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Epilepsy and cognition

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Abstract

Patients with epilepsy are more prone to cognitive and behavioral deficits. Epilepsy per se may induce or exacerbate an underlying cognitive impairment, a variety of factors contribute to such deficits, i.e., underlying neuropathology, seizure type, age of onset, psychosocial problems, and treatment side effects. Epilepsy treatment may offset the cognitive and behavioral impairments by stopping or decreasing the seizures, but it may also induce untoward effects on cognition and behavior. The neurocognitive burden of epilepsy may even start through in utero exposure to medications. Epilepsy surgery can also induce certain cognitive deficits, although in most cases this can be minimized. Clinicians should consider cognitive side effect profiles of antiepileptic medications, particularly in extreme age groups. While no effective treatments are available for cognitive and behavioral impairments in epilepsy, comprehensive pretreatment evaluation and meticulous selection of antiepileptic drugs or surgical approach may minimize such untoward effects.

Keywords: Epilepsy; Seizure; Cognition; Behavior; Antiepileptic drug

1. Introduction

Epilepsy is a biomedical disturbance that results in abnormal episodic bursts of electrical activity in certain neurons, which may spread to the entire brain. Such abnormal neuronal activity may have significant impact on the normal cognitive processes and behavior of the affected individuals [1–5]. As the underlying mechanism of epileptogenicity differs, the clinical representation and consequences of the disease may vary significantly. Although the majority of patients with epilepsy have normal intelligence, overall, they are more likely to suffer from impaired cognitive performance when compared with age- and education-matched healthy controls. The type of neuropathology underlying epilepsy may affect the type of deficit. For example, temporal lobe epilepsy (TLE) can cause memory impairment, and focal epilepsy involving the language-dominant hemisphere may induce word finding and naming difficulties, while certain epilepsy syndromes are associated with severe cognitive or behavioral problems [2,5–7]. In addition to the adverse effects of seizures per se and the resulting psychosocial disruption of patients' lifestyles, therapeutic interventions can also cause untoward cognitive and behavioral effects. Antiepileptic drugs (AEDs) are a common cause of such morbidity [8,9], while cognitive disturbance after epilepsy surgery in most cases can be minimized or avoided [10,11]. On the other hand, epilepsy treatment may have positive effects on patients' cognitive performance by stopping or decreasing the seizures [12,13].

This article reviews these effects and their relevance to functional outcomes and quality of life (QoL) of patients with epilepsy, and addresses methodologic pitfalls in studying cognitive dysfunction in epilepsy.

2. Factors influencing cognitive dysfunction

Cognitive and behavioral dysfunction in epilepsy can be present independently of the state of seizure control. Studies have shown that patients with epilepsy have poorer education, social and personal lives, and employment status despite optimal seizure control [14]. Social and behavioral impairment can be present despite

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normal intelligence [15]. Cognitive deficits involving visual motor tasks, mental flexibility, and memory have been reported in newly diagnosed adult patients with partial or generalized seizures prior to treatment with AEDs [16]. A wide range of variables may underlie cognitive impairment in epilepsy including biologic, psychosocial, and treatment-induced factors [9,17,18].

2.1. Biologic factors

2.1.1. Seizure type and etiology

Different epilepsy syndromes have different effects on cognition. Symptomatic epilepsies can affect certain aspects of cognition and behavior depending on the location and nature of the neuropathology. While a small stroke or tumor may not involve any measurable neurocognitive impairment, seizures associated with lesions in the frontal lobe or limbic system can result in memory, language or psychologic disturbances [19]. A recent study in patients with posttraumatic epilepsy showed the presence of personality disorder, disinhibited behavior, irritability, agitation, and aggressive behavior but no deterioration in memory, language, intelligence, attention, and spatial cognition [20].

Epilepsy syndromes secondary to hereditary metabolic or neurodegenerative disorders are typically associated with neurocognitive deterioration, while idiopathic generalized seizure syndromes, like benign rolandic and juvenile myoclonic epilepsy, are associated with normal intelligence. Idiopathic epilepsies are less likely to be associated with intellectual abnormality than are localization-related seizure disorders. TLE, particularly when bilateral, is commonly associated with language difficulties, verbal and visual memory problems, or postictal psychotic features [2,9,21–23]. More recently, a genetic epilepsy syndrome has been associated with mental retardation in one kindred while the same mutation did not affect cognitive status in other kindreds. This strongly suggests a multifactorial and polygenic mechanism(s) involved in a complex phenomenon such as cognition [24].

2.1.2. Neuropathology

The type and anatomic location of the brain pathology have crucial impact on the type of cognitive deficit. Verbal memory deficit is more commonly associated with left-sided TLE and nonverbal or visual memory is typically affected in right temporal seizures [1,2]. Similarly, frontal lobe seizures may induce executive dysfunction (i.e., difficulties with attention and problem solving) or motor uncoordination [25]. However, the extent of the neurocognitive dysfunction in focal epilepsies is usually more widespread. Hermann et al. [26] studied the whole brain and lobar quantitative MRI volumes, and performed comprehensive neuropsychologic testing in 58 patients with uncontrolled TLE. They found widespread anatomic changes, such as decreased total cerebral tissue volume, including both white and gray matter in the frontal, temporal, and parietal areas, as well as increased subarachnoid CSF. These anatomic changes were directly associated with the generalized nature of neuropsychologic abnormalities and poorer cognitive performance [26]. York et al. [27] have shown that patients with typical hippocampal sclerosis have more generalized cognitive impairment than do patients with atypical or tumor-related temporal lobe pathologies. Those with atypical sclerosis are left with more severe nonverbal memory loss following temporal lobectomy.

The degree of hypoperfusion detected in SPECT scans of patients with posttraumatic epilepsy was strongly correlated with irritability, agitation, and disinhibited behavior [20]. In the same group of patients, those who had hypoperfusion in the left posterior temporal lobe also showed verbal memory disturbance [20].

2.1.3. Age at seizure onset

Studies in both humans and animals suggest that immature brain, although resistant to the development of mesial temporal sclerosis (MTS), may develop age-specific functional and anatomic pathologies in the hippocampus [28]. Patients with childhood-onset TLE have reduced total white matter volume associated with poorer cognitive status [29]. On the other hand, there is evidence suggesting that patients with childhood-onset left TLE have less chance of developing postepileptic surgery dysnomia, possibly because of intrahemispheric reorganization of language earlier in life that provides some protective benefits [30]. Upton and Thompson [31] have shown that motor skills are not impaired in childhood-onset right frontal lobe epilepsy compared with lesions incurred at a later age within the same hemisphere. This selective preservation of function was not seen in the left hemisphere. These findings suggest that different pathologies at different ages of epilepsy onset and during different stages of development may induce different types of neuropsychologic impairments [31]. Children with age of seizure onset <5 years have lower IQ regardless of the type of seizures, while those with age of onset >5 years show more behavioral problems than cognitive deficits [9].

2.1.4. Seizure frequency

Evaluation of the effects of seizure frequency independent from effects of duration or severity of epilepsy may not be feasible. However, there is convincing evidence showing that higher frequency and duration of TLE are associated with more severe hippocampal atrophy and cognitive deficiency, possibly through secondary neuronal metabolic and structural deterioration [32–35]. Generalized cognitive impairment with global decline in attention, memory, and general intelligence is

more likely to be seen with increasing seizure frequency and epilepsy duration [36]. Seizure frequency has also been reported as among the most relevant determinants of poor QoL scores in chronic epilepsy [37].

2.1.5. Seizure duration

Development of hippocampal sclerosis (HS) and atrophy in patients with chronic TLE has been correlated with age at seizure onset, epilepsy duration, and a history of atypical and prolonged febrile seizures. Theodore et al. [35] examined MRIs of 35 patients with refractory TLE and found a significant correlation between the duration of TLE, history of febrile seizures, and severity of HS. However, the age at onset was not predictive of HS [35]. Comparing patients with unilateral TLE of >30 years' duration to those with 15–30 years' duration, Jokeit and Ebner [34] showed that psychometric intelligence of patients with longer duration of refractory TLE were more severely impaired.

2.1.6. Seizure severity

Status epilepticus and prolonged or repetitive seizures may induce permanent neuronal injury and result in neurocognitive damage. However, this issue requires further evaluation as some authors have correlated the development of mental deterioration with repeated "convulsive" seizures or status epilepticus only [9,32,38,39].

2.1.7. Intra- and interictal dysfunction

Brief disruption of cognitive and behavioral function as a presentation of interictal epileptiform activity has been well described [9]. It has been reported in up to 50% of patients with subclinical epileptiform activity and even in patients during single spike discharges. While these effects can be shown during tests involving attention, verbal (left-sided focal spiking), or nonverbal (right-sided focal spiking) functions, their impact on psychosocial function in daily life is not clear [18,40].

2.1.8. Structural cerebral damage

Brain abnormalities that are present prior to seizure onset may have detrimental cognitive and behavioral effects depending on location and the type of lesion. On the other hand, seizures can induce structural damage that may in turn cause cognitive deficits. However, the relative role of the above factors is unclear. Whether hippocampal sclerosis is the result of an initial insult, such as head trauma, ischemia, or status epilepticus leading to TLE, or is induced by the habitual seizures once epilepsy has developed, is still a matter of debate. Experiments in animal models support the notion that early life seizures can induce structural and physiologic changes in the developing neural circuits that may, in turn, result in permanent changes presenting as neurocognitive derangement and chronic seizures [41].

2.2. Psychosocial factors

A variety of psychosocial problems associated with epilepsy can give rise to, or exacerbate, cognitive and behavioral dysfunction. Although the true incidence and prevalence of morbid psychologic disturbances in epileptic patients are not clear, they are more common in patients with epilepsy than in the general population. The most common forms of psychologic morbidity in these patients are depression, anxiety, psychosis, and attention deficit disorder [8,42]. The incidence of depression and suicide is four to five times higher in epilepsy patients as compared with the general population [42]. A recent study suggested that depression contributed more to poor QoL than did ongoing seizure activity [8,42]. Health-related quality of life (HRQoL) in patients with psychogenic nonepileptic seizures is lower than in epilepsy patients. It has been shown that psychiatric history, depression, and mood disturbance are more common in the former group and that they have a lower HRQoL than epilepsy patients. Mood problems are a strong predictor of low HRQoL that may explain the lower HRQoL in nonepileptic seizure patients compared with those with epilepsy [43].

Findings of bilateral inferior frontal hypometabolism in PET [44] and left hemispheric hypometabolism in PET and SPECT studies in patients with partial epilepsy and interictal depression are suggestive of a biologic basis for depression [45]. These two conditions may share a common pathogenic mechanism. This hypothesis is supported by data from animal models of epilepsy showing decreased serotonin, norepinephrine, dopamine, and GABA activity that facilitates the kindling process of seizure foci and is blocked by antidepressant drugs [45]. Higher incidences of depression have also been observed in patients whose seizure focus is of limbic origin [46]. Episodic emotional changes, like fear, anxiety, and aggression, may also occur in association with seizure discharges [47,48].

More recently, epilepsy patients taking levetiracetam have been reported to have an overall lower incidence of behavioral side effects compared with those treated with other AEDs. However, when compared with patients with cognitive or anxiety disorders treated with levetiracetam, the epilepsy patients had a higher incidence of behavioral side effects. The authors concluded that some features related to epilepsy per se rather than a specific AED might be the cause of behavioral events in these patients [49].

2.3. Treatment-related factors

Although cognitive and behavioral side effects of epilepsy have been known for a long time, new therapeutic interventions, such as pharmacotherapy and epilepsy surgery, are also associated with cognitive and

behavioral effects. These treatments may have both negative and positive effects on cognition and behavior. Seizure reduction may improve cognition and behavior, although it may be somewhat counteracted by inducing changes in the underlying neurochemical systems that control thinking and mood. Appropriate management of AED therapy can minimize side effects of the AEDs, and potential cognitive deficits after epilepsy surgery can be minimized by tailoring the resection to the individual patient's condition. We review the neurocognitive side effects of the currently available therapeutic antiepileptic modalities, i.e., AEDs, epilepsy surgery, and vagal nerve stimulation.

2.3.1. AED-related cognitive and behavioral morbidity

By virtue of their mechanism of action, AEDs decrease neuronal excitability and, therefore, suppress epileptiform discharges. However, as they exert their effects indiscriminately, other neuronal networks that maintain normal neurocognitive functions may also become affected. Strategies, such as avoiding unnecessary polytherapy, using the lowest effective dose of a single AED, keeping drug levels within therapeutic ranges, and slow up-titration, have been associated with fewer cognitive side effects [6,50,51]. In particular, for patients with disabilities, such as developmental delay, it is advised to avoid sedative side effects of AEDs that might further diminish QoL [52]. While these guidelines should be respected, in individual cases of refractory epilepsy, seizure control may not be achieved without using polytherapy and/or epilepsy surgery, even with their untoward side effects.

Reducing seizure frequency and intensity may, however, offset the negative cognitive effects of the drugs [6,53]. Thus, a balance of seizure control and side effects must be sought for each patient. Reducing the number and dosage of AEDs has been associated with improved cognition, the latter being true primarily when the anticonvulsant level is above the standard therapeutic range. Adverse cognitive and behavioral effects are most common with some of the older drugs, i.e., barbiturates and benzodiazepines, while data regarding other first-generation AEDs, carbamazepine, phenytoin, and valproate, have been somewhat controversial. We review the methodologic limitations that may contribute to this variability. The side effect profiles of the newer AEDs are not fully established yet [53].

2.3.1.1. First-line (older) AEDs. Older AEDs have been studied extensively for their cognitive effects. Meador et al. compared the cognitive effects of carbamazepine and phenytoin and found no differences, while there was evidence of worse cognitive performance on phenobarbital [54]. Dodrill and Troupin found similar results, i.e., no cognitive differences between carbamazepine and phenytoin after controlling the data for AED blood levels [55]. Barbiturates and benzodiazepines seem to have the worst cognitive profiles, including decreased arousal and deterioration in most areas of cognitive performance [56].

When following the aforementioned standard practice guidelines, such as avoiding polytherapy, carbamazepine, phenytoin, and valproate show only modest and almost similar effects on cognition. Cognitive components that have been measured in such studies include motor speed, attention, response accuracy, and memory. Treatment with valproate improved IQ scores in epileptic children after a 9- to 12-month interval [57]. This study did not show the same effect in those treated with phenobarbital, and long-term phenobarbital therapy induced a significant impairment in learning ability [57].

In a double-blind, randomized, crossover, monotherapy study in healthy volunteers, Meador et al. examined the effects of several AEDs and found no overall differences comparing carbamazepine with phenytoin [58,59]. However, 52% of the variables were statistically significantly worse on AEDs compared with the nondrug conditions [58,59]. The same investigators compared phenobarbital, phenytoin, and valproate and found that 32% of the variables were statistically significantly worse for phenobarbital compared with the other two drugs. Compared with the nondrug conditions, 55% of the variables were worse on AEDs. The authors concluded that there were greater untoward cognitive effects for phenobarbital but no clinically significant differences between carbamazepine, phenytoin, and valproate [56].

Compared with acute doses of over-the-counter antihistamines, carbamazepine, phenytoin, and valproate appear to exert fewer side effects when given for several weeks, to allow some habituation [6]. Nevertheless, in certain circumstances, such as during neurodevelopment or highly demanding tasks, this effect might have greater consequences [6]. In patients involved in educational activities or professions that require focused attention or learning, even modest effects can have serious impacts on patients' lives. It is advised that clinicians focus on improving patients' cognition initially by achieving better seizure control, as it may offset some untoward effects of AEDs [8].

Cognitive effects of carbamazepine, phenobarbital, phenytoin, and primidone in patients with new-onset epilepsy were compared in a parallel study by the Veterans Administration Cooperative Study (VACS) group [60]. There was no consistent pattern across AEDs, and little change in cognition from pre- to postAED treatment conditions was found [60]. Another study by the VACS group found no cognitive differences between carbamazepine and valproate [6]. However, design limitations in these studies may have obscured differences. Further studies have found modest, negative cognitive effects for carbamazepine and phenytoin despite few

differential effects [61,62]. In a study that examined neuropsychologic performance of patients with epilepsy over a 5-year period, Dodrill addressed the role of duration of treatment on cognitive side effects [6]. Patients were on stable phenytoin monotherapy, phenytoin with other AEDs, or AED regimens exclusive of phenytoin, and no differences were found in cognitive performance over time [6].

Some of the older AEDs are known to have positive effects in psychiatric disorders. Valproate has been used to treat obsessive–compulsive disorder and to prevent panic attacks. Carbamazepine and valproate are in use as mood stabilizers in bipolar disorder and may be helpful for managing impulse control [63]. Benzodiazepines and barbiturates may help anxiety and insomnia, but they can result in adverse psychotropic effects, such as hyperactivity, irritability, and depression [8].

2.3.1.2. New-generation AEDs. These drugs have been marketed since the early 1990s and have raised hopes of achieving optimal seizure control while minimizing the untoward side effects of older AEDs. Although their cognitive and behavioral side effects have not been comprehensively studied as yet, preliminary data suggest more favorable side effect profiles for several of the new-generation AEDs. Some have been shown to have positive psychotropic effects; for example, gabapentin may promote a general sense of well-being regardless of seizure control and, therefore, might be used in treating mood disturbance [64]. Lamotrigine can be used as an effective maintenance treatment in bipolar disorder, particularly to prevent depression [65].

Felbamate. Although it is still in limited use because of its potential hepatic and hematologic side effects, there are no formal data on felbamate's cognitive effects. Anecdotal reports of felbamate-induced insomnia as well as its alerting effect require further investigation [6].

Gabapentin. Gabapentin is a well-tolerated, nonenzyme-inducing AED that has minimal interaction with other medications. Gabapentin does not interact with the hepatic metabolism of other AEDs or psychotropic agents. While being well tolerated, it also significantly reduces seizure frequency in mentally retarded children [52]. However, it has been associated with a reversible behavioral syndrome in children consisting of tantrums, aggression directed toward others, hyperactivity, and defiance [66]. In a randomized, double-blind, parallel-group study of gabapentin and carbamazepine in healthy volunteers, only prolonged use of carbamazepine induced greater EEG slowing and cognitive complaints [67]. A large, double-blind, parallel-group study with dose conversion to gabapentin monotherapy revealed no cognitive changes in patients with epilepsy compared with the control group, while there were positive changes in adjustment and mood [68]. Other studies comparing gabapentin with placebo have reported inconsistent results, including significantly more drowsiness [6].

In a double-blind, randomized, crossover-design study, Meador et al. directly compared the cognitive effects of carbamazepine and gabapentin in healthy subjects [69]. Treatment with gabapentin showed significantly better performance on 26% of the variables compared with carbamazepine. Although both drugs produced some untoward effects compared with nondrug controls, gabapentin produced significantly fewer cognitive effects compared with carbamazepine [69]. Using attention/vigilance, psychomotor speed, motor speed, verbal and visual memory tests, Martin et al. compared gabapentin and carbamazepine in a group of senior adults [70]. Both AEDs induced comparable and mild cognitive effects compared with the nondrug condition, with a better overall tolerability and side effect profile for gabapentin [70].

Mortimore et al. [71] studied the effect of gabapentin on cognition and QoL in epilepsy using a controlled pre- and posttreatment design. They found no adverse short-term effects of gabapentin on cognition or QoL in patients with chronic epilepsy [71].

Lamotrigine. Aldenkamp and Baker [72] have reviewed lamotrigine monotherapy and add-on clinical studies to evaluate the impact of lamotrigine therapy on cognitive functioning. The data suggested an equivalent or superior cognitive effect for lamotrigine, with its possible secondary effect on the QoL [72]. In a double-blind, single-dummy, parallel-group study comparing the cognitive and mood effects of low-dose lamotrigine versus valproate and placebo in healthy volunteers, the investigators aimed at differentiating the mood effects of lamotrigine from those of better seizure control. Lamotrigine showed a "mood activating" property and improved cognitive activation on simple reaction time measurements compared with placebo and valproate, as well as a more positive subjective report about the impact of the drug [73].

In patients with epilepsy, the cognitive effects of lamotrigine have not been different from those of placebo based on a limited neuropsychologic test battery [74]. In other studies that involved healthy adults, lamotrigine had fewer cognitive side effects compared with carbamazepine, phenytoin, and diazepam [75,76]. Meador et al. directly compared the cognitive and behavioral effects of carbamazepine and lamotrigine in 25 healthy adults using a double-blind, randomized, crossover design with two 10-week treatment periods [77]. The neuropsychologic test battery included 40 variables. The test results showed significantly better performance on more than half of the variables (e.g., cognitive speed, memory, mood factors, sedation, perception of cognitive performance, and other QoL perceptions) for lamotrigine compared with carbamazepine [77].

In assessing QoL measures, the beneficial effects of lamotrigine compared with both placebo and carbamazepine have been shown by patients' perception of psychologic well-being [6]. Lamotrigine is also used as an effective maintenance treatment for bipolar disorder, in particular to prevent depression [65].

Investigations of lamotrigine in the developmentally disabled population have indicated seizure reduction rates of up to 50% in some trials. It is usually well tolerated in this population; however, its pharmacokinetics may be influenced by other AEDs [52]. More recently, Brown et al. studied the effects of 12 weeks of open-label lamotrigine treatment on negative mood and cognition changes in patients receiving corticosteroids and found a significant improvement [78].

Levetiracetam. This AED with a novel mechanism of action, approved in the United States as adjunctive therapy for partial epilepsies, has an overall favorable side effect profile. A water-soluble, nonenzyme-inducing AED with minimal protein binding, it does not cause any pharmacokinetic interactions. A small preliminary study by Neyens et al. showed no significant changes in cognitive performances in levetiracetam-treated patients with chronic epilepsy [79]. However, the study was single-blind with only 10 patients and without a control group. In normal and amygdala-kindled rats, valproate, clonazepam, and carbamazepine, but not levetiracetam at proper therapeutic doses, reduce cognitive (learning) performance [80].

Cramer et al. reviewed behavioral side effects in adult patients taking levetiracetam in a series of short-term, placebo-controlled studies in epilepsy, cognitive or anxiety disorders, and epilepsy patients observed in long-term trials [49]. Compared with other AEDs, epilepsy patients on levetiracetam had a lower incidence of behavioral events. However, these patients had a higher incidence of such side effects compared with levetiracetam-treated patients with cognitive or anxiety disorders. It is possible that behavioral findings in these patients are caused by the seizure disorder itself rather than the AED [49]. However, Kossoff et al. reported an acute reversible syndrome in children consisting of visual or auditory hallucinations, insomnia, agitation, hyperreligiosity, and screaming behavior which developed within days to months of initiation of levetiracetam. It has been suggested that slow titration and low initial dose might prevent such untoward effects [81].

Oxcarbazepine. Oxcarbazepine is a homolog of carbamazepine with fewer drug interactions that is appropriate for use in epilepsy, and it is also used in neuropathic pain conditions and bipolar disorders. It is slightly better tolerated than carbamazepine, phenytoin, and valproate. A double-blind, low-dose, crossover study with healthy volunteers comparing oxcarbazepine to placebo indicated that oxcarbazepine improved performance on a focused attention task and on manual writing speed [82]. It had a slight stimulant effect on some aspects of psychomotor functioning and improved feelings of alertness, with no effect on long-term memory [82]. However, the low dose limits generalization to epilepsy patients. In contrast, a small randomized, double-blind, parallel-group, monotherapy study of patients with new-onset epilepsy showed no cognitive differences between oxcarbazepine and phenytoin [83].

Tiagabine. A GABA reuptake inhibitor, tiagabine increases the availability of this major inhibitory neurotransmitter. It is extensively protein bound and is, therefore, subject to displacement interactions by other protein-bound drugs. Despite reports of nervousness, difficulty with concentration, depressive mood, and language problems [84], there were no reports of major cognitive effects during large randomized, double-blind, placebo-controlled, parallel-group, add-on studies [6]. No significant cognitive effects were reported in a large randomized, double-blind, placebo-controlled, parallel-group, dose–response, add-on study in patients with epilepsy [85]. It is advised to titrate the dose slowly and take it with food to avoid rapid increases in drug level and to reduce the risk of side effects.

Topiramate. Topiramate, a broad-spectrum AED approved as adjunctive therapy for partial and primary generalized tonic–clonic seizures, has been associated with language problems, somnolence, psychomotor slowing, and difficulty with memory, particularly at higher doses or with a rapid titration rate. Following such findings during double-blind, placebo-controlled, multicenter trials, a postmarketing antiepileptic drug survey prospectively collected standardized data forms before and during treatment with topiramate for epilepsy. The results showed that psychomotor slowing was the most common complaint, but the majority of patients chose to continue the drug and experienced both a global improvement and better seizure control [86].

Martin et al. compared gabapentin, lamotrigine, and topiramate in 17 healthy volunteers by using a single-blind, randomized, parallel-group study design. The topiramate group developed selective, statistically significant declines on measures of attention and word fluency at acute doses at 1 month of treatment. The gabapentin and lamotrigine groups had no performance changes. This finding might have been affected by the faster than currently recommended titration rate for topiramate [6,87]. Topiramate appears to be particularly effective in patients with Lennox–Gastaut syndrome and in those with cognitive disabilities. It also seems to be better tolerated in developmentally disabled patients [52]. More recently, topiramate has been used for its mood-stabilizing properties and for promoting weight loss and affecting satiety. It has been used in treating binge eating disorder [88].

Comparing the cognitive effects of (slowly up-titrated) topiramate and valproate as add-on therapy with carbamazepine, Aldenkamp et al. found that only short-term verbal memory was significantly worse with topiramate after a long-term maintenance phase [89]. Using a moderate dose-escalation rate and higher target doses of the same medications in a similarly designed study, Meador et al. found significant differences on 2 of 24 variables (i.e., Symbol Digit Modalities Test and Controlled Word Association) compared with valproate at the end of the maintenance phase [88]. In both of the above studies, the cognitive side effects for topiramate were greater at the end of titration than at the end of maintenance [90].

Vigabatrin. A GABA transaminase inhibitor, vigabatrin was developed in the mid-1980s and has been in use in other countries. There were reports of white matter cyst formation in rats and reports of visual field defects in patients. Vigabatrin has not been approved for clinical use in the United States. It has been extensively studied for its cognitive effects. It has been reported to produce few adverse effects on cognition or QoL compared with placebo [6,91,92]. In another study, vigabatrin added at a dose of 2 g/day to patients' existing AEDs appeared to have no negative impact on attention, mental speed, motor speed, central cognitive processing, and perceptuomotor performance [93]. Controlled clinical trials with vigabatrin have shown serious cognitive and behavioral side effects, such as depression and psychosis, in 3.4% of adult patients, particularly those with severe epilepsy or a history of psychosis, but other studies have not shown a greater risk from the drug than from other AEDs [6,94].

Zonisamide. Zonisamide has been reported to affect cognitive functions, such as acquisition and consolidation of new data, including verbal learning but not visual-perceptual learning or psychomotor function. However, patients may develop tolerance to the adverse cognitive effects [95]. It has been effective in the developmentally disabled population by achieving a seizure reduction of 50% in 41% of children studied [52]. Additional studies are needed to further delineate its cognitive and behavioral effects.

The known effects of AEDs on cognitive function and the relative effects of AEDs that have been studied in direct comparative (head-to-head) trials are summarized in Table 1. Epilepsy treatment may offset cognitive and behavioral impairments by stopping or decreasing seizures. However, AEDs may also induce untoward effects. Strategies to minimize cognitive side effects include selecting those agents known to have the least liability for causing cognitive impairment, using the lowest AED dose possible, using AED monotherapy if possible, and avoiding pharmacokinetic drug–drug interactions [96].

2.3.2. Epilepsy surgery

The laterality and locality of the resection influence deficits following epilepsy surgery. The most common epilepsy surgery is temporal lobectomy. Typically, left-sided temporal lobectomy induces verbal memory and learning deficits, while right-sided resections are associated with visual–spatial memory and cognitive declines; however, the changes are more consistent in left-sided resections. It appears the potential deficits are affected by the degree of seizure control, level of functioning, and duration of seizure prior to surgery [97]. A large study has shown that the risk of postsurgical verbal memory deficits after standard anterior temporal lobectomy (ATL) is increased in patients who have higher preoperative scores, in older patients, and in left-sided resection [98]. Patients without hippocampal atrophy and sclerosis are at greater cognitive risk following ATL. Resection of a nonatrophic hippocampus was associated with poorer verbal/visual memory (left ATL) and visual–spatial learning deficits (right ATL) [99]. Other factors that may predict cognitive deficits after ATL include Wada memory asymmetries [100] and preoperative asymmetry in temporal lobe metabolism, as evidenced by PET [101].

In a recent longitudinal study, Rausch et al. [10] showed both early and late postoperative memory

Table 1
Summary of effects of AEDs on cognition and relative cognitive effects of AEDs observed in direct comparative studies

Effects of AEDs on cognition	Relative effects of AEDs
• Effects of most AEDs are relatively modest.	• Carbamazepine is similar to phenytoin.
• Polypharmacy and high AED doses/blood levels increase risk for cognitive impairment.	• Phenytoin is similar to valproate.
• AED-associated cognitive impairment is clinically significant in some patients	• Phenobarbital has a worse side effect profile than carbamazepine, phenytoin, and valproate.
• AED-associated cognitive impairment may, in part, be offset by reduced seizures.	• Gabapentin has a better side effect profile than carbamazepine.
• Attention and vigilance are impaired.	• Lamotrigine has a better side effect profile than carbamazepine.
• Psychomotor speed is impaired.	• Topiramate (if dosed correctly) is slightly worse than valproate.
• These are secondary effects on other domains of cognitive function (e.g., memory).	

Source. Adapted, with permission, from Meador [96].

decline in patients with en bloc left temporal lobe resection. While nonmemory scores remained stable over an average follow-up period of 12.8 years, further decreases in verbal as well as visual memory were evident. An initial high memory score and left-sided resection were predictors of verbal memory deficit early after surgery. Higher 1-year postoperative scores were predictors of late memory declines. Despite the possibility of memory loss caused by chronic seizures or aging, patients with left temporal lobectomy may be at risk for a more rapid decline in selective verbal memory skills. Better long-term QoL was associated with both improved seizure control and a better verbal memory skill [10].

Helmstaedter et al. explored the effect of surgery on verbal learning and memory in two groups of elderly epilepsy patients who underwent either selective left-sided amygdalohippocampectomy or anterior two-thirds temporal lobectomy. The results confirmed worsening of verbal learning and memory in both groups, particularly in temporal lobectomy patients. The investigators emphasized the importance of considering memory prognosis in older patients given that the negative outcome might accelerate lifetime memory decline [102].

Temporal lobectomy in pediatric age groups may improve QoL during the first year after surgery with only mild cognitive effects, e.g., some decrease in delayed verbal memory [103]. However, another study reported significant language-related cognitive declines after left temporal lobectomy in children before the age of 16 years. While the right temporal lobectomy group did not have significant declines, the lobectomy patients had deficits in verbal learning (most common), verbal IQ, naming, and reading comprehension, leading to declines in educational performance. As noted before, average or high preoperative functioning was suggested as a predisposing factor for postoperative deficits in these children [104].

2.3.3. VNS-related factors

Several studies have shown no or mild cognitive and behavioral improvement following vagus nerve stimulation (VNS). This may be related to a better seizure control or to other unknown central mechanisms that affect brain functioning. A single-arm, follow-up study showed no changes in attention, motor, short-term memory, learning, and executive functions at 6 months [105]. Findings of another study suggested significant improvement in mood and possibly depression but not in level of HRQoL at 6 months of follow-up [106]. VNS may also improve mental functioning, behavior, and mood in children with Lennox-like syndrome independently of seizure control [107]. A longer-term follow-up at 24 months of treatment with VNS did not show any negative effects on mood, behavior, cognition, or QoL [108].

3. Clinical presentation and evaluation of cognitive and behavioral dysfunction in epilepsy

Cognitive dysfunction includes deficits in one or more of the following areas: attention, perception, concept formation, reading, thought process, learning, memory, and problem solving. Clinical complaints reported by the patients or their families usually include difficulty with word finding, short-term memory problems, difficulty concentrating, inability to study and learn, slowing of mental activity, and grammatical and paraphrasic errors [109,110]. Only a comprehensive neuropsychologic evaluation may be able to assess patients' problems and detect some of the subtle deficits in these areas. For example, the correlation between neuropsychologic measures and subjective memory complaints in epilepsy patients is weak, as they may reflect depression rather than actual memory impairment [111]. Behavioral difficulties that are most commonly seen in epilepsy consist of depression, anxiety, a wide range of emotional disorders (agitation and irritability, aggression, hyperactivity, decreased attention span or inattention, autistic disorder, attention deficit hyperactivity disorder [ADHD], distractibility, mood lability, neuroticism), and psychosis. Epilepsy patients are four to five times more likely to suffer from depression and suicide compared with the general population. Depression may contribute more to poor QoL than seizures per se. Different types of QoL scales are available for different age groups and cover physical, psychologic, social, and academic functioning [17,42,112].

As there is no agreement on the timing or circumstances in which neuropsychologic testing should be performed, an evaluation plan needs to be tailored to the individual patient. For example, it is believed that the need for early identification of learning and mental health problems in children mandates early testing. This evaluation should include measurements of intelligence, academic skills, attention, and memory skills (working memory, retrieval, consolidation, and recognition skills) as well as depression, anxiety, and symptoms of possible ADHD [113,114]. The effects of cognitive and behavioral dysfunction in the extreme age groups, their effects on QoL, and available therapeutic interventions are discussed below.

3.1. AED effects in utero

Before further studies clarify the exact effect of in utero exposure to each and every AED, these drugs should be considered of potential harm to fetal neurocognitive development. However, the risks due to seizures usually outweigh the side effects of AEDs. Furthermore, the great majority of children born to women who took AEDs during pregnancy are normal. Neurodevelopment is influenced by a series of variables,

such as the type of AED, occurrence of seizures during pregnancy, type of seizure, heredity, maternal age and parity, and socioeconomic status. The relative magnitudes of the effect of these variables have yet to be established. For example, there is evidence that both AED polytherapy and (frequent) seizures per se increase the chance of damage to the developing brain. However, avoiding polytherapy may not be possible in some patients with refractory seizures, as exacerbating seizures may pose a greater risk to the fetus. It is advised to use monotherapy at the lowest effective dose along with folate and multivitamins during pregnancy. There is evidence from animal experiments suggesting neuronal deficits secondary to in utero phenobarbital exposure, and behavioral abnormalities (e.g., impaired motor coordination and learning) following phenytoin exposure [6,115]. Similar reports exist on the effects of AEDs in humans [116]. One study suggested that exposure to phenytoin but not to carbamazepine during early development may have negative effects on neurobehavioral development [60]; however, design flaws leave this finding in doubt. In utero exposure to phenobarbital may have long-term deleterious effects on cognitive performance [117].

Investigations of functional development of children born to mothers taking AEDs have not been able to clearly identify the AED(s) that increase the risks of birth defects and neurodevelopmental deficits [6,53]. Recently Mawer et al. monitored developmental delay and structural anomalies in children exposed in utero to valproate or carbamazepine and found a positive association between severe adverse outcome and valproate at doses more than 1000 mg/day but not with carbamazepine [118]. Another study suggests a higher risk of developmental problems in children exposed to valproate in utero: these children had a markedly higher incidence of additional educational needs compared with children exposed to other antiepileptic drugs in utero [119].

4. Cognitive dysfunction in children and adolescents with epilepsy

Children with epilepsy are about five times more prone to behavioral and other mental health impairments, such as depression, anxiety, and attention problems. They are also 2.5 times more likely to suffer from a psychiatric disorder than are children with other diseases that do not involve the CNS [17]. Except for those with neurologic abnormalities, children with epilepsy have the same IQ distribution as the general pediatric population. Children with epilepsy have a higher risk of learning disabilities and academic weakness. It has been suggested that even in the absence of ADHD, children with epilepsy are at risk for attention problems. This, in turn, may affect encoding of new information leading to memory problems. However, it is likely that retrieval of consolidated memory is affected independently in epilepsy [4]. In fact it is postulated that the higher rate of behavioral problems in children with epilepsy is also independent of the seizures and possibly secondary to a common abnormality [17,120]. About one-third of children with epilepsy have been found to suffer from ADHD, mostly of inattentive type, suggesting attention disorders may be the most frequent behavioral problem in this group [114].

The additive effects of medications on the underlying cognitive and behavioral problems constitute a special risk for children during neurodevelopment. This notion has been supported by data from animal studies showing subtle deficits in behavior and cognition induced by seizures early in life, even in the absence of gross neuronal damage [8,121]. These studies suggest that early seizures can induce permanent deficits in cognitive function and increase seizure susceptibility by changing the developing neural circuits, which emphasizes the importance of early intervention in this age group. More importantly, the behavioral and cognitive deficits may not be detectable for a long time while imposing their detrimental effects on a youngster's development [41,121]. This again emphasizes the importance of early neuropsychologic testing of children with epilepsy [113].

5. Cognitive dysfunction in the elderly with epilepsy

Although this issue has not been thoroughly studied in the elderly, the whole spectrum of neurocognitive side effects of epilepsy appear in this age group, perhaps with more deleterious effects. Elderly patients are more susceptible to the cognitive effects of AEDs for pharmacokinetic and pharmacodynamic reasons. Studies have shown increased susceptibility of the elderly to untoward cognitive effects of benzodiazepines. However, one study comparing phenytoin with valproate and comparing both AEDs with nondrug baselines showed minimal differences in cognitive effects of AEDs in the elderly with epilepsy [6,8,113].

6. Effect on outcomes and QoL

Assessment of outcome after treating epilepsy is a major component of epileptologists' overall treatment plans. HRQoL questionnaires have been used to study the effects of chronic illnesses and how they interfere with patients' day-to-day life [4]. These measures have been studied in both medically and surgically treated epilepsy patients. Such trials have consistently shown the detrimental effects of epilepsy, both independent from treatment and affected by the therapeutic interventions, more commonly the AEDs [122]. HRQoL

outcome in TLE patients treated with ATL was compared with that of similar patients who did not have surgery. Markand et al. [123] showed significant improvement in overall QoL, emotional well-being, attention/concentration, language, social isolation, health perception, role limitations—physical, work/drive/social—health discouragement, and seizure worry. Follow-up studies showed that this improvement was a continual process, as it was significantly improved after 2 years compared with the first year [123].

Gilliam [124] studied the effect of ATL for refractory epilepsy on patients' concerns of living with epilepsy and HRQoL following surgery. The patients reported better HRQoL and less concern of living with epilepsy compared with a similar group of patients who were waiting for surgery. Mood status, employment, driving, and discontinuation of AEDs, rather than seizure-free status or IQ, were the important postoperative predictors of HRQoL [122]. Gilliam also demonstrated that depression and AED side effects have greater impacts on the perceived quality of life in patients with epilepsy than does seizure frequency [124]. Response to VNS in terms of improvement in HRQoL has been unclear. There has been little or no difference in HRQoL between responders and nonresponders, as both groups report improvements after 3 months of VNS [125,126].

The Side Effect and Life Satisfaction Inventory (SEALS) has shown that patients taking two or more AEDs have lower SEALS scores than those taking only one [126]. Polytherapy with vigabatrin and one other AED resulted in lower scores than did lamotrigine and one other AED. SEALS scores significantly improved after a 4-week, double-blind trial of lamotrigine but became worse in those taking carbamazepine. These scores were even lower in patients who dropped out of the study because of side effects of carbamazepine than in patients who continued the drug [127].

7. Methodologic pitfalls of cognitive dysfunction in epilepsy research

Cognitive dysfunction in epilepsy is a multifactorial symptom. Identifying the exact contributing factor(s) in individual cases is difficult. Seizures, the underlying neuropathology, and the treatment(s), most notably AED therapy, each could be a culprit. Furthermore, in studying such side effects, selection bias, neuropsychologic tests used, study design, and statistical shortcoming (i.e., sample size) come into play. Neuropsychologic testing is the usual method for objective evaluation of cognitive changes related to medical or surgical treatment of epilepsy. Brunbech and Sabers have reviewed the methodologic pitfalls in clinical trials examining the cognitive effects of new AEDs [128]. These studies have enrolled different groups including healthy volunteers, refractory seizure patients, newly diagnosed patients, and different age groups of different cognitive status. Sample sizes in these studies are usually not large enough for a statistically reliable conclusion, and the study designs are not always ideal, i.e., randomized, double-blind, placebo-controlled monotherapy in seizure-free patients retested following several months of stable treatment. Inconsistency of the batteries of neuropsychologic tests, with their limited coverage of different aspects of cognitive dysfunction, adds to the inaccuracy of the results. Although we have some knowledge, such reviews conclude that, currently, there remains uncertainty regarding the degree and relative cognitive effects of AEDs [128,129].

Inventories for measuring effects of AEDs on cognition and behavior clearly need to be standardized. Baker and Marson reviewed the neuropsychologic and behavioral measures used in 46 randomized, controlled trials to assess cognitive and behavioral effects of AED therapy in epilepsy patients [130]. They found inconsistency in test selection, reliability, validity, and sensitivity to change accompanied by poor reporting and diversity of neuropsychologic and behavioral measures. The authors found it difficult to draw accurate conclusions from these studies and suggested development of a more standardized approach to assessing these effects [130].

8. Recognition and treatment of cognitive dysfunction in epilepsy

The traditional approach to ameliorate the cognitive side effects of epilepsy is based on controlling the seizures, choosing AEDs that best control seizures with minimal cognitive side effects, avoiding polypharmacy, and treating any associated depression or other mood disorders. Despite the potential adverse effects of pharmacotherapy, achieving complete or acceptable seizure control using AEDs should be the initial approach to treat cognitive side effects of epilepsy. The beneficial effect of reducing seizures may offset the adverse cognitive effects [6,19,111,131].

The presence of overlapping variables complicates a targeted management of cognitive deficits. Therefore, direct treatment of the cognitive side effects of epilepsy has rarely been attempted. Recently, pharmacologic interventions have gained some attention. Donepezil, an anticholinesterase inhibitor, at 5–10 mg, improved memory but not attention, visual sequencing, mental flexibility, psychomotor speed, or QoL in 18 patients with epilepsy [132]. Improvement in memory was not related to changes in attention. The drug was well tolerated except for dizziness and mild gastrointestinal complaints [132]. An open-label, nonrandomized, 3-month study using the stimulant drug methylphenidate (MPH) in adult patients on multiple AEDs for partial

epilepsy resulted in improved cognition and QoL and relief from sedation with no increase in seizure frequency [133]. There are mixed reports on the effects of VNS on cognition in epileptic patients. Antidepressants, herbal supplements, and nonpharmacologic approaches have been tried to treat cognitive deficits in epilepsy [111].

Psychopharmacology may be another option to treat behavioral problems in patients with seizures, but this should not substitute for the attempts to control the seizures or to treat any underlying conditions [19]. Despite the controversial possibility of decreasing the seizure threshold, tricyclic antidepressants and serotonin reuptake inhibitors (SSRIs) are used successfully to treat depression and anxiety in patients with epilepsy. Some SSRIs (fluoxetine, paroxetine, fluvoxamine, and, to a lesser degree, sertraline) are inhibitors of the cytochrome P450 enzyme system, which, in turn, may increase phenytoin, carbamazepine, and valproate levels. Haloperidol has little effect on seizure threshold, but antipsychotic agents, such as chlorpromazine and clozapine, are not recommended for use in children with psychosis due to possibly increased risk of seizures [45,112]. However, clozapine has been reported not to clinically affect seizure threshold. Langosch and Trimble treated six children with epilepsy and severe psychosis with clozapine with no increase in seizures in three of them and substantial reduction in the other three [134].

It is important not to discourage epilepsy patients from living normal lives as much as possible. A randomized, controlled study showed the positive effects of moderate exercise in these patients. After a 12-week period, there was an improvement in their overall quality of life and no negative effect on seizure control [135].

9. Conclusion

Cognitive and behavioral deficits are more common in patients with epilepsy than in the general population. These deficits are multifactorial in etiology, ranging from biologic factors, such as the type of seizures, neuropathology, or age of onset, to a variety of psychosocial problems and, in particular, therapeutic interventions that may adversely affect epilepsy patients. The neurocognitive burden of epilepsy may even start before birth through in utero exposure to AEDs. Although epilepsy per se may cause or exacerbate an underlying cognitive impairment, the underlying etiology is commonly a major contributing factor. While treating epilepsy is necessary and by itself may resolve or alleviate the cognitive and behavioral deficits of the disease, it may also be associated with its own side effects. The major therapeutic modalities (i.e., AEDs and epilepsy surgery) are associated with cognitive and behavioral risks. While the majority of such dysfunctions are reversible, some are not remediable or even avoidable. Currently, there are no effective treatments available for cognitive deficits of epilepsy. Therefore, treatment of epilepsy must be tailored to the individual patient with the potential risks in mind. Treating physicians should be aware of these risks and the contributing factors to avoid or minimize negative consequences. Of particular importance are AEDs and their potential cognitive and behavioral side effects. In patients with medically refractory epilepsy, a meticulous and comprehensive presurgical evaluation can predict and reduce the cognitive and behavioral risks of epilepsy surgery.

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