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Review

Treatment of epilepsy in patients with Alzheimer's disease

Filippo Sean Giorgi*, Melania Guida, Andrea Vergallo, Ubaldo Bonuccelli, Gaetano Zaccara

Authors names & affiliations:

Filippo Sean Giorgi

Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa-Pisa University Hospital, Pisa, Italy

Melania Guida

Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa-Pisa University Hospital, Pisa, Italy

Andrea Vergallo

Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa-Pisa University Hospital, Pisa, Italy

Ubaldo Bonuccelli

Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa-Pisa University Hospital, Pisa, Italy

Gaetano Zaccara

Neurology Unit, Department of Medicine, Florence Health Authority, Firenze, Italy.

***Author for correspondence:**

Dr Filippo Sean Giorgi, MD, PhD
Department of Clinical and Experimental Medicine, Section of Neurology,
University of Pisa - Pisa University Hospital.
Via Roma 67, I56126, Pisa, ITALY.
e-mail: giorgifs@gmail.com; f.giorgi@ao-pisa.toscana.it
phone: +39-050992000. Fax: +39-050554808

Abstract

Introduction: Epilepsy is significantly more frequent in AD patients than in age-matched controls, even though the precise entity of the phenomenon is not clear yet.

Areas covered: In this review, we describe in detail the available data on the pharmacological treatment of epilepsy in patients with AD. We also briefly describe general principles of AEDs use in elderly, as well as the potential cognitive profile of AEDs and safety of concomitant psychotropic drugs in patients with epilepsy and AD.

Expert Commentary: As some preclinical data suggest a role of epileptiform discharges in cognitive decline in AD, a prompt diagnosis and treatment of seizures in these patients should be pursued. The few data on the use of AEDs in AD patients suggest that newer AEDs (in particular lamotrigine and levetiracetam) might be good choices. Experimental data even support a potential role of some AEDs in modifying the disease course of AD.

Keywords

Alzheimer's Disease; antiepileptic drugs; complex partial seizures; dementia; EEG; elderly patients; epilepsy; focal epilepsy; generalized epilepsy; pharmacokinetics.

1. Introduction

Alzheimer's Disease (AD) is a common neurodegenerative disorder affecting up to 11% of adults over 65 years of age, and up to 32 % of the population over 85[1,2]**.** AD is associated with a progressive impairment of cognitive functions which usually starts with isolated episodic memory alteration, and leads progressively to an impairment of instrumental activities of daily living and, eventually, also of common daily living activities. The main pathological features of AD are the deposition of β amyloid plaques (APs) and neurofibrillary tangles (NFT) in the brain. Furthermore, in AD there is an impairment of the cholinergic system pertaining to the Meynert Basal Nucleus[3] and of brain noradrenergic system[4].

An increase in the incidence of epileptic seizures in AD patients has been repeatedly observed (see below). Seizures are the effect of an abnormal and/or excessive activation of large populations of

cortical neurons, and epilepsy is defined as an enduring predisposition to having seizures. Thus, in most cases a diagnosis of epilepsy is made after the recurrence of at least two unprovoked epileptic seizures at least 24h apart[5]. Seizures can be either of focal (i.e. originating from a restricted part of the cortex, with or without secondary generalization) or of generalized origin (when involving *ab initio* simultaneously the whole cortex). As AD prevalence is progressively increasing in parallel with the increased age of the general population in developed countries, the treatment of epilepsy in AD patients is becoming a matter of growing clinical importance.

Thus, the main topic of this review is to report in detail the current evidences on the role of specific AEDs in the treatment of epileptic seizures in patients with AD, based on the available literature on this subject. Furthermore, in order to better define the *scenario* of the treatment of epilepsy in AD patients, we provide also a brief overview on the potential link between AD and epilepsy, on the specific issues of epilepsy treatment in the elderly and on specific aspects to consider when treating epilepsy in demented people. These latter three aspects will be described shortly, as each one of them might need *per se* a full length review based on all the available literature (including reviews) published in these fields.

2. Epilepsy in AD: a brief overview

Even though AD affects the range of ages during which there is also the highest incidence of epilepsy[6], it is widely accepted among neurologists that seizures occur more frequently in AD patients than in the general elderly population. This has been shown by several retrospective studies, some of which date back even to the early '60s[7]. While all of them suggest such a higher incidence, there is a huge discrepancy in numbers among the different casistics (reviewed recently in [8]). The reasons for such discrepancies go beyond the aims of this review, but they might be related, among others, to: a) the classification criteria of dementia, which have been changing significantly during the last years, b) to the degree of concomitant vascular alterations in the populations included in the different series, c) to the type(s) of concomitant treatments (some of them with antiepileptic, and other with pro-epileptic properties), d) to the varying number of patients included, and, e) to the approaches used to investigate the occurrence of previous seizures in AD patients[9] . In any case, it seems that seizures might be more frequent among AD patients of younger age and/or affected by early-onset familial AD. In particular, the high occurrence of seizure in familial AD, in which there is a pathogenic mutation involving amyloid precursor protein (APP) or presenilin genes, and a significant APs/NFT accumulation in the brain, confirms, indirectly, the strict potential link existing between AD pathology and epilepsy proneness[10,11]. Which are the types of seizures most represented among AD patients is also a matter of debate, as generalized tonic-clonic seizures are predominant in many AD casistics[12], while complex partial seizures seem to be

prevalent in other studies[13]. Another potential important reason for the discrepancies among different casistics concerning the true incidence of seizures and epilepsy in AD, as well as the specific types of seizures most represented in these patients, might be the difficulty of making a clear diagnosis of epilepsy in these specific types of patients. Indeed, while an epilepsy diagnosis is easily performed in patients with reliable caregivers reporting episodes featured by typical generalized tonic-clonic features, in other occasions a diagnosis is challenging, especially when reliable caregivers lack. Furthermore, focal seizures are often missed in these patients: not only focal limbic seizures are often misinterpreted as confusional states or episodes of alert reduction, which can be part of the AD patients clinical features, but even brief focal motor seizures (or the automatic gestures often associated to limbic seizures) might be missed in these patients. To the best of our knowledge, no specific diagnostic criteria keeping into account such diagnostic difficulties have been proposed up to now by ILAE or national Epilepsy societies.

Even though these aspects are beyond the aims of this review, it is worth mentioning that the interplay existing between epilepsy and AD has been assessed also experimentally. Nowadays, transgenic mice bearing gene mutations which cause familial AD in humans (mainly APP), are largely available: they are considered currently the animal models more closely mimicking the human disease, although they reproduce only in part the pathological features of AD[14]. In some mice strains over expressing the mutated form of APP, EEG interictal epileptiform discharges and electrographic seizures have been observed, and these alterations have been related to Aβ-induced increases in network excitability[15]. The interplay existing between such an epileptiform activity and cognitive impairment is a matter of debate: it is worth mentioning that it has been proposed that the compensatory inhibitory mechanisms taking place due to the epileptiform activity, might interfere significantly, by themselves, with cognitive functions[15,16]. A complete review of studies and hypothesis on these aspects is beyond the aims of this report.

Interestingly, an early occurrence of temporal lobe seizures has been recently proposed to be the hallmark of a subgroup of patients with prodromal AD by Cretin et al.[17], who defined them as "epileptic prodromal Alzheimer's Disease" patients, confirming previous observations[13]. Actually, the low incidence of this hypothesized AD phenotype in those casistics, might represent an underestimation of the true occurrence of epileptic abnormalities in the limbic system early in the course of AD. This might be due to the retrospective features of the above mentioned studies, to the already mentioned difficulties of recognizing subtle temporal lobe seizures, and to the lack of sensitivity of skull surface EEG recordings in detecting mesial temporal lobe epileptiform activity. Future research might reveal that epileptic prodromal AD is more common than expected.

3. A short overview on the treatment of epilepsy in elderly

It is well known that epilepsy is an age-dependent condition, whose incidence shows a bimodal distribution. In fact it shows the highest peak of incidence in childhood and again a increased incidence in subjects older than 60 years, up to 159/100.000 depending from the different casistics (summarized in [18,19]).

Cerebrovascular diseases are the commonest causes of new-onset epilepsy in the elderly, followed by AD, other neurodegenerative dementias, brain tumors and head injury[20].

Diagnosis of new-onset epilepsy in the elderly is often challenging, mainly due to difficulty in detecting "milder" seizures (especially complex partial ones -i.e. focal seizures affecting limbic structures, during which there is an impairment of consciousness) in cognitively impaired subjects, as well as to the often difficult differential diagnosis with other causes of loss of consciousness in patients frequently affected by concomitant diseases.

Antiepileptic drugs (AEDs) selection in the elderly needs more attention than in younger patients for many reasons. Among them, a significant role is played by patient cognitive/neuropsychiatric status and motor functioning (often strictly related one another) that could strongly affect therapeutic compliance[21].

Drug pharmacokinetics changes occurring with ageing play a critical role in AEDs selection/use and concur in affecting the therapeutic range and the tolerability profile of AEDs in elderly. In fact, drug absorption can be significantly affected in elderly patients, which are more likely to have concomitant gastrointestinal disorders (anatomical/functional alterations, or alterations of gastric pH, gastric emptying rates, and intestinal transit timing) as compared with younger ones[22] . Moreover, age-related decrease in blood albumin levels results in reduced drug protein binding and/or impaired drug displacement from binding sites. In the elderly, there is also reduced total body water content, which is associated with decreased distribution volume of lipophilic AEDs[23,24]. Metabolism and drug clearance varies significantly with age, since elderly patients tend to show an age-related decrease in glomerular filtration rate and in liver metabolic rate due to lower cytochrome P450 enzyme (CYP) function. There is also a general organ-system impaired blood flow, and organ-system functional burden due to comorbidities/concomitant medical treatments, and all of the above mechanisms affect AEDs clearance[25] .

The abovementioned changes in pharmacokinetics might result in a higher risk of drug toxicity and neurologic and somatic side effects[26,27]. This is particularly true concerning those AEDs with higher protein binding [carbamazepine (CBZ), valproic acid (VPA), phenytoin (PHT)[23,24]], even though with often unpredictable effects.

On the other hand, it has been shown by several studies that elderly patients with epilepsy tend to be better responders to AEDs compared to younger patients, with higher seizure-free ratio at lower serum drug concentrations. This might partly counteract the higher potential rate of adverse events

(AEs) which tend to be present at lower blood concentrations than those causing AEs in younger patients[27,28]. As a general rule, keeping in mind both these two aspects (i.e. higher risk for AEs and better therapeutic response to AEDs), AEDs in elderly patients should be started at dosages lower than the usual ones, and titrated slowly, according to the so-called called "start slow and go slow" approach [21,29].

Remarkably, even though this age group of patients is the one which more often is treated with AEDs, only few clinical trials have specifically assessed the treatment of epilepsy in elderly patients with new-onset epilepsy.

When considering which are the commonest AEDs used in the management of new-onset epilepsy in elderly patients, it is useful to differentiate data obtained in nursing-homes (NH) and those in community dwelling (CD)[30]. In CD, older AEDs, especially CBZ and VPA, are the drugs of choice in new-onset epilepsy in Europe, while PHT is the most prescribed AED in USA [31] . This might be due at least in part to etiological features of new-onset epilepsy in elderly patients, but also to the remarkably lower cost of these AEDs [32,33].

Elderly persons in NH, have higher prevalence and incidence of epilepsy compared to those in CD, and in these settings there is a larger use of AEDs. Furthermore, they also have a greater frailty and more comorbidities, and this potentially affects AEDs choice. Observational studies showed that, in NH setting, CBZ and VPA are the most used AEDs; it should be noted, however, that both in Europe and USA, gabapentin (GBP) followed by pregabalin (PGB), are being increasingly used for managing concomitant psychotic, anxiety and mood disorders in NH patients [34-36].

In light of their much better profile in terms of pharmacokinetics, new AEDs appear the theoretical drugs of choice in elderly patients, as they have in general a linear dose/plasma concentration correlation, a much lower binding to blood proteins, less metabolic interactions with other drugs, and also their pharmacodynamics features themselves reduce the risk of AEs and drug-drug interactions [37].

Many prospective open label or retrospective data confirm the higher tolerability profile of newer AEDs in elderly patients [37], even though not showing statistically significant differences in terms of efficacy between old and new AEDs.

In particular, among the new AEDs, levetiracetam (LEV) and lamotrigine (LTG) are increasingly used in elderly patients, and this is likely to be due mainly to their favorable pharmacokinetic profile and lack of significant interaction with other drugs [38-41].

In a recent review, inconclusive data were reported concerning the efficacy and tolerability of zonisamide (ZNS) in the treatment of elderly patients with epilepsy, mainly concerning cognitive side effects [42]. Few data are reported about topiramate (TPM) use in elderly, but they suggest that,

despite a generally good efficacy and tolerability profile, it seems to be a second choice in treatment of epilepsy in these patients due to both its cognitive and psychiatric AEs [43,44].

Only a handful of controlled clinical trials have specifically assessed the treatment of epilepsy in elderly patients with new onset epilepsy.

In the first double-blind study designed ad-hoc [39] a sample of elderly patients with newly diagnosed epilepsy were randomized to antiepileptic treatment with either LTG or CBZ: no significant differences in term of efficacy were found between the two AEDs, but the drop-out rate due to AEs was significantly higher in the CBZ harm. This result was confirmed in the study by Saetre and colleagues (2007)[45], which found a similar efficacy of LTG and controlled release CBZ (CR-CBZ), but a better tolerability of LTG in elderly patients with newly diagnosed epilepsy.

Recently, CR-CBZ, LTG and LEV were compared in a similar population of epilepsy patients, showing a similar efficacy profile, but a higher retention rate for LEV and LTG [41] .

CBZ and LTG had also been compared with GBP in a randomized, double-blind, parallel trial in elderly patients by Rowan and colleagues (2005)[46]: these authors found no significant differences in efficacy outcome, and observed a higher retention rate in GBP and LTG groups compared to CBZ.

Finally, another randomized trial in elderly epilepsy patients was performed by Ramsay et al. in 2008[47] , who evaluated TPM at two dosages (50 or 200 mg/daily), tested either as monotherapy or as add-on. TPM efficacy in monotherapy was similar at the two dosages, while as an add-on the higher dosage was the most efficacious. No significant difference was reported in the incidence of AEs for the two dosages (either as monotherapy or polytherapy).

4. Evidences on the use of antiepileptic drugs in epilepsy associated with AD

To our knowledge only few studies assessed the efficacy and tolerability of AEDs treatment in patients with AD and epilepsy. All of them confirmed that seizures in AD patients are generally well controlled by AEDs therapy, even though the tolerability profile differs from one AED to another (see below). Thus, as a general rule, AEDs choice in these particular population (but similarly to the elderly population in general) should be guided mainly by side effects and pharmacokinetic profile[48] .

As reported by Mendez and Lim (2003)[49], PHT is still the most prescribed AEDs in elderly and in NH patients and the same is likely to apply also to the sub-group of AD patients. The wide use of PHT in elderly with cognitive impairment was supported by a retrospective study by Rao et al. (2009)[50]. These authors examined 39 patients with cognitive impairment (mild cognitive impairment, AD, vascular dementia or Lewy body disease) and epilepsy, treated with PHT, VPA, CBZ, GBP, phenobarbital (PB) and clonazepam in monotherapy or, in a minority of subjects, in

polytherapy. The most common seizures types in this group of patients were complex partial seizures (72%) and generalized tonic-clonic seizures (52%). Seventy-nine % of patients obtained seizure freedom or a reduction > 95% in seizure frequency and a total of approx. 92% of patients had experienced a seizure reduction>50% , while only three subjects (7,7%) could be considered as non-responders. Twelve patients (31%) reported mild dose-related adverse events. The authors did not compare the efficacy and tolerability of the different AEDs used, because of the small sample size analyzed, but they concluded that seizures in demented patients are in general controlled quite well by AEDs treatment. Considering that most of their patients were taking PHT (38,5%), we could conclude that in these sample PHT was effective and well tolerated. However, the latter statement was not confirmed in a subsequent study by Tsiouris et al. (2002)[51], who retrospectively reviewed the outcome of 17 patients with Down Syndrome and AD treated with PHT for epileptic seizures. They found an unexpected decline in cognitive performance and activity of daily living and a high rate of adverse events (sedation, dizziness, ataxia, etc.) in these patients. Both the cognitive decline and the adverse effects were reversed by PHT withdrawal. Similar results had been already reported by the same group in a previous study on a similar patient population, but including only five subjects[52] . Even though the neuropathology of Down Syndrome associated with AD is considered to be overlapping with sporadic AD[53], we cannot rule out the possibility that the population of Down Syndrome/AD/epilepsy, might differ from patients with AD/epilepsy alone. By the same token, we cannot exclude that the significant efficacy of PHT reported in the study mentioned above by Rao et al. (2009)[50], could be related at least in part to a more specific effect in patients with dementia forms other than AD, even though a sub-analysis was not provided.

Concerning another widely used classical AED, VPA, there are some indirect evidences suggesting that it should not be a first choice in patients with AD. In fact, even though there are some experimental evidences that VPA may have neuroprotective properties in preclinical studies[54,55], some studies in human have suggested that VPA could increase cognitive decline and brain atrophy. In particular, in two studies by the Alzheimer's Disease Cooperative Study Group[56,57], 313 patients with mild or moderate AD (MMSE 12-20), treated with VPA as mood stabilizer, were recruited in a 24-month randomized placebo-controlled trial in order to evaluate the progression of cognitive decline and behavioral disturbance. Considering cognitive performance, the authors reported a statistically significant difference between patients treated with VPA and placebo group in MMSE score after 6 (-2,4 for VPA group and -1,04 for placebo group) and 12 months (-3,9 for VPA group and - 2,0 for placebo group)[56], while these differences were no longer present after 18 and 24 months of treatment[56]. Interestingly, VPA did not show any significant effect on behavioral disturbances[56]. In any case, VPA was tolerated quite well, as the percentage of patients who discontinued the drug because of adverse event was slightly higher in VPA group (16,3%) than in

placebo group (7,5%) but not statistically significantly[57] . Both studies[56,57] included also an elegant analysis of the effects of VPA on brain volumetry showing a significant difference in annualized percent volume changes in ventricular volume, brain volume and bilateral hippocampal volume. As they found a positive correlation between change in MMSE score and brain and ventricular volume, as well as between VPA serum concentration and brain and ventricular volume, Fleischer et al. (2011) concluded that VPA treatment was associated with accelerated brain volume loss and cognitive decline in AD patients. Concerning the use of VPA in elderly patients, and especially in patients with severe AD, it should kept into account also the well-known extrapyramidal side effects (mainly tremorigenic) of this drug[58,59] which might further complicate its use in these types of patients, even though no specific studies on AD patients assessing this specific side effects have been preformed to our knowledge.

It is worth noting that no studies have been performed on other classical AEDs and AD/epilepsy.

Surprisingly, also concerning newer AEDs not so many studies as expected have been performed in AD patients. Theoretically, however, just the observation of a similar efficacy toward seizures of newer and older AEDs in patients with AD might be sufficient to favor the choice of second generation AEDs in this patients population in light of their better tolerability profile (see above).

Belcastro and colleagues (2007)[60] administered LEV to 25 patients with severe AD with recent onset focal epilepsy and at least two seizures in the previous three months. Eighteen subjects (72%) obtained a 1-year period of seizure freedom with LEV dosages up to 1500 mg/day (in 11 of them with just 1000 mg/day dosage), while only 2 patients were non-responders, despite a further dose increase up to 2000 mg/day. Four patients (16%) withdrew because of AE (somnolence, gait disturbance, confusion, psychomotor agitation). The authors concluded that LEV is efficacious and well tolerated at low doses (1000-1500 mg/day) in patients with advanced AD and recent onset epilepsy.

In a more recent prospective, open-label, study by Lippa et al. (2010)[61], 24 patients with cognitive decline (AD, vascular dementia and mild cognitive impairment) and seizures were treated with LEV for 12 weeks. Sixty-eight % of 16 patients who completed the trial were seizure-free, while the remaining ones experienced only a seizure during the study. The most common AE reported was fatigue (20,8% of patients). The authors reported an improvement of MMSE and ADAS-Cog scores by an average 2,2 points and 4,3 points, respectively, at the end of treatment period. Also these authors concluded that LEV is a good therapeutic option for treatment of epilepsy in patients with cognitive impairment.

Cumbo and Ligori (2010)[62] studied the efficacy and tolerability of LEV, PB and LTG in 95 patients with AD and focal epilepsy in a prospective, randomized, single-blind, three-arm parallel-group, case-control trial. They treated 28 patients with LEV, 28 with PB and 29 with LTG for 12 months, all of them titrated to the lowest effective dose during the first 4-week dose-adjustment period. After 12 months of treatment, the responder rate was 71% for LEV group, 64% for PB group and 59% for LTG group. Even though the responder rate was higher in LEV group, the differences between the three groups were not statistically significant. Concerning tolerability, only 17% of patients treated with LEV referred mild and transient adverse events (somnolence, asthenia, headache, and dizziness). The percentage of adverse events raised up to 28% in the group of patients taking LTG and to 43% in patients treated with PB. In this latter group, the AEs (somnolence, asthenia, sedation) were considered often moderate or severe and led to withdrawal of 4 patients, which were the only ones interrupting the study. Although the tolerability profile of LEV and LTG seem to be better than PB, no statistically significant difference in the incidence of adverse event between the three drugs were found, probably because of the small size of sample assessed. The patients were also evaluated from a neuropsychological and psychological point of view at baseline and at the end of the study to assess cognitive effect of AEDs. Interestingly, subjects treated with LEV showed a mild cognitive improvement, especially in attention, verbal fluency and short-term memory, but a mood worsening compared with baseline. Patients taking PB experienced a significant worsening of both cognitive performance and mood scores. Finally, in the LTG group, patients showed a slight decline in cognitive performance but an improvement of mood. Although no significant differences between the three drugs were found, the authors concluded that LEV was the best choice for treatment of seizure in AD patients, since this drug combines high efficacy with a good tolerability profile and a good effect on cognitive performance[62] .

In a recent retrospective study by Vossel et al. (2013)[14], the authors identified from their hospital database 12 patients with mild cognitive impairment and epilepsy and 35 cases with AD and epilepsy treated with LTG (17 patients), LEV (16 patients), PHT (6 patients) or VPA (9 patients) in monotherapy for at least 3 months. Considering patients achieving seizure-freedom and a decrease of seizure frequency as a whole, the authors found that the responder rate of LTG (94,1%) and LEV (93,8%) was significantly superior to that of PHT (50%). Moreover, they found that tolerability of PHT was significantly worse than LTG, LEV and VPA. In particular, a cognitive worsening during the evaluation period was reported in four patients, three of which were taking PHT. Thus, the authors concluded that LEV and LTG were the best options for epilepsy treatment in mild cognitive impairment and AD, as they provided a good seizure control, even at low doses, and a good tolerability.

5. Aspects of epilepsy treatment specific for AD patients

5.1 Potential proconvulsant effect of specific AD treatments and psychotropic drugs

One of the main concerns regarding epilepsy in AD patients is related to the possibility of seizure threshold reduction by drugs commonly prescribed for treatment of AD and related behavioral disturbances. As cholinergic receptor agonists are commonly used to induce seizures in animal models[63], it could be hypothesized that acetyl-cholinesterase inhibitors used for treatment of AD could theoretically worsen seizures. According to this hypothesis, regulatory drug agencies have considered epilepsy as a contraindication for the use of these drugs. However, the evidences for such proconvulsant role in human are inconsistent. In a pilot study in 18 patients with AD treated with donepezil, the authors reported an increase in seizure frequency in 2 patients[64] . Conversely, no seizure worsening was reported in a more recent randomized double-blind study in epileptic patients with subjective memory impairment treated with donepezil[65] . Accordingly, in a prospective observational study by Scarmeas et al. (2009)[66], the use of acetyl-cholinesterase inhibitors was not a predictive factor of seizure onset in AD patients. Similar results were reported in a population of patients with mild to moderate AD who had been enrolled in different clinical trials[67] .

Also the use of memantine, which is a glutamate NMDA receptor antagonist commonly prescribed in AD patients, is debated in patients with AD and epilepsy. In some case reports memantine was considered to be associated with seizures onset in patients with AD[68,69] . In the abovementioned study analyzing data from various clinical trials in AD, memantine was even found to be a predictor of seizure onset[67]. On the contrary, memantine showed anticonvulsant properties in some animal models of epilepsy[70-73].

Seizure occurrence has been reported during treatment with almost all antidepressant and antipsychotic drugs tested so far, and the risk of seizures seems to increase in parallel with drug dose. Concerning antidepressant drugs, the tricyclic antidepressants (TCAs) clomipramine and bupropion, and the tetracyclic drugs maprotiline and mianserine are associated to a higher risk of seizure occurrence. Other TCAs, such as imipramine and amitriptiline, show an intermediate risk, while some Monoamine Oxidase Inhibitors (MAOIs), i.e. phenelzine and tranylcypromine, and most Selective Serotonin Reuptake Inhibitors (SSRIs), such as fluoxetine, paroxetine and sertraline, trazodone, mirtazapine and venlafaxine, seem to bear a lower proconvulsant activity[74,75]. Concerning antipsychotics, clozapine and chlorpromazine have been frequently associated to

seizures, while haloperidol, olanzapine and quietapine showed an intermediate risk; fluphenazine, pimozide, risperidone, thioridazine and trifluoperazine had a safer profile[74,75].

The latter aspect is particularly important to be considered, as antipsychotics are one of the classes of drugs which are most often used in patients with AD for concomitant behavioral disturbances.

Also the risk of pharmacokinetic interactions between AEDs and psychotropic drugs should be taken into account when using in the same patient different compounds. In most cases, these pharmacokinetic interactions are related to the induction or inhibition of specific CYP isoenzymes and could determine both an increase in drug toxicity and a decrease in drug efficacy[75]. Among others, one might mention the interactions existing between CYP-inducers AEDs (CBZ, PB, PHT) and drugs which are substrates of CYP1A2, CYP2C19 and CYP3A4 (amitriptyline, imipramine, fluvoxamine, setraline, citalopram, mirtazapine, clozapine, clomipramine, haloperidol, olanzapine, risperidone), as well as the interactions between CYP-inhibitor fluoxetine and fluvoxamine and AEDs substrates of CYP2C9 (VPA, PB, PHT) and between fluvoxamine and AEDs substrate of CYP2C19 (PHT) and CYP3A4 (CBZ, ethosuximide, tiagabine and ZNS)[76] .

As the use of psychotropic drugs is very frequently reported during the disease history of patients with AD, in these patients it could be preferable to avoid AEDs whose metabolism is mediated by CYP.

5.2 Cognitive side effect of AEDs

When using AEDs in patients with AD, the possibility of cognitive side effects should be taken into account as well. Antiepileptic therapy has been often associated with cognitive adverse effects, such as sedation, distractibility, memory disturbances and attention problem. Even though these effects are often mild, their impact in elderly and demented people may be significant[77,78] .

To our knowledge, only a few data on the cognitive adverse effect of AEDs in patients with cognitive impairment are available in literature. As cited above, Cumbo and Ligori (2010)[62] have evaluated cognitive performance of AD patients with epilepsy treated with LEV, PB and LTG for 12 months. Even though they did not find a statistically significant difference between the three drugs, they reported a mild cognitive improvement in LEV group, a mild cognitive decline in LTG group and a significant cognitive worsening in PB group compared with baseline. Also Lippa et al. (2010)[61] have reported an improvement of cognitive performance after 12 weeks treatment with LEV in patients with cognitive impairment and epilepsy.

Further indications could be drawn from studies on cognitive effect of AEDs in healthy subjects or epileptic patients. Older AEDs have a worse cognitive profile. Among them, PB has the less favorable profile, determining dose-related cognitive effects[79-81]. Also PHT [81-83], CBZ[83-84] and VPA [81,85,86] are associated to mild cognitive dysfunction, although no significant differences between the

three drugs have been reported in comparative studies [83,84,86,87] . Among the newer AEDs, TPM has the worse cognitive profile, as a decline in verbal fluency, especially with very high doses regimen (>300 mg/day), has been reported in various studies [88-90]. Mild cognitive effects have been described for oxcarbazepine in comparative studies versus PHT-[91,92]. Finally, LTG[93,94], GBP[95,96] and LEV[97,98] did not seem to affect cognitive performance, but they were rather associated, in some cases, to a mild cognitive improvement.

6. Literature search strategies and selection criteria

References for the paragraph 4 of this review were detected via PubMed searches of original research contributions published till February 2016, using the terms “Alzheimer Disease”, or “Dementia”, and "Antiepileptic Drugs", or “carbamazepine”, or "eslicarbazepine", or "gabapentin", or “lamotrigine”, or “levetiracetam”, or “oxcarbazepine”, or "perampanel", or “phenobarbital”, or “phenytoin”, or "pregabalin", or "retigabine", or “topiramate”, or “valproic acid”, or "vigabatrin", or “zonisamide”.

For paragraph 3 and 5 a less systematic analysis of the literature was performed as these paragraph were intended to provide an overview rather that extensive analysis. For paragraph 3 we selected specific articles from the items identified via PubMed using the terms “elderly” or “aged population”, and "Antiepileptic Drugs", or “carbamazepine”, or "eslicarbazepine", or "gabapentin", or “lamotrigine”, or “levetiracetam”, or “oxcarbazepine”, or "perampanel", or “phenobarbital”, or “phenytoin”, or "pregabalin", or "retigabine", or “topiramate”, or “valproic acid”, or "vigabatrin", or “zonisamide”. For paragraph 5.1 we selected specific articles from the items identified via PubMed using the terms “psychotropic drugs”, or “antypsychotics”, or “neuroleptics”, or “antidepressant”, or "rivastigmine", or “donepezil”, and “epilepsy”, or “seizures”, or “epileptic”. For paragraph 5.2, we selected specific articles from the items identified via PubMed using the terms “cognitive”, or “memory”, or “attention”, and "Antiepileptic Drugs", or “carbamazepine”, or "eslicarbazepine", or "gabapentin", or “lamotrigine”, or “levetiracetam”, or “oxcarbazepine”, or "perampanel", or “phenobarbital”, or “phenytoin”, or "pregabalin", or "retigabine", or “topiramate”, or “valproic acid”, or "vigabatrin", or “zonisamide”. A further search “Alzheimer”, or “Dementia”, or “amyloid”, or “cognitive impairment”, and “epilepsy”, or “seizures”, or “EEG”, or “interictal”, was performed and selected papers retrieved by this search and the abovementioned searches were used for the remaining paragraphs.

For all searches, additional, other items were identified among the references of the papers previously published about this topic. Only contributions published in peer-reviewed journals and written in English were taken into consideration.

7. Expert Commentary

The proportion of patients with AD will increase dramatically in the coming years, due to increase of life expectancy. Even though the precise incidence of epilepsy in AD has not been established yet, a raised epilepsy incidence in this type of patients has been clearly established and needs appropriate answers. Experimental data, not only have confirmed the link existing between the pathological features of AD and the increased incidence of epilepsy, but they have even suggested that the ictal/interictal epileptiform activity might concur to the cognitive decline and pathological features in these patients. In fact, in 2012 it was shown that LEV significantly ameliorates synaptic and cognitive deficits in transgenic models of AD[99] , and similar exciting results were obtained with TPM[100] and LTG[101], thereafter.

This prompts researchers in the field: a) on one side to increase the accuracy of epilepsy diagnosis in the single AD patient, with a special emphasis on those types of epilepsy syndromes which are (especially in these patients) a diagnostic challenge, such as temporal lobe epilepsy with complex partial seizures; b) on the other side to treat epilepsy in these patients as early and as effectively as possible. In fact, in the presence of a brain disorder as severe as AD, clinicians might be tempted to under treat concomitant "milder" diseases, including partial complex or partial seizures. In other words, in every AD patient any attempt to establish the concomitant diagnosis of epilepsy should be performed, and all of these patients should be treated with the best possible antiepileptic approach.

The complexity of these types of patients requires that their concomitant epilepsy should be treated by expert epileptologists rather than by non–specialists. In particular, a special emphasis should be given to: a) the analysis of concomitant medications which potentially interfere with seizure threshold, especially concerning mood stabilizers and antipsychotics, which are often prescribed for behavioral disorders in AD patients; b) evaluating concomitant medications, with a special emphasis on their interaction with the same metabolic pathways of AEDs catabolism, as well as with the same pharmacodynamic targets; c) the analysis of the potential pharmacokinetics issues occurring in the elderly population. Last, but not least, the cognitive and neuropsychiatric profile of AEDs should be kept particularly into account when choosing the most appropriate treatment in AD patients with epilepsy. Thus, it is worth being emphasized the, for an optimal handling of these types of patients, it would be particularly useful a team work among psychiatrists, epileptologists-neurologists and neuropsychologists dealing with mental decline and memory disturbances.

For the above mentioned reasons newer AEDs are to be preferred to classical AEDs (PHT, PB, CBZ, VPA), in elderly patients in general, including also in those with AD. Furthermore, indirect

data seem to show even an additive "atrophy" effect of VPA in these patients. However, even though all newer AEDs have in general a better pharmacokinetic profile, they differ significantly from one another.

Data obtained in some case series, including a single-blind randomized study, suggest LEV as a good treatment option in these patients, as it might show a lower AEs incidence (even though mainly a positive trend, rather than significant difference vs. other AEDs has been shown) and a "good" cognitive profile, together with a low drug-drug interaction potential. Similar efficacy data and low-cognitive impact effects have been obtained also for LTG.

However, as underlined in the paragraphs above, to date there are not enough controlled data on the use of AEDs in patients with AD, and they are mandatory in order to be able to disclose the potential role of each of them in this type of patients. Retrospective analysis and even single-blind controlled studies are not sufficient to give enough information on these aspects. Furthermore, in the last decades newer AEDs (lacosamide, perampanel, retigabine, eslicarbazepine) have been introduced in the market, even though they can be presently prescribed only as add-on therapy in pharmacoresistant epilepsy. In light of the above mentioned higher efficacy of AEDs at lower serum concentrations in elderly, the combination of two AEDs with different modes of actions, with little drug-drug-interactions, both given at low doses, might be a feasible treatment option in AD patients whose seizures have not been controlled by monotherapy, even though no studies designed ad-hoc to explore this topic are available.

Finally, it is obvious that drug cost should be a further matter to be kept into account when choosing the best antiepileptic drug in these patients; thus older antiepileptic drugs might be preferred in some socio-economic context for this reason. However, as the cost of lamotrigine and levetiracetam, is becoming lower, this aspect might become less important in the drug choice in the future years.

8. Five-year view

In the coming years there are a number of questions which need to be answered in order to treat in the best way possible AD patients with epilepsy.

First, prospective studies in large cohorts of AD patients should be performed to clarify in detail the incidence and prevalence both of epilepsy as a whole, and of its subtypes. Such studies should include validated detailed questionnaires (administered to compliant caregivers and patient relatives) designed ad-hoc to detect epilepsy (including "minor" seizures), as well as at least standard EEG, to detect interictal epileptiform discharges, which are sometimes extremely helpful for confirming the diagnosis of epilepsy, as well as for its differential diagnosis with other causes of

loss of consciousness. Studies performed to date, lack such an approach, and this is likely to cause an underestimation of epilepsy occurrence in AD[8,9] .

Second, prospective double-blind randomized trials exploring the role of different AEDs (especially the newer ones) in AD patients with epilepsy should be planned and performed in the next years, in order to clarify in detail the efficacy and safety profile of these drugs (and the more appropriate dosages) in such a particular population of subjects; these studies should include also the evaluation of surrogate safety markers such as neuropsychological testing and, if possible, brain volumetry.

Third, the potential role of early interictal/ictal activity on the rate and degree of cognitive impairment in patients with AD should be further explored. If the fascinating hypothesis of a potential concomitant role of EEG interictal epileptiform discharges in the progression of the disease would be confirmed, the effect of any potential anti-dementia drug on seizures in this population of patients could be even considered as a surrogate marker. Thus, it would be worth quantifying subclinical activity and better monitoring seizures during trials with new potentially disease-modifying anti-dementia compounds, and use these parameters to monitor the potential efficacy of these drugs. Furthermore, the recently proposed "epileptic prodromal Alzheimer's Disease" phenotype of some patients [17] might be shown, in the future, to be present in a proportion of patients larger than that expected by recent retrospective analysis[17]. The AD evolution of these patients, and its relation with anti-dementia and antiepileptic drugs, might disclose new data on the interplay existing between epilepsy and AD.

However, in the meanwhile the role of interictal EEG discharges in AD progression should be better clarified experimentally. Furthermore, as some experimental data have suggested a significant beneficial role of early administration of LEV (but also TPM and LTG) on interictal epileptiform discharges and subsequent cognitive decline rate in animal models of AD (see above), these types of experimental studies should be replicated and extended also to the other AEDs available, in order to disclose any drug-specific additive effect in this phenomenon. If such potential beneficial effect should be confirmed experimentally, in the future it might be worth it to test it also in MCI and/or mild AD patients.

9. Key Issues

- Alzheimer's disease affects a significant proportion of elderly patients, and such a number is likely to increase further in the next decades, due to the increase of life expectancy in developed countries.

- Epilepsy, i.e. the occurrence of at least two unprovoked epileptic seizures, is reported to occur more frequently in AD patients than in age-matched cognitively intact elderly subjects.

- Despite these concepts date back to more than 50 years ago, so far the real incidence of seizures as a whole and seizure subtypes, as well as EEG interictal activity, have not been clarified in detail yet among AD patients.

- Epilepsy treatment in elderly patients is by itself already challenging, due mainly to the concomitant diseases, concomitant medications and to the pharmacodynamic/pharmacokinetics modifications occurring during normal ageing.

- There are no large randomized controlled studies assessing specifically AEDs in AD patients, but only a few studies in small series.

- Levetiracetam and lamotrigine might bear some beneficial effects in terms of efficacy, tolerability and low-impact on cognitive functions. These data need to be confirmed by specific randomized controlled trials in patients with cognitive impairment/AD. Valproic acid might increase cognitive decline and brain atrophy, even though some experimental studies show neuroprotective effects.

- In patients with AD and epilepsy the choice of concomitant psychotropic drugs, including antipsychotics and antidepressants-which affect seizure threshold to a varying degree- must be carefully evaluated as well. This, and other reasons mentioned above, confirms the need for a specialist/super specialist approach to treating epilepsy in AD patients.

- Some experimental data suggest even a potential protective effect of an early treatment with some AEDs, on subsequent cognitive decline in AD patients.

- The peculiarity of these types of patients, together with the potential additional benefits both on seizures and disease progression of AED treatment, prompts the planning ad-hoc designed randomized-controlled trials in the next years.

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*** Of considerable interest*

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