https://doi.org/10.47183/mes.2025-317

DIAGNOSTIC SIGNIFICANCE OF SUBCLINICAL EPILEPTIFORM ACTIVITY IN PATIENTS WITH ALZHEIMER'S DISEASE

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Introduction. The high prevalence and significant disability of patients with Alzheimer's disease (AD) necessitate the search for new markers of disease progression and novel treatment approaches. Recent evidence is increasingly attracting the research attention to the value of electroencephalography (EEG) in detecting epileptiform activity in this patient population.
Objective. Detection of the frequency of epileptiform activity in patients with AD and evaluation of its clinical and diagnostic significance.
Discussion. EEG, in particular, prolonged sleep-deprived EEG, is capable of detecting subclinical epileptiform activity, which is associated with more severe cognitive impairments and contributes to disease progression. This review examines research data on the prevalence and clinical significance of subclinical epileptiform activity in AD patients without an epilepsy diagnosis. It also highlights key pathophysiological mechanisms linking epileptiform activity to the progression of cognitive decline in AD. Furthermore, it addresses the rationale for prescribing specific antiepileptic therapy upon detection of subclinical epileptiform activity.
Conclusions. The high clinical significance of performing electroencephalography and detecting epileptiform activity in patients with Alzheimer's disease, due to its potential negative impact on the progression of cognitive impairments and increased risks of developing epileptic seizures, has been demonstrated.

Keywords: neurodegenerative disease; Alzheimer's disease; electroencephalography; video-EEG monitoring; subclinical epileptiform activity; antiepileptic drugs; epilepsy

For citation: Burd S.G., Bogolepova A.N., Lebedeva A.V., Rubleva Yu.V., Kovalenko E.A., Makhnovich E.V., Osinovskaya N.A., Gileva E.A., Pantina N.V., Kovaleva I.I. Diagnostic significance of subclinical epileptiform activity in patients with alzheimer's disease. *Extreme Medicine.* 2025. https://doi.org/10.47183/mes.2025-317

Funding: the study was carried out without sponsorship.

Potential conflict of interest: the authors declare no conflict of interest.

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Received: 12 May 2025 **Revised:** 1 Aug. 2025 **Accepted:** 5 Sept. 2025 **Online first:** 10 Oct. 2025

УДК 616.8

ДИАГНОСТИЧЕСКАЯ ЗНАЧИМОСТЬ СУБКЛИНИЧЕСКОЙ ЭПИЛЕПТИФОРМНОЙ АКТИВНОСТИ У ПАЦИЕНТОВ С БОЛЕЗНЬЮ АЛЬЦГЕЙМЕРА

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Введение. Высокая распространенность и значительная инвалидизация пациентов с болезнью Альцгеймера (БА) требуют поиска новых маркеров прогрессирования этого заболевания, а также новых подходов к его лечению. В последнее время накапливается все больше сведений о значимости применения электроэнцефалографии у пациентов с БА с целью выявления эпилептиформной активности у данной категории.
Цель. Определение частоты встречаемости эпилептиформной активности у пациентов с БА и оценка ее клинической и диагностической значимости.
Обсуждение. Установлено, что проведение ЭЭГ, особенно продолженной, с включением сна, позволяет выявить субклиническую эпилептиформную активность, которая ассоциирована с более выраженными когнитивными нарушениями и способствует прогрессированию заболевания. В обзоре рассмотрены данные исследований по распространенности и клинической значимости субклинической эпилептиформной активности у пациентов с БА без диагноза «эпилепсия». Также освещены основные патофизиологические механизмы взаимосвязи эпилептиформной активности и прогрессирования когнитивных нарушений в рамках БА. Кроме того, рассматривается вопрос о целесообразности назначения специфической противоэпилептической терапии при выявлении субклинической эпилептиформной активности.
Выводы. Показана высокая клиническая значимость проведения электроэнцефалографии и выявления эпилептиформной активности у пациентов с болезнью Альцгеймера вследствие ее потенциального негативного влияния на прогрессирование когнитивных нарушений и повышения рисков развития эпилептических приступов.

Ключевые слова: нейродегенеративное заболевание; болезнь Альцгеймера; электроэнцефалография; видео-ЭЭГ-мониторинг; субклиническая эпилептиформная активность; противоэпилептические препараты; эпилепсия

Для цитирования: Бурд С.Г., Боголепова А.Н., Лебедева А.В., Рублева Ю.В., Коваленко Е.А., Махнович Е.В., Осиновская Н.А., Гилева Е.А., Пантина Н.В., Ковалева И.И. Диагностическая значимость субклинической эпилептиформной активности у пациентов с болезнью Альцгеймера. *Медицина экстремальных ситуаций*. 2025. https://doi.org/10.47183/mes.2025-317

Финансирование: исследование выполнено без спонсорской поддержки.

Потенциальный конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Статья поступила: 12.05.2025 **После доработки:** 01.08.2025 **Принята к публикации:** 05.09.2025 **Online first:** 10.10.2025

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and one of the most prevalent diseases in the elderly, affecting 10–20 million people worldwide [1]. The disease is characterized by the formation of neurofibrillary tangles and amyloid plaques in the brain, manifesting as progressive cognitive impairment. Annual direct and indirect costs associated with this disease amount to $100 billion, making the search for new diagnostic and therapeutic methods critically important. It is predicted that delaying disease progression by five years could reduce healthcare costs related to AD by half [2–5].

Despite significant advances in laboratory and genetic diagnostics, as well as modern neuroimaging methods (magnetic resonance imaging (MRI) of the brain with morphometry, positron emission tomography), diagnosing dementia-related diseases remains challenging and, in many cases, inaccessible due to the cost of examinations. Currently, electroencephalography (EEG) is not part of the standard examination protocol for patients with dementia, including those with AD. However, numerous literature sources report that pathological brain activity (e.g., slowing of the background rhythm or epileptiform activity) may be recorded during EEG in AD patients, which could exacerbate the progression of cognitive impairments and increase the risk of epileptic seizures, further disadapting patients with AD [6, 7].

EEG with functional tests is a simple diagnostic method that allows assessment of the bioelectrical activity of the brain. Non-epileptiform pathological activity, such as theta or delta slowing (regional/diffuse) of bioelectrical brain activity, is a common finding in AD patients during routine EEG [6]. There is evidence suggesting that increased relative power of theta oscillations may be an early sign preceding dementia, thus being an important biomarker of disease progression [8, 9].

The detection of epileptiform activity in AD patients holds a great significance. However, routine EEG is often insufficient for capturing epileptiform activity, since approximately 85% of standard EEG recordings fail to detect epileptiform activity even in AD patients with epileptic seizures [10]. This highlights the need for more sensitive methods, such as prolonged video-EEG monitoring including sleep, magnetoencephalography (MEG), or invasive electrode placement through the *foramen ovale* to identify this pathological activity [10]. Some authors emphasize the higher prevalence of epileptiform activity in AD patients compared to the healthy population, as well as its significance in the progression of cognitive impairments in neurodegenerative disease. Thus, this pathological activity may represent a promising target for intervention in treating cognitive impairments in AD.

The aim of the study is to detect the frequency of epileptiform activity in patients with AD and verify its clinical significance.

MATERIALS AND METHODS

The search for scientific literature was conducted in electronic bibliographic databases in the Russian (eLibrary, CyberLeninka) and English (PubMed, Google Scholar) languages. The search queries included the following keywords or their combinations: Alzheimer's disease, electroencephalography, video-EEG monitoring, subclinical epileptiform activity.

The inclusion criteria for publications were literature systematic reviews and meta-analyses with data on the prevalence of subclinical epileptiform activity in AD, the pathophysiology of its occurrence, and the relationship between the neurodegenerative process, epileptiform activity, and cognitive impairments. The exclusion criteria were publications covering theoretical models, abstracts, and conference materials. In total, 52 articles published from 1998 to 2024 were reviewed.

RESULTS AND DISCUSSION

Subclinical epileptiform activity (SEA) in patients with Alzheimer's disease (AD)

Subclinical epileptiform activity (SEA) typically refers to epileptiform activity detected in EEG in patients without a history of epileptic seizures. According to scientific research, data on the prevalence and diagnostic significance of epileptiform activity in patients with AD are limited and contradictory. The reviewed publications show a significant variability (ranging from 2% to 54%) in the reported prevalence of SEA among patients diagnosed with AD, likely due to substantial methodological differences across the studies (Table) [11].

The presence of epileptiform activity may exacerbate the progression of cognitive impairments in AD patients. Moreover, its detection may serve as a marker for the potential development of epileptic seizures. For example, Kang and Mendez et al. observed the

development of epilepsy in approximately 10–22% of AD patients [7, 12].

When investigating the prevalence and significance of epileptiform discharges in patients with various types of dementia, Liedorp et al. [15] found that routine 30-min EEG detected epileptiform activity (predominantly regional in the temporal areas) only in 2% of patients with AD, mild cognitive impairment (MCI) and in 1% of patients with other types of dementia. These rates are similar to those in the general population. Only in 10% of patients with dementia, whose EEG showed epileptiform activity, developed seizures later in the course of the disease [15].

The low detection rate of epileptiform activity in patients with AD prompted researchers to use additional *foramen ovale* EEG electrodes for its identification. Thus, Lam et al. applied *foramen ovale* electrodes and showed that subclinical epileptiform activity, predominant during sleep (affecting memory consolidation), can be detected in the early stages of AD, in the absence of changes in the routine scalp EEG [21]. This highlights the need for larger EEG studies using additional techniques, including *foramen ovale* recording, to determine the diagnostic value of EEG in clinical practice.

According to a number of studies, a significant prevalence of SEA has been detected in AD patients, which is likely associated with the use of prolonged video-EEG monitoring including during sleep. Recently, increasing attention has been paid to the presence of SEA in AD patients due to evidence of a more pronounced cognitive decline and a faster disease progression in patients with SEA compared to those without it [16, 18, 22, 23].

Thus, Horvath et al. analyzed SEA in 52 AD patients and detected significantly more frequent subclinical epileptiform discharges (54%) among this group compared to healthy elderly people of corresponding age (25%) [18]. SEA was detected predominantly in the temporal regions, mostly on the left side, with bitemporal and right-temporal epileptiform activity being less common. The vast majority of SEA episodes occurred during sleep, most frequently recorded during stages 2 and 3 of sleep, while fewer spikes were detected in stage 1 sleep. Moreover, the presence of SEA was associated with more severe cognitive impairments. Horvath et al. showed that in patients with AD combined with SEA, cognitive decline over the observation period (3 years) occurred 1.5 times faster than in patients without epileptiform activity [18]. According to Vossel et al., epileptiform activity was detected in 42.4% of patients with AD and only in 10.5% of individuals in the control group of corresponding age without cognitive impairments [16]. Patients with SEA showed a faster decline in executive functions and global cognition, as measured by the instrument of Mini-Mental State Examination (MMSE), averaging 3.9 points/year compared to 1.6 points/year in patients without SEA [16].

Nous et al. studied patients with different stages of AD (preclinical, MCI, dementia) using such various methods as prolonged EEG, 50-min MEG, and high-density EEG [11]. The prevalence of SEA in these patients was 31% compared to the control group (8%) without cognitive dysfunction. The frequency was increasing along with the disease progressed, i.e., in 50% of cases with developed dementia, in 27% with MCI, and in 25% at the preclinical stage of AD. Although the use of MEG did not lead to a more frequent detection of SEA in AD compared to prolonged EEG and high-density EEG, MEG significantly outperformed other methods in terms of spike detection rate per 50 min (epileptiform activity representation index). Furthermore, in AD patients, the presence of SEA was associated with more pronounced impairments in visuospatial functions and attention, as well as with a relatively larger volume of the left frontal, left temporal, and entorhinal cortex compared to patients without epileptiform activity [7].

Pathophysiological mechanisms of the relationship between epileptiform activity, neurodegenerative process, and cognitive impairment in Alzheimer's disease

A number of authors consider epileptiform activity to be part of the pathophysiological mechanisms leading to cognitive impairment in AD. The proposed mechanisms include compromised glutamatergic system, excitotoxicity-induced neurodegeneration, accelerated amyloid and tau protein deposition under the influence of epileptiform discharges, remodeling due to increased excitability leading to functional network disconnection, and sleep architecture changes [23].

One hypothesis describes a vicious cycle where molecular changes in AD promote neuronal hyperexcitability [24], which in turn exacerbates the neurodegenerative process in AD [25]. It was reported that in AD, soluble oligomeric Aβ (amyloid-beta), rather than Aβ plaques, is the primary cause of neuronal hyperexcitability [24]. For instance, Aβ1-42 (the most toxic form of soluble Aβ peptides) was to increase neuronal excitability through selective inhibition of K+ currents [26]. It was described that under the influence of Aβ, AD patients experience impaired neuronal and glial glutamate reuptake, leading to excitotoxicity. Similarly, glutamate excitotoxicity is also exacerbated by the effect of Aβ on the function of the N-methyl-D-aspartate receptor (NMDA-R) [27]. It was suggested that activation of cholinergic receptors and Ca^{2+} channels under the influence of Aβ may cause early subclinical epileptic activity preceding the development of clinical Alzheimer's disease [28]. Furthermore, it was shown that beta-secretase 1 (BACE1 is a key protein involved in Aβ formation) cleaves the β2 and β4 subunits of the voltage-gated Na^{+} channel [24]. Cleavage of β2 alters transcription and receptor expression on the cell surface [21]; cleavage of β4 significantly increases intracellular

Table. Prevalence of subclinical epileptiform activity in patients with Alzheimer's disease

No	Literature reference	Cognitive impairment severity	People amount	SEA prevalence, %	Epileptiform Activity Index (EAI)	SEA localization	EEG type
1	Brunetti et al. [13]	AD MCI CG	50 50 50	AD – 6.38; MCI – 11.63; CG – 4.43	0.015–0.025/ hour	No data available	LTVEM + PSG + MEG
2	Vossel et al. [14]	AD + MCI	113	6	No data available	No data available	routine EEG
3	Liedorp et al. [15]	AD MCI other dementias	510 225 193	2 AD; 2 MCI; 1 other dementia	No data available	No data available	30-min EEG
4	Vossel et al. [16]	AD CG	33 19	42.4 AD; 10.5 CG	0.03–5.18/ hour	9.9% wakefulness; 25.7% N1, 64.4% N2-N3; 43% left temple; 29% left central area; 14% right frontal area; 14% bifrontotemporally	Nighttime PSG + MEG
5	Horvath et al. [17]	AD	42	28	No data available	No data available	24-h EEG
6	Horvath et al. [18]	AD CG	52 20	54 AD; 25 CG	0.29–6.68/ hour	8% wakefulness; 23% N1, 21% N2, 34% N3; 4% REM; 52% left temple; 22% right temple; 26% bitemporally; 3% biparietal; 3% right frontal area; 9% bifrontal	24-h EEG
7	Lam et al. [19]	AD CG	41 43	22 AD; 4.7 CG	1.5–3/day	20% N1, 80% N2; 85.7% left temporal region; 28.6% bifrontal	24-h EEG
8	Babiloni et al. [20]	AD c MCI; MCI without AD	56 32	No data available AD + MCI; 41 MCI without AD	No data available	No data available	routine EEG
9	Nous et al. [11]	AD+ dementia; AD + MCI; AD preclinical stage	49	31 among all patients with AD; 50 in dementia; 27 in MCI; 25 on clinical stage	Number of spikes per 50 min: Prolonged EEG: 0,19 spikes/min; 50-min MEG: 64.5 spikes/min; High-Density EEG: 3 spikes/min	Fronto-temporal regions (more often on the left). Single cases: central region, bifrontotemporal, bitemporal, right parietal, right temporal, right frontal regions. More often, stages 1 and 2 of sleep	Prolonged EEG and/ or 50-min MEG and/ or 50-min High-Density EEG

Table compiled by the authors based on data from sources [11, 13–20]

Note: MCI — mild cognitive impairment; CG — healthy control group; SEA — subclinical epileptiform activity; EEG — electroencephalography; LTVEM — long-term video-EEG monitoring, MEG — magnetoencephalography; PSG — polysomnography; N1 — sleep stage 1; N2 — sleep stage 2; N3 — sleep stage 3; REM — rapid eye movement sleep.

Na^+ levels [26]. Both processes contribute to overall neuronal hyperexcitability, which may promote the development of epileptic seizures.

Both epilepsy and Alzheimer's disease involve neuroinflammation induced by Aβ, characterized by the induction of an immune response in the central nervous system (CNS) in reaction to the pathological process [29]. Inflammation in the CNS is primarily mediated by microglia, astrocytes, and oligodendrocytes [30]. Aβ-induced glial activation leads to the release of numerous pro-inflammatory cytokines (e.g., TNF-α, IL-6, or IL-1β), triggering generalized neuroinflammation. This process, in turn, promotes neurotoxic effects that ultimately result in neuronal hyperexcitability, exacerbating the neurodegenerative process [24]. It was also described that pro-inflammatory cytokines, such as IL-1β, increase neuronal hyperexcitability either by enhancing glutamate release from astrocytes and reducing its reuptake [31], or by up-regulating NMDA-R, which increases intracellular Ca^{2+} influx [32].

Tau protein plays a distinct role in epileptogenesis during AD, given that this protein is one of the key mediators of Aβ-induced epileptogenic mechanisms [33]. Tau protein contributes to neuronal excitotoxicity by increasing extracellular glutamate and causing NMDA-R dysfunction [34]. Tau protein is also associated with abnormal neuronal migration in the hippocampus—a brain structure closely linked to the development of epilepsy [35, 36]. Furthermore, animal models of epileptogenesis confirmed reduced activity of phosphatase 2A, leading to increased p-tau in epileptogenic brain regions [37].

The neurosteroid allopregnanolone was also linked to the development of Alzheimer's disease [38]. Some authors reported decreased levels of allopregnanolone in the plasma and brain, particularly in the prefrontal cortex, of patients with AD. Reduced allopregnanolone levels lead to diminished neuroprotection, activation of astrocytes and microglia, which in turn promotes the production of neurotoxic cytokines, chemokines, and reactive oxygen and nitrogen species. These mechanisms contribute to the progression of neurodegenerative disease and neuronal hyperexcitability [38].

The key components of the pathogenetic relationship between epileptiform activity and the neurodegenerative process are presented in the Figure below. Increased activity of the glutamatergic system in AD leads to

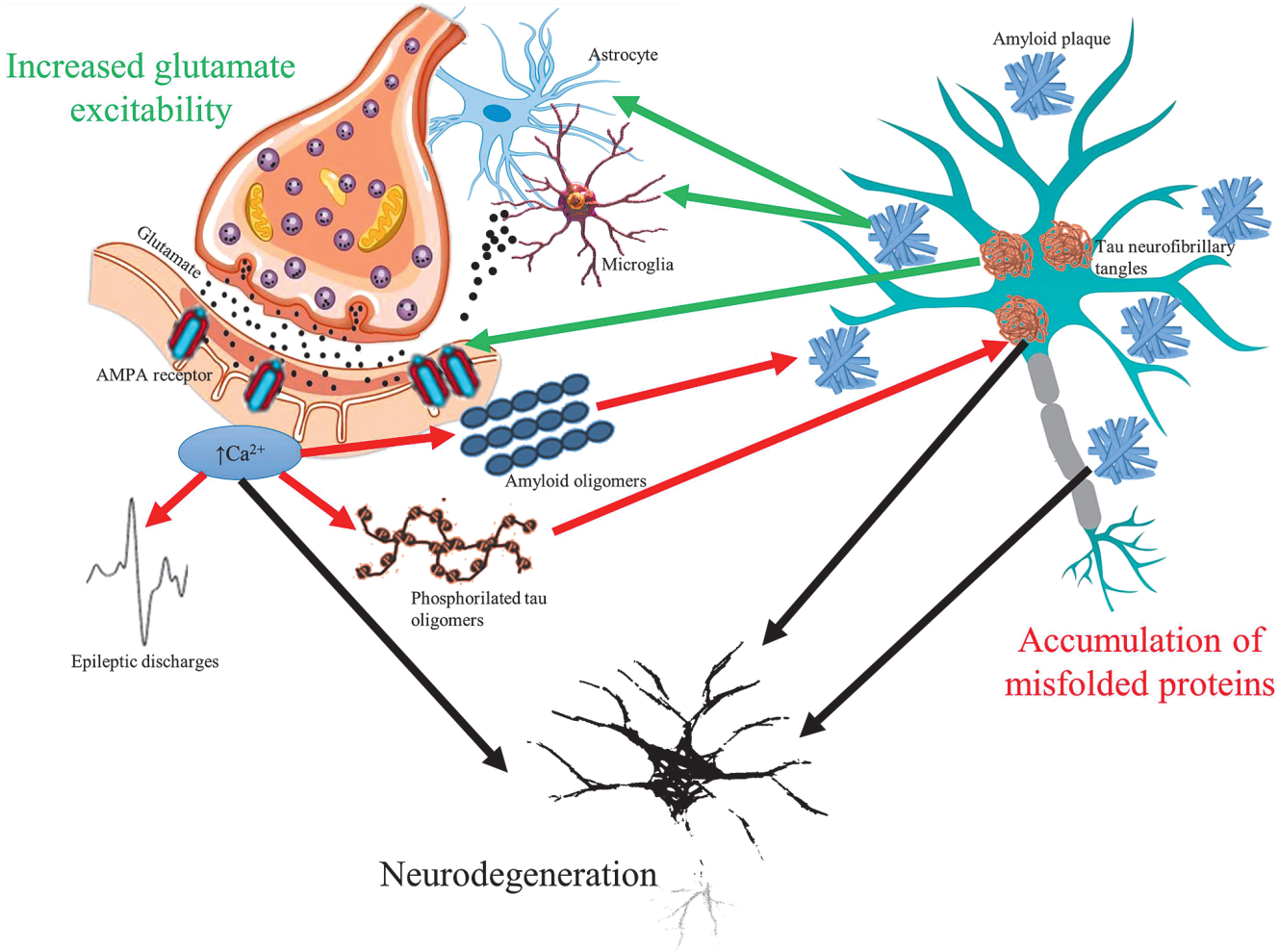

Figure prepared by the authors based on data from [23], CC BY license

Fig. Vicious cycle of glutamate-mediated hyperexcitability and accumulation of pathological proteins in cognitive impairment in Alzheimer's disease

elevated expression of AMPA receptors and mobilization of intracellular calcium. The rise in intracellular calcium levels results in the release of amyloid oligomers into the extracellular space and enhanced phosphorylation of tau oligomers (red arrows). Increased neuronal excitation, manifested as epileptic discharges, is also a consequence of glutamate-mediated hyperexcitability. On the other hand, the accumulation of amyloid plaques and tau neurofibrils alters the expression of glutamate receptors and triggers excessive glutamate release from microglial cells and astrocytes (green arrows). This bidirectional pathological interaction can lead to progressive neurodegeneration (black arrows), which is typically accompanied by cognitive impairment [23].

Pathological remodeling of hippocampo-cortical connections is also considered to play a major role in the presence of epileptiform activity. As a result of epileptiform activity, local intrahippocampal connections are strengthened, while the strength and number of long-range connections are reduced. This remodeling of neural networks leads to relative isolation of the hippocampus from the cortex, impairing the functioning of hippocampo-cortical circuits [23].

Furthermore, the presence of epileptiform activity disrupts physiological sleep patterns and impairs the memory consolidation process. Thalamic sleep spindles at a frequency of 12–16 Hz are crucial for memory formation, synchronizing hippocampal activity with cortical neurons. Slow waves associated with cortical sleep provide the highest degree of synchronization, promoting the activation of hippocampal activity and thalamic sleep spindles. Epileptiform activity contributes to:

- transformation of hippocampal activity;
- disorganization of sleep spindle architecture;
- reduction of cortical slow waves due to cortical hyperpolarization.

In combination, these changes reduce the efficiency of memory consolidation [23].

Treatment of subclinical epileptiform activity as an alternative approach to AD therapy

Given the existing concept of SEA potentiating the pathophysiological mechanisms that contribute to the progression of cognitive impairment in AD, some authors propose therapeutic approaches for treating AD patients with SEA, such as prescribing antiseizure medication (ASM). There is a wide range of ASMs available; however, due to the negative effects of most of them on cognitive functions and memory, the choice of ASM in such patients is limited.

According to numerous studies on the effects of ASMs on cognitive functions in patients with epilepsy, some drugs exhibit a so-called “pro-cognitive” effect. Levetiracetam is one example of such drugs. Due to the potentially beneficial effects of levetiracetam on cognitive functions, most studies aimed at treating SEA and epilepsy in AD patients focus on this particular medication [14, 39–44]. Experiments showed that levetiracetam modulates neuronal hyperexcitability, reduces the number of amyloid plaques, and regulates neurotrophic factors [39, 45]. It is known that in AD patients with epileptiform activity, cognitive functions deteriorate faster than in those without such activity. For instance, Vossel et al. studied the effects of levetiracetam on various domains of cognitive function in a group of 34 participants with AD. The analysis showed that in the group of patients with seizures or SEA, the use of levetiracetam led to positive dynamics in tests of executive function and visuospatial memory [46].

Lamotrigine, which has no negative effect on cognitive functions, may also be considered for use in patients with AD and SEA [12, 45, 47–50]. Lamotrigine prevents the accumulation of extracellular β-amyloid, suppresses glutamate excitotoxicity, thereby exerting neuroprotective properties [51, 52]. A study by Tekin et al. of AD patients without epilepsy showed that the use of lamotrigine at a dose of 300 mg/day for eight weeks had a positive effect on cognitive indicators (in performing tasks on recognition and naming of objects and matching names with objects) and mood [52]. However, there are currently no clear clinical guidelines for prescribing antiseizure therapy to AD patients with SEA having no seizures, which requires further study.

CONCLUSION

The conducted review indicates the high clinical significance of performing electroencephalography and detecting epileptiform activity in patients with Alzheimer’s disease due to its potential negative impact on the progression of cognitive impairment and increased risk of epileptic seizures in such patients. The frequency of SEA in AD patients can vary (2–54%) depending on the duration of EEG recording, sleep inclusion, and the use of additional techniques (MEG, *foramen ovale* electrodes). Most literature data emphasize a higher incidence of SEA in AD patients compared to those with other types of dementia or healthy individuals of the corresponding age. Pathophysiological mechanisms highlight common etiopathogenetic links in the progression of AD and the formation of neuronal hyperexcitability, which is associated with the appearance of epileptiform activity on EEG. The use of ASM for SEA therapy may become a new treatment strategy for AD patients, not only as a means of preventing epileptic seizures but also in the treatment of cognitive impairment. However, the advisability of treating subclinical epileptiform activity in Alzheimer’s disease patients remains a subject for further investigation.

References

1. Levin OS. *Diagnostics and treatment of cognitive disorders and dementia in clinical practice.* 3rd ed. Moscow: MEDpress-Inform; 2023 (In Russ).
2. Prince M, Wimo A, Guerchet M, Ali GC, Wu YuT, Prina M. *World Alzheimer Report, 2015. The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends*. London: ADI; 2015.
3. Belousov YB, Zyryanov SK, Belousov DY, Beketov AS. Clinical and economic aspects of Alzheimer's disease therapy in Russia. *Good Clinical Practice.* 2018;1:3–28 (In Russ.).
4. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *The New England Journal of Medicine.* 2013;68(14):1326–34. https://doi.org/doi:10.1056/nejmsa1204629
5. Koberskaya NN. Alzheimer's disease. *Neurology, Neuropsychiatry, Psychosomatics*. 2019;11(3S):52–60 (In Russ.). https://doi.org/10.14412/2074-2711-2019-3S-52-60
6. Babiloni C, Carducci F, Lizio R, Vecchio F, Baglieri A, Bernardini S, et al. Resting state cortical electroencephalographic rhythms are related to gray matter volume in subjects with mild cognitive impairment and Alzheimer's disease. *Human Brain Mapping*. 2013;34(6):1427–46. https://doi.org/doi:10.1002/hbm.22005
7. Kang JQ. Epileptic mechanisms shared by Alzheimer's disease: Viewed via the unique lens of genetic epilepsy. *International Journal of Molecular Sciences*. 2021;22(13):7133. https://doi.org/10.3390/ijms22137133
8. Musaeus CS, Engedal K, Høgh P, Jelic V, Mørup M, Nail M, et al. EEG theta power is an early marker of cognitive decline in dementia due to Alzheimer's disease. *Journal of Alzheimer's Disease*. 2018;64(4):1359–71. https://doi.org/10.3233/jad-180300
9. Cretin B, Bousiges O, Hautecloque G, Philippi N, Blanc F, Dibitonto L, et al. CSF in epileptic prodromal Alzheimer's disease: No diagnostic contribution but a pathophysiological one. *Frontiers in Neurology*. 2021;12:623777. https://doi.org/10.3389/fneur.2021.623777
10. Csernus EA, Werber T, Kamondi A, Horvath AA. The significance of subclinical epileptiform activity in Alzheimer's disease: A review. *Frontiers in Neurology*. 2022;13:856500. https://doi.org/10.3389/fneur.2022.856500
11. Nous A, Seynaeve L, Feys O, Wens V, de Tiege X, van Mierlo P, et al. Subclinical epileptiform activity in the Alzheimer continuum: association with disease, cognition and detection method. *Alzheimer's Research and Therapy.* 2024;16(1):19. https://doi.org/10.1186/s13195-023-01373-9
12. Mendez MF, Lim GTH. Seizures in elderly patients with dementia. *Drugs and Aging.* 2003;20(11):791–803. https://doi.org/10.2165/00002512-200320110-00001
13. Brunetti V, D'Atri A, Della Marca G, Vollono C, Marra C, Vita MG, et al. Subclinical epileptiform activity during sleep in Alzheimer's disease and mild cognitive impairment. *Clinical Neurophysiology*. 2020;131(5):1011–8. https://doi.org/10.1016/j.clinph.2020.02.015
14. Vossel KA, Beagle AJ, Rabinovici GD, Shu H, Lee SE, Nassan G, et al. Seizures and epileptiform activity in the early stages of Alzheimer disease. *JAMA Neurology*. 2013;70(9):1158–66. https://doi.org/10.1001/jamaneurol.2013.136
15. Liedorp M, Stam CJ, van der Flier WM, Pijenburg YAL, Scheltens P. Prevalence and clinical significance of epileptiform EEG discharges in a large memory clinic cohort. *Dementia and Geriatric Cognitive Disorders.* 2010;29(5):432–7. https://doi.org/10.1159/000278620
16. Vossel KA, Ranasinghe KG, Beagle AJ, Mizuiri D, Honma SM, Dowling AF, et al. Incidence and impact of subclinical epileptiform activity in Alzheimer's disease. *Annals of Neurology.* 2016;80(6):858–70. https://doi.org/10.1002/ana.24794
17. Horváth A, Szűcs A, Hidasi Z, Csukly G, Barcs G, Kamondi A. Prevalence, semiology, and risk factors of epilepsy in Alzheimer's disease: An ambulatory EEG study. *Journal of Alzheimer's Disease.* 2018;63(3):1045–54. https://doi.org/10.3233/JAD-170925
18. Horvath AA, Papp A, Zsuffa J, Szucs A, Luckl J, Radai F, et al. Subclinical epileptiform activity accelerates the progression of Alzheimer's disease: A long-term EEG study. *Clinical Neurophysiology.* 2021;132(8):1982–9. https://doi.org/10.1016/j.clinph.2021.03.050
19. Lam AD, Sarkis RA, Pellerin KR, Jing J, Dworetzky BA, Hoch DB, et al. Association of epileptiform abnormalities and seizures in Alzheimer disease. *Neurology.* 2020;95(16):e2259–70. https://doi.org/10.1212/WNL.0000000000010612
20. Babiloni C, Noce G, Di Bonaventura C, Lizio R, Pascarelli MT, Tucci F, et al. Abnormalities of cortical sources of resting state delta electroencephalographic rhythms ere related to epileptiform activity in patients with amnesic mild cognitive impairment not due to Alzheimer's disease. *Frontiers in Neurology.* 2020;11:514136. https://doi.org/10.3389/fneur.2020.514136
21. Lam AD, Deck G, Goldman A, Eskandar EN, Noebels J, Cole AJ. Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease. *Nature Medicine*. 2017;23(6):678–80. https://doi.org/10.1038/nm.4330
22. Ung H, Cazares C, Nanivadekar A, Kini L, Wagenaar J, Becker D, et al. Interictal epileptiform activity outside the seizure onset zone impacts cognition. *Brain*. 2017;140(8):2157–68. https://doi.org/10.1093/brain/awx143
23. Horvath AA, Csernus EA, Lality S, Kaminski RM, Kamondi A. Inhibiting epileptiform activity in cognitive disorders: possibilities for a novel therapeutic approach. *Frontiers in Neuroscience.* 2020;14:557416. https://doi.org/10.3389/fnins.2020.557416
24. Giorgi FS, Saccaro LF, Busceti CL, Biagioni F, Fornai F. Epilepsy and Alzheimer's disease: potential mechanisms for an association. *Brain Research Bulletin*. 2020;160:107–20. https://doi.org/10.1016/j.brainresbull.2020.04.009
25. Vossel KA, Tartaglia MC, Nygaard HB, Zeman AZ, Miller BL. Epileptic activity in Alzheimer's disease: causes and clinical relevance. *The Lancet Neurology*. 2017;16(4):311–22. https://doi.org/10.1016/S1474-4422(17)30044-3
26. Ye CP, Selkoe DJ, Hartley DM. Protofibrils of amyloid β-protein inhibit specific K^+ currents in neocortical cultures. *Neurobiology of Disease*. 2003;13(3):177–90. https://doi.org/10.1016/s0969-9961(03)00068-8
27. Lei M, Xu H, Li Z, Wang Z, O'Malley TT, Zhang D, et al. Soluble Aβ oligomers impair hippocampal LTP by disrupting glutamatergic/GABAergic balance. *Neurobiology of Disease.* 2016;85:111–21. https://doi.org/10.1016/j.nbd.2015.10.019
28. Kam K, Duffy ÁM, Moretto J, LaFrancois J, Scharfman HE. Interictal spikes during sleep are an early defect in the Tg2576 mouse model of β-amyloid neuropathology. *Scientific Reports*. 2016;6:20119. https://doi.org/10.1038/srep20119

29. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. *Alzheimer's and Dementia.* 2016;12(6):719–32. https://doi.org/10.1016/j.jalz.2016.02.010
30. Regen F, Hellmann-Regen J, Costantini E, Reale M. Neuroinflammation and Alzheimer's disease: implications for microglial activation. *Current Alzheimer Research.* 2017;14(11):1140–8. https://doi.org/10.2174/1567205014666170203141717
31. Vezzani A, Friedman A, Dingledine RJ. The role of inflammation in epileptogenesis. *Neuropharmacology.* 2013;69:16–24. https://doi.org/10.1016/j.neuropharm.2012.04.004
32. Postnikova TY, Zubareva OE, Kovalenko AA, Kim KK, Magazinik LG, Zaitsev AV. Status epilepticus impairs synaptic plasticity in rat hippocampus and is followed by changes in expression of NMDA receptors. *Biochemistry.* 2017;82(3):282–90. https://doi.org/10.1134/S0006297917030063
33. Roberson ED, Scearce-Levie K, Palop JJ, Fengrong Y, 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. https://doi.org/10.1126/science.1141736
34. Decker JM, Krüger L, Sydow A, Dennissen FJA, Siskova Z, Mandelkow E, et al. The Tau/A152T mutation, a risk factor for frontotemporal-spectrum disorders, leads to NR2B receptor-mediated excitotoxicity. *EMBO Reports.* 2016;17(4):552–69. https://doi.org/10.15252/embr.201541439
35. Tian FF, Zeng C, Ma YF, Guo TH, Chen JM, Cai XF, et al. Potential roles of Cdk5/p35 and tau protein in hippocampal mossy fiber sprouting in the PTZ kindling model. *Clinical Laboratory.* 2010;56(3–4):127–36.
36. Thom M, Liu JYW, Thompson P, Pladke 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(10):2969–81. https://doi.org/10.1093/brain/awr209
37. Liu SJ, Zheng P, Wright DK, Deszi G, Braine E, Nguen T, et al. Sodium selenate retards epileptogenesis in acquired epilepsy models reversing changes in protein phosphatase 2A and hyperphosphorylated tau. *Brain.* 2016;139(7):1919–38. https://doi.org/10.1093/brain/aww116
38. Luchetti S, Huitinga I, Swaab DF. Neurosteroid and GABA-A receptor alterations in Alzheimer's disease, Parkinson's disease and multiple sclerosis. *Neuroscience.* 2011;191:6–21. https://doi.org/10.1016/j.neuroscience.2011.04.010
39. Sanchez PE, Zhu L, Verret L, Vossel KA, Orr AG, Cirrito JR, et al. Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. *PNAS.* 2012;109(42):E2895–903. https://doi.org/10.1073/pnas.1121081109
40. Corbett BF, You JC, Zhang X, Pyfer MS, Tosi U, Iaskone DM, et al. ΔFosB regulates gene expression and cognitive dysfunction in a mouse model of Alzheimer's disease. *Cell Reports.* 2017;20(2):344355. https://doi.org/10.1016/j.celrep.2017.06.040
41. Shi JQ, Wang BR, Tian YY, Xu J, Gao L, Zhao SL, et al. Antiepileptics topiramate and levetiracetam alleviate behavioral deficits and reduce neuropathology in APPswe/PS1dE9 transgenic mice. *CNS Neuroscience and Therapeutics.* 2013;19(11):871–81. https://doi.org/10.1111/cns.12144
42. Nygaard HB, Kaufman AC, Sekine-Konno T, Huh LL, Going H, Feldman SJ, et al. Brivaracetam, but not ethosuximide, reverses memory impairments in an Alzheimer's disease mouse model. *Alzheimer's Research and Therapy.* 2015;7(1):25. https://doi.org/10.1186/s13195-015-0110-9
43. Fu CH, Iascone DM, Petrof I, Hazra A, Zhang X, Pyfer MS, et al. Early seizure activity accelerates depletion of hippocampal neural stem cells and impairs spatial discrimination in an Alzheimer's disease model. *Cell Reports.* 2019;27(13):3741–51. https://doi.org/10.1016/j.celrep.2019.05.101
44. Cumbo E, Ligori LD. Levetiracetam, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer's disease. *Epilepsy and Behavior.* 2010;17(4):461–6. https://doi.org/10.1016/j.yebeh.2010.01.015
45. Horváth A, Szűcs A, Barcs G, Noebels JL, Kamondi A. Epileptic seizures in Alzheimer disease: A review. *Alzheimer Disease and Associated Disorders.* 2016;30(2):186–92. https://doi.org/10.1097/WAD.0000000000000134
46. Vossel K, Ranasinghe KG, Beagle AJ, La A, Pook KA, Castro M, et al. Effect of levetiracetam on cognition in patients with Alzheimer disease with and without epileptiform activity: A randomized clinical trial. *JAMA Neurology.* 2021;78(11):1345–54. https://doi.org/10.1001/jamaneurol.2021.3310
47. Nicastro N, Assal F, Seeck M. From here to epilepsy: the risk of seizure in patients with Alzheimer's disease. *Epileptic Disorders.* 2016;18(1):1–12. https://doi.org/10.1684/epd.2016.0808
48. Rowan AJ, Ramsay RE, Collins JF, Pryor F, Boardman KD, Uthman BM, et al. New onset geriatric epilepsy: A randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology.* 2005;64(11):1868–73. https://doi.org/10.1212/01.wnl.0000167384.68207.3e
49 Vossel KA, Tartaglia MC, Nygaard HB, Zeman AZ, Miller BL. Epileptic activity in Alzheimer's disease: Causes and clinical relevance. *The Lancet Neurology.* 2017;16(4):311–22. https://doi.org/10.1016/s1474-4422(17)30044-3
50. Javed A, Cohen B, Detyniecki K, Hirsch LJ, Legge A, Chen B, et al. Rates and predictors of patient-reported cognitive side effects of antiepileptic drugs: An extended follow-up. *Seizure.* 2015;29:34–40. https://doi.org/10.1016/j.seizure.2015.03.013
51. Rizzello E, Pimpinella D, Pignataro A, Titta G, Merenda E, Saviana M, et al. Lamotrigine rescues neuronal alterations and prevents seizure-induced memory decline in an Alzheimer's disease mouse model. *Neurobiology of Disease.* 2023;181:106106. https://doi.org/10.1016/j.nbd.2023.106106
52. Tekin S, Aykut-Bingöl C, Tanridağ T, Aktan S. Antiglutamatergic therapy in Alzheimer's disease — effects of lamotrigine. Short communication. *Journal of Neural Transmission.* 1998;105(2–3):295–303. https://doi.org/10.1007/s007020050059

Authors' contributions. All authors confirm that they meet the ICMJE criteria for authorship. The greatest contribution was made by: Sergey G. Burd — approval of the final version of the manuscript; Anna N. Bogolepova — project supervision and scientific justification; Anna V. Lebedeva — editing of the manuscript; Yulia V. Rubleva — administration and writing of the conclusions and summary; Ekaterina A. Kovalenko — research methodology and data analysis; Ekaterina V. Makhnovich — setting the goal and conceptualization of the manuscript; Nina A. Osinovskaya — visualization and formatting of tables and figures; Ekaterina A. Gileva — formatting of the reference list; and Nina V. Pantina — searching for sources in abstract databases; Irina I. Kovaleva — writing the subsection "Results and Discussion".

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