Neurol.* 2010;**67**(2):250–7. doi: 10.1002/ana.21896. [PubMed: 20225290].
56. Corbett BF, Leiser SC, Ling HP, Nagy R, Breysse N, Zhang X, et al. Sodium channel cleavage is associated with aberrant neuronal activity and cognitive deficits in a mouse model of Alzheimer's disease. *J Neurosci.* 2013;**33**(16):7020–6. doi: 10.1523/JNEUROSCI.2325-12.2013. [PubMed: 23595759].
57. Roberson ED, Scearce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T, et al. Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. *Science.* 2007;**316**(5825):750–4. doi: 10.1126/science.1141736. [PubMed: 17478722].
58. Zarow C, Sitzer TE, Chui HC. Understanding hippocampal sclerosis in the elderly: epidemiology, characterization, and diagnostic issues. *Curr Neurol Neurosci Rep.* 2008;**8**(5):363–70. [PubMed: 18713571].
59. Kordower JH, Chu Y, Stebbins GT, DeKosky ST, Cochran EJ, Bennett D, et al. Loss and atrophy of layer II entorhinal cortex neurons in elderly people with mild cognitive impairment. *Ann Neurol.* 2001;**49**(2):202–13. [PubMed: 11220740].
60. Du F, Whetsell WJ, Abou-Khalil B, Blumenkopf B, Lothman EW, Schwarcz R. Preferential neuronal loss in layer III of the entorhinal cortex in patients with temporal lobe epilepsy. *Epilepsy Res.* 1993;**16**(3):223–33. [PubMed: 8119273].
61. Scharfman HE. "Untangling" Alzheimer's disease and epilepsy. *Epilepsy Curr.* 2012;**12**(5):178–83. doi: 10.5698/1535-7511-12.5.178. [PubMed: 23118602].
62. Tariot PN, Schneider LS, Cummings J, Thomas RG, Raman R, Jakimovich LJ, et al. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. *Arch Gen Psychiatry.* 2011;**68**(8):853–61. doi: 10.1001/archgenpsychiatry.2011.72. [PubMed: 21810649].
63. Koh MT, Haberman RP, Foti S, McCown TJ, Gallagher M. Treatment strategies targeting excess hippocampal activity benefit aged rats with cognitive impairment. *Neuropsychopharmacology.* 2010;**35**(4):1016–25. doi: 10.1038/npp.2009.207. [PubMed: 20032967].
64. Koh MT, Rosenzweig-Lipson S, Gallagher M. Selective GABA(A) alpha5 positive allosteric modulators improve cognitive function in aged rats with memory impairment. *Neuropharmacology.* 2013;**64**:145–52. doi: 10.1016/j.neuropharm.2012.06.023. [PubMed: 22732440].
65. Devi L, Ohno M. Effects of levetiracetam, an antiepileptic drug, on memory impairments associated with aging and Alzheimer's disease in mice. *Neurobiol Learn Mem.* 2013;**102**:7–11. doi: 10.1016/j.nlm.2013.02.001. [PubMed: 23416036].
66. Raudino F. Non-cognitive symptoms and related conditions in the Alzheimer's disease: a literature review. *Neurol Sci.* 2013;**34**(8):1275–82. doi: 10.1007/s10072-013-1424-7. [PubMed: 23543394].