Antiepileptic drugs as a new therapeutic concept for the prevention of cognitive impairment and Alzheimer’s disease. Recent advances

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SUMMARY

Introduction. Excessive accumulation of amyloid-beta (Aβ) peptides in the brain results initially in mild cognitive impairment (MCI) and finally in Alzheimer’s disease (AD). Evidences from experimental and clinical studies show that pathological hyperexcitability of hippocampal neurons is a very early functional impairment observed in progressive memory dysfunctions. Therefore, antiepileptic drugs (AEDs) whose mechanism of action is aimed at inhibition of such neuronal hyperexcitability, seems to be an rationale choice for MCI and AD treatment.

Aim. To provide data from experimental and clinical studies on: 1. The unfavorable impact of neuronal hyperexcitability, mainly within the hippocampus, on cognitive processes. 2. Efficacy of AEDs against such abnormally elevated neuronal activity for the prevention of progressive cognitive impairment.

Methods. A literature review of publications published within the last fifteen years, was conducted using the PubMed database.

Review. The authors describe Aβ-induced hyperexcitability of hippocampal nerve cells as the cause of cognitive deficits, the connection of such activity with an increased risk of seizures and epilepsy in patients with MCI/AD, and finally the efficacy of AEDs: valproic acid (VPA), phenytoin (PHT), topiramate (TPM), lamotrigine (LTG), ethosuximide (ESM) and levetiracetam (LEV) in the prevention of cognitive impairment in experimental models and patients with MCI/AD.

Conclusions. The majority of the studied AEDs improve cognitive dysfunction in various experimental models of Aβ-induced brain pathology with accompanied neuronal hyperexcitability. The promising results achieved for LEV in animal models of cognitive impairment were also confirmed in patients with MCI/AD. LEV was well-tolerated and it’s beneficial antidementive effect was confirmed by memory tests and fMRI examination. In conclusion, the use of AEDs could be a novel therapeutic concept for preventing cognitive impairment in patients with Aβ-associated brain pathology.

Key words: antiepileptic drugs • neuronal hyperexcitability • cognitive impairment • amyloid-beta

INTRODUCTION

Cognitive impairment, which initially presents as mild cognitive impairment (MCI), and often, in the final stage, becomes Alzheimer’s disease (AD), is inseparably linked with a longer average lifespan in developed countries. The neurodegenerative process involves a progressive loss of neurons and disintegration of the brain’s synaptic networks (Bokde et al., 2009). Atrophy of the cerebral cortex, frontal and medial temporal lobes in particular, is an anatomical consequence of this process, while progressive cognitive impairment is a major functional consequence.

Despite years of research, the pathomechanism of AD is not fully understood (Armstrong, 2013). The amyloid cascade hypothesis is still the most widely accepted pathophysiological concept of AD (Hardy and all-sop, 1991). The hypothesis assumes that excessive cere-
bral deposition of Aβ in the form of senile plaques initiates a whole array of biochemical reactions leading to fibrillary neuronal degeneration and loss via apoptosis, synaptic degeneration, and glial activation (De-Paula et al., 2012). Most recent studies highlight the important role that glial cells and neuron-astrocyte interactions play in neurodegenerative disorders, including AD (Rama Rao and Kielian, 2015; Fu et al., 2015).

The apolipoprotein (APO) gene polymorphism is a significant AD-related genetic factor. Carriers of APOE4 are at increased risk of AD. A single APOE4 allele causes a 4-fold increase in the risk of AD, while two APOE4 alleles result in a 15–20 times higher risk (Strittmatter and Roses, 1995). Callaway showed in his study (2010) that APOE4 carriers, i.e. individuals at a very high risk of AD, score higher in IQ tests and are more likely to enter higher education [84% of APOE4 carriers vs. 55% of APOE4 non-carriers]. Therefore, a hypothesis emerged that AD development may result from initial neuronal “hyperactivity”, which causes “exhaustion” of neuronal function in the elderly (Callaway, 2010).

AIM
This review describes:
1. The meaning of pathological neuronal hyperexcitability, mainly within hippocampal formation, as an important pathophysiological factor of progressive cognitive impairments in different experimental models of Aβ-induced brain dysfunction and in patients with MCI and AD.
2. Antiepileptic drugs (AEDs) as a novel therapeutic concept for improving cognitive impairments in patients with Aβ-associated brain pathology.

METHODS
A literature review, of publications published within the last fifteen years, was conducted using the PubMed database. We provided data from relevant experimental and clinical studies on AEDs in respect to their effects on neuronal hyperexcitability-associated cognitive disturbances.

REVIEW
Neuronal hyperexcitability as the cause of cognitive deficits
The characteristic morphological and functional changes in the medial temporal lobe structures – mainly the hippocampus, a brain region that determines normal functioning associated with the processes of learning and memory (Squire and Zola-Morgan, 1991) – contribute to the progressive cognitive deficit during both natural aging as well as in various neurodegenerative diseases accompanied by dementia. Hippocampus neuronal hyperexcitability is one of the most significant pathophysiological consequences of such changes in this vulnerable region of the brain. This was shown in a number of experimental models of progressive cognitive impairment induced by the amyloid cascade pathway. Experimental studies using different transgenic mouse models of AD showed neural network hyperexcitability causing hippocampal dysfunction and cognitive impairment (Harris et al., 2010; Corbet et al., 2013; Montgomery et al., 2015). Spontaneous epileptiform activity has been shown in hippocampus and neocortex of hAPP transgenic mice (Palop et al., 2007). A deficit, which increased with age, of GABAergic inhibitory interneurons in the hippocampal hilus was shown in transgenic APOE4 knock-in mice (Andrews-Zwilling et al., 2010). The pentobarbital (GABA-A receptor antagonist) used in this model improved cognitive functions in experimental animals. Wilson et al. showed that abnormally high firing rates mainly affected CA3 hippocampal neurons, which are responsible for encoding new information (Wilson et al., 2006). The latest research shows that CA3 neuron hyperexcitability may be due to overexpression and hyperfunction of A-Type K+ channels, which results in a more rapid repolarization of the pyramidal neuron membrane (Simkin et al., 2015). CA3 neurons are most vulnerable to Aβ-induced excitotoxicity. The selective loss of CA3 and CA1 hippocampal neurons is characteristic for hippocampal sclerosis and related association and memory impairment as well as refractory temporal lobe epilepsy (Sendrowski and Sobaniec, 2013). A recent study in a transgenic mouse model of AD showed signs of hyperexcitability also in neocortex neurons, especially in the later stages of the disease. The membrane potential of neurons in old transgenic mice had an increased tendency to fail to transition to the depolarized state, and the depolarized states had shorter durations (Kellner et al., 2014).

Apart from patients with AD, aberrant excitatory neuronal activity was also shown in patients with MCI, indicating that it may represent a very early, accompanying or even pathogenetic sign of progressive dementia (Sperling et al., 2010; Stargardt et al., 2015).

Anatomically and physiologically, major patholog-
ical AD-related changes primarily occur in the frontal cortex and the hippocampus. The toxic effects of Aβ on the neuronal membrane result in the dysregulation of cellular calcium homeostasis, increased inflow of calcium ions into neurons, which triggers the excitotoxic cascade and results in the death of the neuron (Mattson et al., 1993; Crouch et al., 2008). Additionally, it was shown that Aβ oligomers directly activate N-methyl-D-aspartate receptors (NMDA receptors) and potentiate glutamate excitotoxicity (Texido et al., 2011).

It seems that abnormal excessive activity of the hippocampal neurons is, first of all, one of the major pathogenetic causes of AD, and, to a lesser degree, a consequence of the progressive disease process. This is supported by Busche et al., who observed selective increase in hyperactive CA1 hippocampal neurons following soluble Aβ administration before its aggregation into amyloid plaques in a young murine experimental model (Busche et al., 2012). A clinical study performed by Vossel et al. (2013) seems to confirm also such a hypothesis. Widespread EEG epileptiform activity was recorded in MCI patients (Vossel et al., 2013).

The loss of hippocampal neurons in AD is compensated by the process of reorganization of neuronal microstructure and bioelectrical activity as well as glial activation. Similar neuropathological findings were also observed in hippocampal sclerosis, and are considered to be both the cause of memory and cognitive function impairment as well as the anatomical cause of refractory temporal lobe epilepsy (Sendrowski and Sobaniec, 2013).

**Neuronal hyperexcitability and epilepsy in MCI and AD**

Population studies demonstrated a significantly higher risk of unprovoked seizures and epilepsy in patients with AD, which according to different reports ranges 10–22% compared with 1% in the general population (Amatniek et al., 2006). The following factors significantly increase the risk of epilepsy in patients with AD: low Mini-Mental State Examination scores, EEG focal epileptogenic discharges, the administration of NMDA receptor antagonist - memantine and antipsychotics (Irizarry et al., 2012). The latest reports show that patients with genetically determined AD have a very high risk of developing epilepsy (Larner, 2011). Dementia progresses more rapidly in patients with AD and epilepsy, and postmortem examinations showed that the loss of hippocampal neurons is higher in these patients compared with patients with AD but no concomitant epilepsy (Forstl et al., 1992).

Vossel et al. (2013) conducted a large study involving clinical and electroencephalographic assessment in a group of 96 patients with MCI/AD and concomitant epilepsy. The onset of seizures in the early stages of MCI or AD and a concomitant diagnosis of focal epileptiform activity showed by EEG recording in these patients was a significant prognostic factor for more rapid and more aggressive disease progression. The authors also found that non-convulsive status epilepticus, which is clinically difficult to diagnose, occurred in a significant proportion of patients with early AD. Therefore, electroencephalographically-confirmed epileptogenic hypersynchrony in the activity of the neuronal network in patients with early AD may represent a potential therapeutic target (Vossel et al., 2013).

Both structural and functional impairment of the neural brain network in patients with AD is well-documented in MRI, and severity correlates with the degree of cognitive disorders (Filippi and Agosta, 2011). Clinical studies using fMRI showed bioelectrical hyperactivity in the region of the hippocampal cortex not only in patients with MCI, but also in young and healthy APOE4 carriers (Dennis et al., 2010). Similar results were obtained in presymptomatic familial AD (Quiroz et al., 2010). Thus, the hyperexcitability of the hippocampal neurons represents an early functional impairment of the brain and may precede the clinical symptoms of MCI and AD.

**Use of antiepileptic drugs in the prevention of progressive cognitive impairment in experimental models and patients with MCI/AD**

Despite years of research on AD, so far no effective pharmacotherapy has been introduced. The available drugs that have been registered for the treatment of AD, such as acetylcholinesterase inhibitors and memantine, failed to meet expectations. Only a few of them slow the progression of the disease, and their use may involve serious adverse effects (Khairallah and Kassem, 2011). Therefore, an intensive search for new drugs for causative and neuroprotective treatment in patients with AD is necessary. Many have high hopes for drugs that inhibit neuronal hyperactivity, primarily AEDs, in relation to the above mentioned phenomenon of neuronal hyperexcitability at early AD stages and its well-documented pathogenicity in this disease.

The mechanisms of action n of AEDs mainly involve
shifting the imbalance between excitatory and inhibitory neurotransmitters in the brain towards enhanced inhibitory processes. This neurotransmitter imbalance is common for epilepsy and AD. Therefore, inhibiting the hypersynchronous neuronal activity of the brain using AEDs may become a new therapeutic strategy in early dementia patients. Thus far, the outcomes of experimental studies using AEDs, assessing the inhibition of Aβ-induced pathological neuronal hyperexcitability, have been promising.

**Valproic acid (VPA)**
The efficacy of VPA in improving memory performance and its neuroprotective effects have been shown in a number of experimental transgenic animal studies on AD (Qing et al., 2008; Koh et al., 2010; Yao et al., 2014; Xuan et al., 2015) or following dementia induction via Aβ administration (Long et al., 2013).

Unfortunately, these promising experimental findings were not reflected in patients with AD. VPA was poorly tolerated in these patients due to serious adverse effects. Also, the drug had no effects on cognitive function improvement and did not prevent psychotic symptoms in patients with AD (Tariot et al., 2011). Moreover, there is MRI volumetric evidence that long-term VPA administration in patients with AD leads to more rapid cerebral atrophy and secondary pathological dilatation of the cerebral ventricular system (Fleisher et al., 2011). VPA also showed poor efficacy in the prevention of seizures in patients with AD and epilepsy (Vossel et al., 2013).

**Phenytoin (PHT)**
The results of experimental studies assessing the effect of PHT are divergent. Ziyatdinova et al. showed that PHT inhibited epileptogenic discharges in an AD mouse model (Ziyatdinova et al., 2011), and Sanchez et al. observed increased epileptogenic activity following PHT and pregabalin administration (Sanchez et al., 2012).

**Topiramate (TPM)**
Shi et al. showed the beneficial effect of TPM on behavioral deficit in an AD transgenic mouse model. In the same experiment, the authors also demonstrated that TPM administration prevented neuropathological changes characteristic of AD in experimental animals (Shi et al., 2013). In another experimental model, Cheng and Li showed that systematic intraperitoneal administration of TPM in rats intracerebrally pre-injected with Aβ solution prevented apoptotic loss of hippocampal neurons. The neuroprotective effects of TPM were due to enhanced anti-apoptotic gene [Bcl-2 and survivin] expression and decreased pro-apoptotic gene [Fas, Bax and Caspase-3] expression (Cheng and Li, 2014).

A study comparing the efficacy of TPM and risperidone in the treatment of behavioral impairment in patients with AD showed that the effectiveness of low TPM doses of 25–50 mg/day was the same as in the case of neuroleptics (Mowla and Pani, 2010).

**Lamotrigine (LTG)**
Zhang et al. showed in a transgenic mouse model of AD that LTG alleviated symptoms of dementia in animals by modulating the neural network and reducing the formation of cerebral senile plaques, as well as stimulating the production of cerebral growth factors, such as brain-derived neurotrophic growth factor [BDNF] and nerve growth factor [NGF] (Zhang et al., 2014).

Although LTG was efficacious in preventing seizures in patients with AD and epilepsy, drug tolerance was worse compared with patients receiving LEV (Vossel et al., 2013). Recently LTG has been shown to be efficacious in the treatment of patients with AD and serious psycho-behavioral impairment (Suzuki and Gen, 2015).

**Ethosuximide (ESM)**
The PubMed database includes only 2 publications from 2015 assessing the effects of ESM on Aβ-induced memory dysfunction in experimental animals. Tiwari et al. observed beneficial effects of ESM, which manifested in enhanced hippocampal neurogenesis, more rapid proliferation and differentiation of neural stem cells, reduced Aβ-induced neurodegeneration of hippocampal neurons, and reversed cognitive impairment in experimental animals (Tiwari et al., 2015). Nygaard et al. assessed the effect of ESM and brivaracetam (BRV) on EEG epileptogenic activity (spike-wave discharges) in a transgenic murine model of AD, as well as the correlation between this effect and memory function in these animals. Both drugs reduced the number of epileptogenic discharges; however, improved memory function was observed only in animals receiving BRV (Nygaard et al., 2015).

**Levetiracetam (LEV)**
LEV is a new generation AED that has thus far had the most promising results in the inhibition of excessive
neuronal activity both in experimental AD models and in patients with MCI/AD.

Sanchez et al. conducted a large experimental study in a transgenic hAPPJ20 murine model of AD, characterized by Aβ overproduction and neural network dysfunction, which manifested, among others, in high spiking activity and periodical epileptic seizures. The authors showed that LEV not only statistically significantly reduced the number of epileptogenic discharges, but also inhibited the pathological synaptic dysfunction as well as the microstructural and functional intrahippocampal remodeling (Sanchez et al., 2012). Other AEDs assessed in the same study, i.e.: valproic acid (VPA), gabapentin (GBP), ethosuximide (ETH), pregabalin (PGB), phenytoin (PHT) and vigabatrin (VGB), did not produce the expected beneficial effects on cognitive functions or the impaired synaptic network in experimental animals; and in the case of PHT and PGB, the authors reported a worsening in these ratios. LEV showed efficacious neuroprotective effects in hippocampal neuronal culture treated with the most neurotoxic 25-35 Aβ fragment. LEV prevented the death of hippocampal neurons even when using high Aβ concentrations (Sendrowski et al., 2015). Koh et al. showed that LEV also improved impaired cognitive functions in experimental animals with excessive CA3 hippocampal neurons activity, which is related to the aging process (Koh et al., 2010).

The particularly beneficial precognitive effects of LEV in experimental AD models are most likely associated with the different mechanism of action compared with other AEDs. LEV selectively binds to a presynaptically located receptor for SV2A protein, which is essential for normal formation and release of synaptic vesicles (Custer et al., 2006). Therefore, it seems that the beneficial effects of LEV modulating synaptic transmission support the use of this drug in patients with MCI/AD. This results from the fact that the Aβ-induced pathogenetic mechanism leading to pathological series of action potential discharges in hippocampal neurons, as well as secondary cognitive impairment, is associated with synaptic network destruction, the loss of inhibitory neurons, and increased release of synaptic vesicles from the presynapses of the excitatory neurons (Palop and Mucke, 2010; Talantova et al., 2013; Fogel et al, 2014). Such observations also confirm the aforementioned studies by Nygaard et al., who showed improved memory function in an experimental AD model following the administration of another SV2A ligand – BRV (Nygaard et al., 2015). Sola et al. recently confirmed the efficacy of a number of new LEV derivatives in Alzheimer-like phenotypic mice (Sola et al., 2015).

The excellent results achieved for LEV in animal AD models were also confirmed in patients with MCI/AD. In their fMRI-based study in patients with MCI, Bakker et al. showed abnormally excessive neuronal activity in the region of the hippocampal dentate gyrus/CA3 compared with those unaffected by cognitive function impairment. The authors showed an fMRI-visible reduction in the hyperactivity in the hippocampal DG/CA3 region as well as improved cognitive functions in patients with MCI, confirmed by memory tests, following the administration of low LEV doses (250 mg/day) for 2 weeks (Bakker et al., 2012). The latest study conducted in the same center in patients with MCI showed the efficacy of LEV administered at a dose of 125 mg/day, as confirmed by both fMRI and behavioral testing. Thus, approximately 10-fold lower LEV doses compared with doses administered in epileptic patients were sufficient in preventing the progressive process of cognitive impairment associated with the pathologically excessive activity of the hippocampal neurons (Bakker et al., 2015). It is worth noting that LEV, as opposed to other AEDs, particularly older generation AEDs, is well tolerated and has negligible adverse effects (Sendrowski and Sobaniec, 2005; Verrotti et al., 2015).

Clinical observations by Cumbo and Ligori in patients with AD and epilepsy, receiving LEV, LTG or PB, showed that antiepileptic efficacy was similar for all drugs, whereas the best drug tolerance was shown in LEV patients, who also had improved attention and fluency of speech. Patients receiving PB showed a clear deterioration of cognitive functions (Cumbo and Ligori, 2010).

Due to the good tolerability and best clinical effects of LEV in preventing the progressive cognitive impairment in patients with MCI/AD compared with all other AEDs, scientists from the University of California, San Francisco, are currently conducting a phase II trial “Levetiracetam for Alzheimer’s Disease-Associated Epileptiform Activity (LEV-AD)” [ClinicalTrials.gov identifier: NCT02002819]. The study has been enrolling patients with probable AD with epileptiform spike activity registered in EEG. Perhaps this trial, by including LEV, will contribute to broadening the potential of drugs used in AD. Summarized results of both experimental and clinical studies have been shown in table 1 and table 2.
Table 1. Summarized results of animal experimental studies focused on effectiveness of antiepileptic drugs (AEDs) for the prevention of Aβ-associated cognitive impairments. Details in the text

| Antiepileptic drug | Experimental model | Results |
|-------------------|--------------------|---------|
| Valproate acid    | APP23 transgenic mice (Qing et al., 2008) | Inhibition of Aβ production and neuritic plaque formation. Improvement of behavioral deficit |
|                   | Memory-impaired aged rats (Koh et al., 2010) | VPA dose-dependently improves retention of new spatial information in aged rats in the Water Maze Task. Decrease number of errors in the Radial Arm Maze Task |
|                   | AD transgenic mice (Yao et al., 2014) | VPA enhanced long-term recognition memory and spatial learning and memory |
|                   | APP/PS1 double transgenic mice (Xuang et al., 2015) | VPA improved memory deficits and decreased Aβ deposition |
| Phenobarbital      | Aβ toxin-induced AD-like rat model (Tiwari et al., 2015) | Induction of hippocampal neurogenesis and neuronal differentiation |
|                   | APP/PS1 transgenic mice (Zhang et al., 2014) | Reduction of the number and the size of amyloid plaques in the brain. LTG enhanced levels of brain-derived neurotrophic growth factor (BDNF) and nerve growth factor (NGF) |
| Ethosuximide       | APP/3xTg-AD transgenic mice (Nygaaard et al., 2015) | Prevention of Aβ-induced neuronal apoptosis |
|                   | APP-APP double transgenic mice (Long et al., 2013) | Suppression of neuronal apoptosis |
| Topiramate         | APPswe/PS1de9 transgenic mice (Shi et al., 2013) | Suppression of neuronal apoptosis |

CONCLUSIONS
In conclusion, the pathological neuronal hyperexcitability observed in AD experimental models, particularly in the hippocampal neurons, is an important pathogenic factor leading to cognitive impairment. Epileptiform activity registered electroencephalographically in patients with MCI often precedes the clinical symptoms of dementia. Therefore, the inhibition of excessive activity of neurons using AEDs may represent a new direction in the prevention of cognitive impairment. The preliminary findings from experimental studies and MCI/AD patients are very promising. The best outcomes and the highest hopes are associated with LEV and its new chemical analogues. A broader assessment of the effects of LEV as a drug preventing progressive dementia will be possible following the completion of the currently conducted clinical trial using this drug in AD patients.

CONFLICT OF INTEREST DISCLOSURE
The authors have no conflict of interest to declare.

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### Table 2. Summarized results of human clinical studies focused on effectiveness of antiepileptic drugs (AEDs) for the prevention of Aβ-associated cognitive impairments and Alzheimer’s disease. Details in the text

| Antiepileptic drug | Clinical study | Results                                                                 |
|--------------------|----------------|-------------------------------------------------------------------------|
| Valproic acid      | 313 individuals with moderate AD (Tariot et al., 2011) | Patients receiving VPA had higher rates of somnolence, gait disturbance, tremor, and weakness. MRI: greater loss in hippocampal and whole-brain volume, accompanied by greater ventricular expansion |
|                    | 89 individuals with moderate AD (Fleisher et al., 2011) | Worsening of cognitive functions in memory tests. MRI study: accelerated brain volume loss over 1 year |
| Topiramate         | 48 AD patients (Mowla and Pani, 2010) | Improvement in behavioral disturbances (Tests: Neuropsychiatry Inventory total score, Cohen-Mansfield Agitation Inventory, Clinical Global Impression) |
| Lamotrigine        | 54 patients with MCI/AD and epilepsy or subclinical epileptiform activity (Vossel et al., 2013) | Improvement in Neuropsychiatric Inventory scores |
|                    | 40 AD patients with behavioral and psychological symptoms of dementia (Suzuki and Gen, 2015) | Improvement of cognitive function. fMRI: Reduction in the hyperactivity in the DG/CA3 region |
| Levetiracetam      | MCI patients, neuropsychological tests and fMRI assessment (Bakker et al., 2012; Bakker et al., 2015) | Improvement of cognitive function. fMRI: Reduction in the hyperactivity |
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