REVIEW ARTICLE

Anti-seizure Medication Induced Cognitive Impairment in Children with Epilepsy: A Narrative Review

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ABSTRACT

Several circumstances, including the etiology of epilepsy, its early onset, recurrent seizures, and the use of anti-seizure medications (ASMs), can lead to cognitive impairment in people with epilepsy. Studies indicate that the etiology of epilepsy may be more closely associated with cognitive problems than the ASMs. However, considering long-term treatment in pediatrics and their developing nervous systems, it is critical to understand the cognitive effects of each anti-seizure medication. Significant methodological challenges exist in studying the cognitive effects of ASMs. Accordingly, this review aims to give a broad overview of recent studies on cognitive impairment caused by first- and second-generation ASMs.

Introduction

A significant quantity of people worldwide suffer from epilepsy, a common neurological condition. The high frequency of psychiatric comorbidities linked to this illness can have a serious adverse effect on the quality of life for those who are impacted. Epileptic seizures arise from the aberrant operation of voltage-gated and transmitter-gated ion channels, leading to excessive electrical activity in neurons (1). Epileptic seizures come in a variety of forms and can manifest as brief or prolonged, minor or dramatic, frequent or infrequent. From a severe generalized tonic-colonic seizure to a small myoclonic flashing of the eyelids or a focal numbing of the thumb and mouth, these symptoms can vary clinically (2). Even though seizures are the most noticeable clinical manifestation of epilepsies, people who have this condition are more likely to experience a wide range of health issues in addition to seizures (3,4). Comorbidities associated with epilepsy frequently encountered include physical comorbidities like migraine and sleep disorders; mental health illnesses like depression or anxiety; and cognitive impairment like memory,

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attention, or processing issues. Comorbidities with epilepsy are frequent and sometimes severe — often causing greater hardships for many people than the episodes themselves (5). Cognitive and neuropsychological abnormalities might result from both morphological and functional alterations in the brain brought on by epileptic seizures. Persistent seizures, particularly those resulting in status epilepticus, are known to induce oxidative stress, alterations in growth factors like BDNF (Brain- derived neurotrophic factor), and neuronal death, mostly in the entorhinal cortex or hippocampal regions, which are also intimately linked to cognitive function (6). Severe cognitive impairment may result from untreated and uncontrolled epileptic episodes. According to specific research, cognitive impairment affects between 60% and 70% of individuals with persistent epilepsy (7, 8, 9). Furthermore, a higher prevalence of low IQs is found in people with epilepsy (PWE), particularly in children with poorly managed seizures, who are more likely to score lower on IQ tests than children with well-controlled seizures. Both children and adults with epilepsy frequently report experiencing memory issues (10).

A significant portion of the cognitive decline experienced by individuals with epilepsy is associated with the underlying cause of the disease. Both acquired disorders, such as trauma, hypoxia, and ischemia, and genetic disorders, such as fragile X and Dravet syndromes, can cause substantial cognitive impairment in addition to causing epilepsy. Apart from the static abnormalities resulting from the underlying etiology, there may also be more dynamic or transitory cognitive impairments produced by the seizures and anti-seizure medications (ASMs). Many individuals' cognitive impairments may be caused by various factors (5, 11). Since ASMs are easier to recognize than other triggers, patients and even some doctors tend to blame cognitive issues on medications. The advantages of ASMs should not be exaggerated in any case. One prevalent cause of cognitive impairment, sometimes disregarded, is psychosocial difficulties. The shame around epilepsy and the anxiety associated with experiencing seizures out in society can result in desperation, social isolation, and low self-confidence, all of which can impair cognitive function. Similarly, another significant factor contributing to cognitive decline but is sometimes overlooked is subclinical epileptiform activity, particularly in patients who have few seizures (12). Even though research indicates PWE who use more ASMs are more likely to experience cognitive impairment. Similar to other medications, individuals using ASMs also experience more severe side effects when they take larger doses of the medications or combine multiple ASMs (11,13). Therefore, even though ASMs are rarely the exclusive cause of cognitive impairments, they do have the ability to have a major impact on cognition in some individuals. Additionally, as this review previously mentioned, ASMs have dosage-dependent impacts on cognitive performance, which can be made worse by ASM polytherapy. Effects on attention, psychomotor speed, and memory are the most important impacts of ASMs. PWE who are taking drugs should be particularly concerned about the possibility of ASM-induced cognitive adverse effects (14). Due to their developing neural systems, young patients are more susceptible to the lasting effects of ASM-induced cognitive dysfunction; hence, it is crucial to recognize and reduce the effects of ASMs on their cognitive development (15).

The present study aims to provide an overview of current research and draw general conclusions to distinguish between cognitive impairment due to epileptic seizures or ASMs in PWE.

Epilepsy's effect on cognition

The specific processes that lead to an elevated risk of cognitive impairment in individuals with epilepsy remain unclear. This section will examine the different pathways that have been suggested as potential causes of such impairment. Most studies indicate a notable relationship between the age at which epilepsy first appears and the duration of the seizures experienced (16,17).

The underlying pathophysiology connecting epilepsy and cognitive function involves direct damage to neuronal networks caused by seizures and epileptiform discharges observed in the EEG. However, as cognitive function is expressly concerned with information processing, sequences of action potential firing in neuronal populations throughout time are thought to be mechanisms of cognition. Moreover, recurrent seizures, particularly status epilepticus, frequently bring on oxidative stress and neuronal death, and these outcomes are ultimately linked to cognitive decline (18, 19, 20).

Overall, different regions of the brain can be affected by seizures, which can lead to hypoxic-ischemic injury. Depending on which brain region is affected, cognitive impairment can result. If the temporal lobe is affected, we may see memory, behavior, speech function, and emotional control impairments. If the frontal lobe is affected, we may see impairments in emotional control, inhibition, and motor control; if the hippocampal region is affected, we may observe impairments in attention, executive function, planning, organization, working memory, and task performance (20).

Whole-brain volume studies have shown correlations between epileptic patients and cognitive decline and brain volume decreases (21). For instance, in individuals with epilepsy, atrophy of the thalamus, amygdala, and mammillary bodies is linked to poor memory function and language difficulties (22,23). Recent research has shown that individual tract integrity in epileptic patients and cognitive impairment are related. For example, verbal memory ability in patients with left temporal lobe epilepsy (TLE) was associated with the integrity of the left uncinate fasciculus.

According to another study, cognitive abilities were connected with the health of the limbic projection tracts and certain cortical-to-cortical association pathways, particularly in the left hemisphere (5, 24). According to some animal studies, extensive seizures are linked to long-term potentiation (LTP) impairments and place cell stability (the hippocampal region contains the place cells). These cells have a role in episodic memory by becoming active at a specific location. LTP, resulting from a progressive increase in synaptic potency, is essential for various behavioral changes, including memory and learning, the functional development of the eyes, and the somatosensory system (25, 26, 27).

A separate study has indicated that individuals with psychogenic non-epileptic seizures (PNES) exhibited greater difficulties in attentional and executive functioning compared to those with epilepsy. Conversely, the epilepsy group showed significantly poorer performance on memory assessments. However, notably, the test outcomes for individuals with PNES may be influenced by inherent unreliability(28). The fact that many PNES individuals struggle with motivation during neuropsychological testing may be the

reason why their cognitive impairment was found to be comparable to that of PWE. Personality disorders are another common ailment among them. Indicatively, the brains of these patients had specific structural abnormalities. On the other hand, the effects of PWE on cognition were largely consistent across numerous trials (13, 17, 29, 30).

According to another study, people with frontal lobe epilepsy were less able to classify the emotions they exhibited and had poorer switching ability than healthy people. The findings might point to a problem with social cognition. They also support the theory that the frontal lobe is critical for adequately operating executive functions, social skills, and emotion control (30).

Overall, according to the data, rather than epilepsy itself, the causes of the cognitive impairments observed in patients and preclinical models of epilepsy are most likely changes in plasticity, modifications to neuronal coding regimes, desynchronization, and disruptions in functional connectivity. Seizures also negatively affect network behaviors, but this effect is not comparable to the etiologic effect (31).

ASM effect on cognition

As already said, numerous factors influence cognitive performance, such as the neuropathology underlying epilepsy, seizures, epileptiform activity, psychosocial issues, and adverse effects of ASMs. Importantly, although ASMs are sometimes mistakenly linked to cognitive impairment, some children actually experience cognitive impairment as a result of these medications (32). Thus, this study now discusses the cognitive impacts of these medications that have been documented in certain research. ASMs reduce neuronal excitability or increase inhibitory neurotransmission, which might negatively impact cognitive function. ASMs primarily affect attention, alertness, and psychomotor speed, while they can also have secondary effects on other cognitive functions (33). PWE who take more ASMs are more likely to experience cognitive impairment. According to numerous studies, two or three different ASMs were given to more than half of the individuals in one investigation. Levetiracetam (LEV) or lamotrigine (LTG) was given to most of them. According to this study, the probability of cognitive impairment rises with each extra ASM. The executive function domain showed more significant signs of cognitive decline, and compared to placebo, nondrug conditions, and more recent ASM, older ASM generally had worse effects on cognition (12).

Obviously, all of the older medications can cause psychomotor slowing, affecting fundamental cognitive functions like working memory, sensory processing, perception, attention, concentration, processing speed, and psychomotor speed (34).

First generation ASMs

Phenytoin (PHT), carbamazepine (CBZ), valproate (VPA), phenobarbital (PB), and benzodiazepines are considered as 'First-Generation' anti-seizure or older ASMs. One must consider the limited availability of information concerning the precise impact of individual medication dosages, as most research focuses on comparisons between different medications. Although there have been reports of cognitive side effects in children with epilepsy using older medications, PB appears to have the most significant negative impact(35).

Long-term PB usage in children is linked to IQ decline; however, the decline is often less than ten IQ points (36). Similar findings were

obtained in a different study, indicating that children who stopped taking PB improved more than those who continued to take PB in terms of total IQ, particularly in performance tasks (37). Another trial comparing PHT, CBZ, and VPA for pediatric epilepsy revealed that the PHT group experienced very slight alterations. Children treated with CBZ in this trial outperformed those treated with VPA, particularly on memory tasks (38).

Significant differences were found in the amount of mental slowness caused by PHT compared to CBZ in specific iinvestigations (39, 40). Nevertheless, other assessments have revealed that the mental slowness and concentration problems linked to PHT are not significantly different from those linked to CBZ and VPA (41). Generally, decreases in mental speed, focus, memory, and visuomotor abilities have all been linked to PHT (42). Furthermore, this drug may have worse memory effects than CBZ, according to particularresearch (43).

When CBZ was compared to several other ASMs, some authors observed advantages supporting the drug, while other authors observed a similar profile (44). Some investigations evaluating the exact impact of VPA sodium found minor to moderate impairments in psychomotor and mental speed (45). Additionally, demonstratively, a small percentage of individuals may experience psychomotor slowness and memory issues related to Parkinsonism (46). In another study, in contrast to CBZ, VPA performed worse in memory and visuomotor abilities when compared to other traditional medications (47). However, the VPA-related cognitive side effects are probably reversible (48). Notably, different studies have shown different results, but one thing is certain: First-generation drugs have a greater potential to impair cognitive function than second-generation drugs. PB is the least preferred ASM regarding its effects on cognitive function, and VPA has been recommended to be more desirable than CBZ, PB, and even topiramate (TPM) (38, 49, 50).

Second generation ASMs

The design and usage of new-generation ASMs have advanced significantly in recent years. These new drugs are on par with or even better than more established ASMs in their ability to control epileptic seizures, as evidenced by their impressive track record. Furthermore, these patients frequently have a better side effect profile, making them more palatable and appropriate for those with epilepsy (Table 1) (51).

Beginning in the early 1990s, several newer ASMs referred to as Second-Generation anti-seizure have become available, such as felbamate (FBM), gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OXC), topiramate (TPM), tiagabine (TGB), vigabatrin (VGB), zonisamide (ZNS), pregabalin (PGB), and levetiracetam (LEV) (12, 52).

Levetiracetam

Levetiracetam (LEV) works differently from other ASMs on the market in terms of structure and mechanics, making it distinctive. For PWE, it effectively lowers partial seizures. For PWE, LEV has numerous therapeutic benefits. Benefiting from high bioavailability, linear pharmacokinetics, minimal protein binding, no hepatic metabolism, and quick-reaching of steady-state concentrations, it possesses desirable pharmacokinetic properties and minimal drug interaction possibility (53). According to research from patients and healthy volunteers, LEV has a few negative effects on cognition (12). Similarly, another study involving

healthy volunteers showed cognitive deficiencies were less pronounced with LEV than CBZ(54). Moreover, the scientists found no discernible alterations in cognitive function in single-blind, add-on, and dose-escalation research (55). A different study comparing the effects of TPM and LEV on attention, executive functions, declarative memory performance, short- and working-term memory performance, visuospatial abilities, and general intelligence revealed that while the TPM group showed worsening language fluency, short-term memory, and cognitive speed, the LEV group showed no change in cognitive abilities (56).

No decline was observed in any of the assessed cognitive domains in a related trial using LEV therapy. Conversely, TPM recipients performed below average throughout the board. Even better attention was noted in the LEV-treated group of patients (57). When LEV was combined with CBZ or PHT, a trial of ten patients revealed no appreciable alterations in psychomotor ability, memory, or information processing (55). Therefore, evidence from patients, as well as healthy volunteers, shows no significant negative effects of LEV on cognition (12). Furthermore, patients on LEV may experience adverse effects such as aggressiveness, anxiety, and depression, but these are generally less common than with other ASMs (58).

Topiramate

Topiramate (TPM) is a broad-spectrum ASM acting through various mechanisms, such as glutamate antagonism, potentiation of GABA-mediated effects, blockage of voltage-dependent sodium channels, and inhibition of carbonic anhydrase. TPM has shown promise in treating patients with chronic partial epilepsies that are refractory (59). TPM is the more recent ASM causing the most worry because of possible detrimental cognitive consequences, such as impaired frontal execution and language function (60, 61). According to a double-blind, randomized study in older adults, about 1% to 5% of individuals using TPM experienced cognitive effects, such as memory loss and language difficulty (62).

In a study with healthy individuals, psychomotor slowdown, language problems, and issues with focus and memory were seen (63). Reduced IQ and cognitive speed, poor verbal fluency and word-finding deficits, language and comprehension issues, cognitive dulling, psychomotor slowing, and impaired concentration are just a few examples of the negative effects on cognition (64, 65, 66, 50). Additionally, research has shown that some people, those who already have cognitive issues or TLE, may be more susceptible to cognitive impairment with TPM (60, 67).

Generally, compared to other ASMs, TPM has been demonstrated to have more detrimental effects on cognition. In clinical trials, TPM has been shown to cause sleepiness, mental slowness, memory loss, and difficulties with language. Comparative investigations between individuals with epilepsy and healthy volunteers have revealed that TPM causes more cognitive deficits than LTG, VPA, GBP, and TGB (68). The higher the dosage of TPM, the higher the cognitive risk. The risk of cognitive decline and the total amount consumed daily appear strongly correlated across various cognitive assessments (69).

Lamotrigine

Lamotrigine (LTG) prevents the release of excitatory neurotransmitters by blocking voltage-dependent sodium channels (53). A few studies have presented data indicating LTG may

have a minor effect on cognitive abilities (70). According to a study, CBZ performed better than LTG in more than half of the cognitive tests evaluated in healthy participants (71). Similar neuropsychological results have been noticed in patient trials when add-on therapies did not significantly increase impairment over a placebo (72). According to specific research, LTG can sometimes enhance cognitive performance in children with refractory epilepsy, even in cases where seizure control is compromised. This has also been demonstrated in adults and children with mental disorders; However, results were not always quantified (73, 74). Some research compared the effects of CBZ, lamotrigine, and topiramate on cognitive functioning. In these trials, lamotrigine was shown to be more beneficial, mainly regarding verbal fluency and attention (68,double-blind, randomized, prospective study was conducted in adults with partial seizures. Lamotrigine or topiramate was introduced as an adjunctive therapy to carbamazepine or phenytoin and titrated over 8 weeks to target doses. These drugs were maintained another 8 weeks (maintenance phase75). Overall, research indicates LTG has no detrimental effects on cognition. Thus, indicatively, LTG was a medication that was safe for use at the cognitive level (76).

Oxcarbazepine

Oxcarbazepine (OXC) is approved as a first or supplemental medication for focal seizures and has a chemical relationship with CBZ (12). Investigations and comparisons between PHT and OXC monotherapy were carried out for verbal memory, sustained attention, and simple psychomotor speed. After using either medication, the cognitive test results showed no differences from baseline (77). A double-blind study reported that no changes were observed in any of the seven cognitive measures assessed at any point in time between OXC and PHT monotherapy in first-time diagnosed individuals (78). In healthy individuals, OXC caused minor cognitive impairment along with a slight slowing of the electroencephalogram (EEG); nevertheless, the effect of OXC was not as strong as that of PHT (79). No differences were observed between OXC and CBZ, VPA, or combination CBZ/VPA polytherapy in children with recently diagnosed focal epilepsy on a variety of standard cognitive tests and specialized computerized tasks (80, 81). Other studies found similar results when comparing OXC with CBZ, VPA, PHT, and PB monotherapy in newly diagnosed patients. These studies included verbal learning and retention, visual learning and retention, digit span, sustained attention, simple psychomotor speed, executive functions, and constructional ability (78).

In conclusion, some research indicates that OXC does not seem to provide a significant cognitive advantage in both adults and kids with epilepsy when compared to traditional ASMs; however, other research indicates that OXC improved motor speed and attention in healthy volunteers and did not exhibit any particular cognitive side effects in adult epilepsy patients (78, 82). Overall, they conclude that OXC seems the same in terms of cognitive safety as LTG. Additionally, a study on children revealed that only drowsiness was a probable cognitive adverse outcome (83).

Vigabatrin

Since vigabatrin (VGB) is a structural analog of GABA, brain GABA levels are raised by irreversibly inhibiting the degradative enzyme GABA-transaminase (12). Due to evidence

of a side effect of constricted visual field, its application in the treatment of epilepsy is limited. In a double-blind, randomized add-on trial, VGB had a negligible negative impact on cognitive or quality-of-life parameters in epilepsy patients when compared to placebo (84). Additionally, in short, open-label, randomized, parallel-group individual research, VGB resulted in fewer adverse events than CBZ (77). Visible field constriction, which may impact 30-50% of individuals, is the primary contraindication to using VGB (85). Children may have these issues less frequently than adults, and the duration of therapy or the total amount of VGB administered may increase a patient's risk of developing visual field constriction (86).

Tiagabine

Tiagabine (TGB) is useful as a supplemental medication for treating patients with recurrent focal epilepsy, according to clinical trials (53). A study showed some evidence of mood effects from add-on treatment with TGB at a higher dosage, which may be related to titration speed, but no cognitive effects from monotherapy with TGB at low or high doses were seen (87). Similarly, in another add-on polytherapy study, TGB treatment did not alter cognitive function compared to placebo at low doses (88). TGB was found to have similar effects on verbal fluency and to have faster perceptual and motor speed in people with partial seizures compared to CBZ, according to another investigation (89). TGB use has also been linked to a few cognitive side effects, including verbal memory decline, according to other studies. However, other research has shown no negative effects on cognition (87, 90).

Discussion

Many different anti-seizure drugs are available on the market, making the therapy options for seizures rather broad. With many alternatives available, choosing the best course of action for patients can be challenging for medical professionals (92). Because early cognitive impairment screening enhances the general level of life quality for epileptic patients, it should be conducted along with treatment follow-up (93). Some of the factors that contribute to cognitive impairment in PWE include early onset of epilepsy, recurrent seizures, frequent interictal discharges, low educational attainment, and polytherapy. Neuroplasticity deficits can result from recurrent seizures, which have a substantial impact mainly on the hippocampus. After only a few documented epileptic seizures and prior to beginning consistent anti-seizure therapy, PWE may experience cognitive impairment, particularly in the memory domain, even without structural MRI abnormalities (94).

Some studies indicate that rather than seizures or ASMs, the cognitive deficits observed in epileptic patients and preclinical models of epilepsy are most likely caused by changes in plasticity, modifications to neuronal coding regimes, desynchronization, and disruptions in functional connectivity as a result of underlying etiology. We firmly contend that the seizure effect is quite tiny compared to the etiology effect, even though we acknowledge that the seizures may potentially have some detrimental effects on network behaviors (31). Thus, it may be concluded that various factors contribute to the etiology of cognitive issues in epilepsy. Additionally, cognitive function may be impacted by seizure frequency, epilepsy duration, and interictal anomalies even prior to a PWE diagnosis. Furthermore, the majority of research that looked into the cognitive adverse effects of

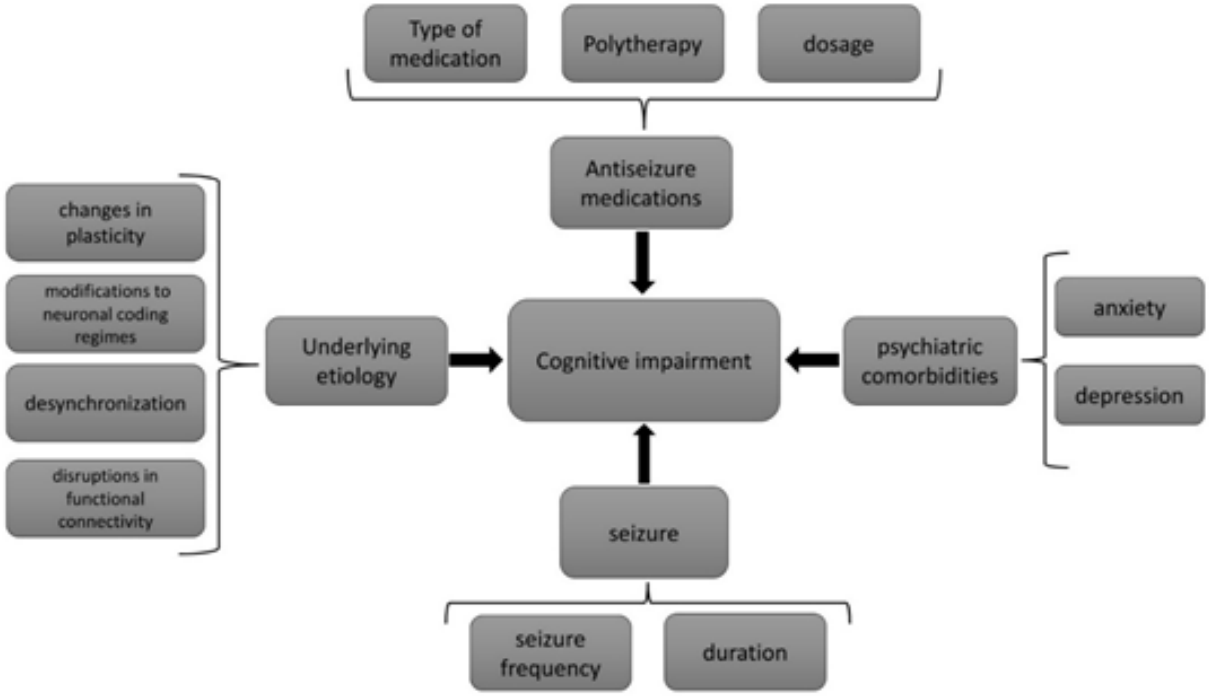

Figure 1. Factors associated with cognitive impairments in patients with seizure

ASMs did not consider all the additional aspects that epilepsy itself causes (Figure 1).

There has been little progress in determining and measuring the cognitive consequences of ASMs. Hundreds of studies have been conducted, but no discernible pattern has emerged due to methodological shortcomings, variations in research methods, and inconsistent findings. Evaluating the cognitive risk of ASMs is a challenging field to research, primarily in a clinical context. There are three main factors to consider: The first comes from the inability to randomize the treatment plan because patients with harder-to-control epilepsy are susceptible to experimenting with new medications, implying that their pre-treatment cognitive abilities are not typical of the general population. The second concern is that patients get treated clinically across a wide range of efficient dosages, which may have variable impacts on cognitive function, making it challenging to establish comparable drug levels. Third, numerous research raises concerns about the lack of blinding. There may be further methodological problems as well (12, 52, 95).

All studies concur that the risk of cognitive impairment rises with each additional ASM. Based on this research, it is recommended to limit the use of combined ASMs to no more than two whenever possible (96). According to a recent polytherapy study, compared to other subgroups, LEV+TPM and LEV + CBZ have considerably worse cognitive test scores. The group taking LEV+TPM had considerably poorer cognitive test scores than the group using LEV+CBZ, and the LEV + LCM and LEV+ LTG groupings do not significantly differ in their cognitive ratings from one another (76).

Moreover, as this review already mentioned, research indicates that except for TPM, older generations of ASMs have substantially more side effects and adversely impact cognitive functioning than newer groups. LEV and LTG turned out to be superior choices because they

had less of an effect on cognitive functions. The drug with the worst effects on cognition was TPM (56, 97). Overall, there has been much research on ASM-induced cognitive impairment; however, many of the more recent studies have produced contradictory findings, and many of the earlier studies have methodological issues already discussed. According to a recent study, no ASM was directly linked to cognitive impairment (98). In contrast to previous research, another recent study reported cognitive side effects of ASMs in both monotherapy and polytherapy (76). In conclusion, the question is not whether different ASMs have potentially harmful effects on cognition (many of them certainly do); undoubtedly, the question is how and when these effects manifest and how to recognize and prevent them. Seemingly, other factors are equally or even more significant. However, it is crucial to remember that ASMs can have a favorable impact on cognitive effects by lowering the frequency or intensity of seizures (99, 100). Considering the long-term care of children with epilepsy, given that children's growing neurological systems may make them more susceptible to the long-term effects of ASM-induced cognitive decline, it is particularly critical to recognize and reduce the cognitive effects of ASMs in children (101, 102). Finally, while several studies have examined how ASMs affect cognitive functioning, only a few of them have included electrophysiological measurements in their publications; instead, most have relied on clinical data and neuropsychological testing. Electrophysiological markers are intimately associated with cognitive processes and may identify minute cognitive alterations that traditional neuropsychological assessments could miss (76, 103). Furthermore, given the contradictory findings even in recent studies, additional research is required to identify ASM-induced cognitive impairment. Additionally, to increase their accuracy, more research incorporating broader clinical biomarkers such as genetic, EEG, epileptic networks, and imaging data into these platforms is also required.

In Conclusion

Selecting the best ASM for a specific individual can be difficult, and evaluating important clinical factors demands knowledge and experience that may not be available in certain situations. This study attempted to explain the effects of epilepsy and ASMs on cognitive function. Clinicians should be aware of the cognitive side effects of ASMs in order to select the appropriate course of treatment for each patient and manage them without exacerbating their cognitive impairment. We can enhance the quality of life and results for those who suffer from this disorder by deepening our understanding of the elements influencing cognitive function.

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Author's Contribution

Negin Armide: writing original draft & Data analysis. Meisam Babaei: supervision, Conceptualization, writing review & editing.

Conflict of Interest

None of declare

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