REVIEW

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The Aspects and Mechanisms of Cognitive Alterations in Epilepsy: The Role of Antiepileptic Medications

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Epilepsy is a major health problem. Several studies suggest a significant influence of epilepsy and its treatment on dynamic and functional properties of brain activity. Epilepsy can adversely affect mental development, cognition, and behavior. Epileptic patients may experience reduced intelligence, attention, and problems in memory, language, and frontal executive functions. Neuropsychological, functional, and quantitative neuroimaging studies revealed that epilepsy affect the brain as a whole. Mechanisms of epilepsy-related cognitive dysfunction are poorly delineated. Cognitive deficits with epilepsy may be transient, persistent, or progressive. Transient disruption of cognitive encoding processes may occur with paroxysmal focal or generalized epileptic discharges, whereas epileptogenesis-related neuronal plasticity, reorganization, sprouting, and impairment of cellular metabolism are fundamental determinants for progressive cognitive deterioration. Also antiepileptic drugs (AEDs) have differential, reversible, and sometimes cumulative cognitive adverse consequences. AEDs not only reduce neuronal irritability but also may impair neuronal excitability, neurotransmitter release, enzymes, and factors critical for information processing and memory. The present article serves as an overview of recent studies in adult and childhood epilepsy literatures present in PubMed that highlighted cognitive evaluation in epilepsy field (publications till 2008 were checked). We also checked the reference lists of the retrieved studies for additional reports of relevant studies, in addition to our experience in this field. Our search revealed that although the aspects of cognitive dysfunction, risk factors, and consequences have been explored in many studies; however, the mechanisms of contribution of epilepsy-related variables, including AEDs, to patients' cognition are largely unexplored. In this review, we discussed the differential effect of AEDs in mature and immature brains and the known mechanisms underlying epilepsy and AEDs adverse effects on cognition. The nature, timing, course, and mechanisms of cognitive alteration with epilepsy and its medications are of considerable clinical and research implications.

Introduction

Epilepsy is a common dynamic neurological disorder with an estimated prevalence of approximately 1% [1]. In clinical practice, while managing patients with epilepsy, most neurologists aim to stop seizures by selecting specific antiepileptic medication(s) depending on clinical experience. However, epilepsy is a complex condition. Seizures are only one aspect of epilepsy. Patients with epilepsy may experience medical, metabolic [2,3], neuroendocrinal [4] as well as cognitive and behavioral problems [5,6], which may have deleterious impact on their overall lives.

Cognitive comorbidity associated with epilepsy is confirmed in clinical [7], experimental [8], pathological [9], psychological [10], physiological [11], and imaging

studies [12]. Epileptic patients may experience problems in various cognitive domains such as reduced intelligence, attention, problems in memory, language, and frontal executive functions [5], despite the side or site of lesion [13].

The association between epilepsy and poor cognitive performance, learning, and long-term memory is correlated with a number of invariant as well as dynamic variables. The invariant variables include genetics, basic brain lesion [14], site and side of structural brain lesion [15], and age at onset [16], together with the duration of epilepsy [17]. The dynamic variables include seizure frequency [18], ictal as well as interictal transient focal or long-lasting electroencephalographic (EEG) epileptic discharges [19,20], adverse effects from antiepileptic medications [21] or surgical intervention [22], and psychosocial variables [23,24].

The potential for antiepileptic drugs (AEDs) to adversely impact cognition is of significant concern as they are the major therapeutic modality for control of seizures. The effects of conventional AEDs on cognition are better studied compared with newer AEDs [25,26]. However, several recent reports have suggested that newer AEDs (such as lamotrigine [LTG], gabapentin [GBP], and levetricetam [LEV]) have fewer adverse effects on cognition than do conventional and other newer AEDs [27–29].

Although the nature or pattern of cognitive abnormalities associated with different epilepsy variables has been explored in several studies; however, a complete understanding of the culprit mechanisms of this association is still a matter of research. Mostly, some of the mechanisms of medication-related cognitive deficits have been explored based on animal studies, with no similar or parallel studies in humans [30,31]. Ongoing research studies are aiming for a further understanding of the pathophysiologic mechanisms underlying cognitive deficits related to epilepsy and its variables. This should include the need for future well-designed, long-term, parallel animal and human outcome studies that are directed to assess cognitive and behavioral performances associated with new as well as conventional AEDs. Special emphasis should also be directed to determine the difference in effect between immature and mature brains. Exploring the mechanisms of cognitive deficits frequently encountered in patients with epilepsy is an important issue for future clinical, psychological, and management recommendations as well as planning of academic and research strategies.

Data in this review were collected through an extensive PubMed search, looking for studies in adult and childhood epilepsy literatures that highlighted cognitive evaluation using these words: epilepsy and cognition, antiepileptic drugs, and cognition and neuronal plasticity in epilepsy (publications till 2008 were checked). We also checked the reference lists of the retrieved studies for additional reports of relevant studies, in addition to our experience in this field [2–4,6]. This review evaluated and summarized recent studies encompassing the main aspects of cognitive alterations in adult and childhood epilepsy. We tried to provide a clear overview of the role of epilepsy itself and the contribution of its variables including antiepileptic medications in the development of cognitive deficits. The differential effect of AEDs and the known mechanisms underlying their adverse effects on cognition were summarized. The vulnerability of immature brains to the cognitive adverse consequences of epilepsy itself and its medications were also discussed.

Cognitive Aspects in Epilepsy

Cognitive function is defined as the ability to deal meaningfully with information from the surrounding world. It includes mental activities associated with thinking, learning, and memory. It is a mental process of acquiring knowledge including aspects like awareness, perception, reasoning, and judgment [32]. Patients with epilepsy are at an increased risk for cognitive deficits. Memory difficulty is the most frequent subjective complaint in patients with epilepsy and is also identified by objective measures. The vulnerable neuropsychologically affected areas are attention, short-term memory, and cognitive information processing [33]. In addition, the changes in EEG peak frequency observed in quantitative occipital EEG are correlated with subjective cognitive complaints [34]. Also, the P300 component of event-related potential (ERP) is impaired in patients with epilepsy and correlates with the degree of cognitive impairment encountered in neuropsychological testing [11]. P300 is considered as a "cognitive" neuroelectrical phenomenon because it is generated in psychological tasks when subjects attend and discriminate stimuli that differ from one another on some dimensions. P300 is an objective, noninvasive, and clinically relevant method for evaluation of mental processing. P300 latency increases as the dementia symptoms increase, whereas P300 amplitude is depressed in all levels of dementia [35]. The hippocampus, thalamus, and frontal cortex are the possible locations of the P300 generators, the structures important for learning and memory.

The cognitive aspects of epilepsy will be discussed within the context of (1) its relation to invariant and dynamic variables, (2) the pathophysiologic mechanisms underlying cognitive impairment in epilepsy, and (3) The vulnerability of immature brain to the cognitive adverse consequences of epilepsy.

Relationship of Cognition to Invariant and Dynamic Variables in Epilepsy

Determining the frequency of cognitive dysfunction due to epilepsy is difficult to estimate. Community-based studies reported that approximately 26.4–30.0% of children with epilepsy when first diagnosed have evidence of subnormal global cognitive function or mental retardation with inferior academic achievement [10]. Problems in attention and memory are observed in about 30% of newly diagnosed and untreated epileptic patients with single or several seizures of cryptogenic origin [36].

Cognitive issues in epilepsy are associated with a number of invariant and dynamic factors. The invariant variables include genetics, basic brain lesion [14], type of epilepsy [37], site and side of brain lesion [15,18,37,38], etiology of epilepsy [36], and age at onset [16,30,39,40], together with the duration of epilepsy [17]. The dynamic variables include uncontrolled seizures in epileptic mother [41], seizure frequency and severity [17], ictal as well as interictal transient focal or long-lasting electroencephalographic (EEG) epileptic discharges [19,20], adverse effects from antiepileptic medications [21], and psychosocial variables [23,24]. In some patients with epilepsy, many of these factors are intercorrelated and independently contributed, making it difficult to clearly delineate the relative contribution of any given factor (e.g., cognitive deficits in epilepsy occur regardless of patients' age, type, and duration of epilepsy or associated diseases).

The limited studies suggest that the offspring of mothers with epilepsy may have an increased risk of problems including prematurity, low birth weight, brain malformation, dysmorphic features, and cognitive deficits [42,43]. Hereditary predisposition to abnormal brain activity has been accounted for 30–50% of phenotypic IQ variance of children born to mothers with epilepsy [44,45]. Koch et al. [42] found abnormal spike activity in children born to mothers with epilepsy. The case reports clearly documented that maternal prolonged seizures and status epilepticus (SE) are serious hazards for both the mother and the fetus; however, the results of cohort studies, in which mainly mothers with generalized tonic–clonic seizures (GTCS) were included, were controversial [46,47]. Adab et al. [41] in their retrospective study found that verbal IQ in children of women with epilepsy was greatly affected by the number of seizures experienced during pregnancy, with significant reduction in IQ being observed in children (17% of all) who were exposed to more than four GTCS. Uncontrolled maternal GTCS increase the risk of fetal perinatal anoxia, placental abruption, premature labor, intracranial hemorrhage, or even death. These risks are high if seizures progress to SE. In addition, the offspring of mothers of epilepsy are exposed to teratogenicity from AEDs [45] and the adverse socio-familial conditions associated with having a chronically ill mother [48].

Cognitive and behavioral functioning in patients with epilepsy is an important area in various age groups. The earlier studies reported that seizure onset before the age of 14 years is a risk factor for cognitive decline. In controlled studies, significant neuropsychological impairment has been demonstrated in children and adolescents with chronic epilepsy [39]. However, recent studies indicated that negative effect on cognition, even progressive cognitive deterioration, might occur in older adults with chronic partial or generalized seizure disorders. In some studies, adults with epilepsy and prior to treatment with AED exhibited poor performance on some cognitive tasks, especially tests of visual motor tasks, motor coordination, mental flexibility, and memory [40,49]. Epilepsy could possibly accelerate common age-associated changes, leading to uncertain and understudied outcome in old age [49].

Some studies found greater cognitive problems in patients with generalized seizures than in patients with partial seizures [50]; others found it *vice versa* [51]. Complaints of memory difficulties are common among patients with temporal lobe epilepsy (TLE), where memory-related brain structures are directly involved in seizure activity. TLE is associated with more memory impairments than extratemporal epilepsies, and both have more memory impairments than those associated with generalized epilepsy [38,52]. Frontal lobe epilepsy is associated with performance deficits in executive functioning [53]. However, most recent case–control and longitudinal studies revealed that patients with generalized as well as localization-related epilepsies may develop poor performance on tests of memory function, as well as on measures of intelligence, language, and executive functions, suggesting that cognitive dysfunction is not limited to limbic-related tasks presented in the hippocampus, amygdala, or piriform cortex but extends to involve diverse brain areas [54–56].

The nature and localization of epilepsy are also important determinants of the extent and nature of cognitive deficits. Patients with secondarily generalized seizures showed greater impairment in concentration and mental flexibility than patients with complex partial seizures [15]. Problems of delayed recall of words were observed in newly diagnosed patients with partial seizures prior to medication [35]. TLE is associated with cognitive decline in confrontational naming, visual memory, verbal memory, and motor speed [39]. TLE affects declarative memory systems (i.e., episodic memory including contextual, autobiographic information, and semantic memory including abstract knowledge) [57], whereas

nondeclarative learning (e.g., procedural learning) appears more or less unaffected. Episodic memory relies on hippocampal functioning [57]. Semantic performance is definitely linked to speech-dominant hemisphere because it is expressed by speech-associated tasks (e.g., semantic fluency, naming, and vocabulary). Verbal-oriented problems are specifically involved in left-sided epileptogenic foci. Left TLE especially impairs verbal episodic memory (e.g., word list learning), long-term verbal associations, learning of semantically related verbal information, speed of learning, and delayed memory, with deficits in consolidation of verbal information [39]. Visuoconstructive memory dysfunction has been found in patients with right TLE [38]. Silva et al. [52] found that epileptic patients with mesial temporal injuries had a low cognitive performance in attentional span, memory, speech, and daily problems resolution, whereas patients without injury showed a more compensated cognitive performance, except mild attentional alterations.

Some cross-sectional cohort studies reported association of cognitive deficits with smaller hippocampal volume in TLE [58]. Hippocampal volume reduction has been linked with the longer duration of epilepsy and is considered a marker as well as a predictor of cognitive decline in patients with epilepsy. However, recent quantitative magnetic resonance imaging (MRI) volumetric studies confirmed the presence of volumetric abnormalities in both temporal and extratemporal regions, consistent with the generalized cognitive compromise associated with early-onset localization-related epilepsy syndromes such as TLE. The abnormalities were identified in amygdale, fornix, entorhinal cortex, parahippocampus [58], thalamus and basal ganglia [57], cerebellum [56], and whole brain volumes [59]. Hermann et al. [59] reported reduction in total cerebral white matter volume, increased total CSF, and reduced gray matter volume, both ipsilateral and contralateral to the side of temporal seizure onset. In a prospective study done by Liu et al. [60], a longitudinal follow-up study of 122 patients with chronic epilepsy, in which serial MRI scans were obtained 3.5 years apart, new focal or generalized neocortical volume loses were identified in 54% of patients with chronic epilepsy and 39% of newly diagnosed patients. Seidenberg et al. [61] reported bilateral thalamic volume reduction in chronic unilateral TLE. Thalamic atrophy was significantly correlated with performance in memory and non-memory cognitive domains. Rzezak et al. [13] found frontal lobe dysfunction in children with TLE, with worse performance in those with mesial TLE, early onset, longer duration of disease, and use of polytherapy. The authors suggested that temporal lobe epileptogenic activity affects the extratemporal regions that mediate attentional and executive functions. Guimarães et al. [62] did a comprehensive neuropsychological assessment in a population of children with TLE including IQ, forward digit, Trail-Making Test For Children part B, Wisconsin Card Sorting Test, block design, Boston naming test, verbal fluency, and Wide Range Assessment of Memory and Learning, including visual learning, verbal memory, visual memory, delayed recall of verbal learning, delayed recall of stories, and recognition of stories. The authors found that TLE presented with several neuropsychological deficits, despite normal IQ. The authors concluded that dysfunction of cerebral areas other than temporal lobe, particularly the frontal lobes, might be present in TLE. In support, generalized reduction of cerebral volume has also been observed in children with mixed seizures, as well as focal temporal and frontal lobe epilepsy, which are proportionately associated with delayed neurodevelopment [63]. The extensive networks and interconnections between cortical regions are considered a contributing factor for the demonstrated widespread and remote cerebral atrophy from the putative epileptic focus. Functional MRI studies revealed that retrieval from working memory is associated with activation of dorsolateral frontal cortex. Other cortical and thalamic brain areas are also activated including the anterior cingulate cortex, which is associated with executive function, and the posterior parietal cortex, which is associated with attention [64]. The results of volumetric quantitative MRI studies are in accordance with generalized reduction in neurospsychological function including intelligence, language, visuoperception, memory, and executive function in the same group of the studied patients [59].

Cross-sectional and longitudinal studies of cognitive change in epilepsy suggest that a longer duration of epilepsy is associated with decline in many areas of cognition [17]. Cognitive impairments are more prevalent in symptomatic and cryptogenic compared with idiopathic epilepsy [36].

Mood state in epileptic patients may be an additional factor that negatively affects cognitive functions. Epileptic patients who are depressed may suffer a double burden of cognitive deficits [65]. Seizures occurring at school or work can result in poor self-perception and reduced social interaction. Stigma resulting from epilepsy and learning problems may lower the parental and teacher expectations. Decreased expectations can negatively affect the academic effort and consequently the performance. Scholastic underachievement, intellectual impairment, lower educational levels, and potential mental retardation are the long-term consequences in children with epilepsy, whereas low functional status, less educational levels, low rates of employment, and poor quality of life (QOL) are the long-term consequences in adults with epilepsy [23,24].

The Pathophysiologic Mechanisms Underlying Cognitive Impairment in Epilepsy

The mechanism of cognitive impairment in epilepsy is complex. Negative effects on cognition may occur in the presence or absence of clinically manifest seizures, convulsive or nonconvulsive SE that occur during awakening or during sleep, and may occur due to focal or generalized EEG epileptic discharges without epileptic symptomatology [37]. Cognitive deficits associated with epilepsy and EEG epileptic discharges may be transient [66,67], persistent [68], or progressive [6,69].

The underlying pathophysiologic mechanisms of cognitive dysfunction due to epilepsy itself will be discussed under the following topics: (1) cognitive impairment with ictal or clinically manifest EEG paroxysms, (2) cognitive impairment with brief interictal or subclinical EEG paroxysms, (3) cognitive impairment with long-lasting EEG activity, and (4) progressive cognitive deterioration in epilepsy.

Cognitive Impairment with Ictal or Clinically Manifest EEG Paroxysms

Three interrelated forms of memory impairment have been recently described in association with manifest seizures [67]: (1) transient epileptic amnesia, in which the main manifestation of seizures is recurrent episodes of amnesia; (2) accelerated long-term forgetting, in which newly acquired memories fade over days to weeks, and (3) remote memory impairment, in which there is loss of memories for personal or public facts or events from the distant past. Accelerated long-term forgetting and remote memory impairment are common with transient epileptic amnesia in patients with TLE, but have also been reported in other forms of epilepsy.

With manifest epilepsy and during paroxysmal epileptic activity, transient disruption of cognitive processing has been attributed to the following: (1) the involvement of a neuronal circuitry in epileptic spiking, rendering the same neurons unavailable for normal physiological processes, (2) antidromic corticothtalmic backfiring, which would collide and annihilate any incoming information through orthodromic thalamocortical pathways, and (3) prolonged membrane hyperpolarization following paroxysmal depolarization shift mediated by recurrent postsynaptic inhibitory mechanisms that elelctrophysiologically correspond to the after-coming slow wave [33,70]. The presence of slow EEG activity in the same regions showing abundant spike wave has been interpreted as reflecting increased cortical inhibition mediated by hypersynchronous GABAergic inhibitory postsynaptic potentials. This increment of cortical inhibition might temporarily alter normal physiological processing of cognitive disruptions [71]. High seizure frequency disrupts the first encoding state of the memory process and specifically disrupts attention, concentration, and working memory. However, in individual cognitive performance, even single seizures can generate long-term attentional slowing in the post-ictal period, which exists for at least 24 hours. A singleGTCS may have a lasting negative effect on attention for about 30 days [50].

Cognitive Impairment with Brief Interictal Subclinical EEG Paroxysms

The phenomenon of association between transient cognitive deficits and transient EEG epileptiform (generalized or focal) discharges that are not accompanied by obvious clinical events is defined as a state of transient cognitive impairment (TCI) [66]. It is found in about 50% of patients and is regarded as subclinical or interictal [72]. These brief subclinical EEG paroxysms or TCI may cause deficits that usually pass unrecognized by standard memory tests; however, sensitive methods of observation, such as continuous psychological testing, commonly show brief episodes of impaired cognitive function during such discharges. TCI was first demonstrated during 3 cycles/second generalized spike-and-wave discharges [66]. Sirén et al. [73] found that the duration of generalized 3-Hz spike-wave discharges and the clinical absence of seizures were negatively correlated with the performance on the visual memory tasks. TCI was also demonstrated in many cases of benign childhood epilepsy with centrotemporal spikes, a disorder once thought to have no adverse psychological effects [20]. TCI is not simple inattention. The effects of TCI are material and site specific, that is, lateralized discharges are associated with deficits of functions mediated by the hemisphere in which the discharges occur (e.g., left-sided focal spiking frequently produces errors in verbal tasks, whereas right-sided discharges are often accompanied by impairment in handling nonverbal material). Conversely, specific tasks can activate or suppress focal discharges over the brain regions that mediate the cognitive activity in question. In patients with benign childhood epilepsy with centrotemporal spikes, deficits in IQ were found to be significantly correlated with the frequency of EEG spikes but not with the frequency of seizures [74]. Autistic features observed in come children with epilepsy have been suggested as a consequence of apparently subclinical spikes interfering with specific cerebral processes [75].

The studies pointed out that TCI may contribute to abnormalities in psychological test profiles that adversely affect the patient's psychosocial functioning in daily life such as educational skill, learning tasks, disorders of attention, behavior, sleep disruption, and motor

dysfunction [37]. An important practical issue is to determine whether patients with TCI have impaired psychosocial function, and if so, whether drug treatment is desirable or effective. Together with our personal experience in the field, uncontrolled reports and some preliminary randomized controlled trials of antiepileptic treatment of TCI have suggested that suppression of discharges by AEDs is associated with significant improvement in psychosocial function [20].

Cognitive Impairment with Long-Lasting EEG Activity

Recently, the mechanism of cognitive impairment of some specific epileptic syndromes with continuous spikes and waves during sleep (CSWS) has been explored [68]. Landau–Kleffner syndrome (LKS) and the syndrome of CSWS represent a spectrum of epileptic conditions that share many common features including: (1) onset during childhood, (2) deterioration of cognitive functions that were normally acquired in the past, (3) continuous spike-and-wave discharges during slow wave sleep, (4) pharmacological reactivity, (5) regression of the neuropsychological symptoms when the EEG abnormalities improves (spontaneously or after drugs such as corticosteroids), and (6) the absence of obvious structural lesion detected by CT or MRI scan [76,77]. The cognitive deficits of children with CSWS are long lasting, present for months or years, and complete recovery is unusual. The pathophysiology of cognitive deficits CSWS and LKF is complex and different from that described with TCI as some patients with CSWS or LKS may have a completely normal awake EEG, whereas cognitive deficits are present in the awake state when interictal epileptiform discharges are rare or absent. Recently, positron emission tomography (PET) studies using [18F]-fluorodeoxyglucose (FDG) during acute and recovery phases of CSWS in a group of children with epilepsy showed that increased glucose metabolism at the epileptic focus was associated with hypometabolism in distant connected areas and both hypermetabolism and hypometabolism resolved at the recovery phase of CSWS [78,79]. An altered effective connectivity between focal hypermetabolism (centroparietal regions and right fusiform gyrus) and widespread hypometabolism (prefrontal and orbitofrontal cortices, temporal lobes, left parietal cortex, precuneus, and cerebellum) was found at the acute phase of CSWS, and it markedly regressed at recovery, whether spontaneously or with corticosteroids [79]. The parietofrontal altered connectivity observed in patients with hypermetabolism is interpreted as a phenomenon of remote inhibition of the frontal lobes induced by highly epileptogenic and hypermetabolic posterior cortex [78].

Progressive Cognitive Deterioration in Epilepsy

Many animal and human studies reported progressive cognitive decline and behavioral impairment in developing and mature brains with epilepsy [6,39,69,80]. Persistent and progressive cognitive dysfunctions are the result of progressive structural brain damage as a long-term consequence of uncontrolled epilepsy, for example, hippocampal sclerosis in complex partial and generalized epilepsy [39,69]. In TLE, a specific stereotypical pattern of pathology occurs in the hippocampus, amygdale, entorhinal region, piriform cortex, and mesdiodorsal thalamus, the areas primarily involved in memory processing. In complex partial and generalized epilepsy, a characteristic pattern of hippocampal sclerosis occurs [9]. Loss of neural density in the left mesial temporal regions (i.e., CA3 of the hippocampus) and right hippocampal structures can explain the verbal and nonverbal memory impairments in patients with epilepsy [81]. The progressive damaging effect of epilepsy is also confirmed by neuroimaging follow-up studies. A growing number of multiparametric MRI follow-up and prospective longitudinal imaging studies in TLE indicate that progressive atrophy after the first SE evolves over a prolonged period of time, weeks, months, or even years, in the hippocampus, amygdala, thalamus, and piriform cortex [82]. Using quantitative MRI, Briellmann et al. [12] reported a hippocampal volume loss by almost 10% in 24 patients with mild TLE studied over a period of 3.5 years. Fuerst et al. [69] reported hippocampal volume loss in 12 patients with intractable TLE studied over 3.5 years. Liu et al. [60] reported progressive cortical volume loss in patients with neocortical epilepsy. Repeated seizures in kindling models of limbic epilepsy induce a sequence of complex activity-dependent neurodegenerative changes including neuronal synchronization, abnormal neuronal plasticity, sprouting, gliosis, and delayed hippocampal neurodegeneration. This type of neuronal plasticity or persistent epileptogenesis may then contribute to the appearance of adverse cumulative neurological deficits involving learning, memory, emotional, and behavioral changes as the number of seizures increases [6]. Animal studies have shown that behavioral changes are in parallel to the changes in brain connectivity, dendritic morphology, excitatory and inhibitory receptor subunits, ion channels, and neurogenesis. Human neuropsychological studies indicate that hippocampal N-methyl-D-aspartate (NMDA) receptors are necessary for mediating repetition/recognition effects of limbic ERPs to continuous word recognition paradigms as well as for intact verbal memory performance [83]. These changes occur even in the absence of overt cell loss. Recent studies revealed that abnormalities in intracellular

functions of specific neurons occur after exposure to multiple seizures [80]. Unfortunately, the current AEDs are unable to prevent progressive brain damage due to epileptogenesis.

The Vulnerability of Immature Brain to the Cognitive Adverse Consequences of Epilepsy

Normally, biological development and organization of the brain in human are very rapid *in utero* and start to slow down in the second year of postnatal life [84]. Although the gross organization is nearly complete by 2 or 3 years of age, maturation may continue through adolescence and beyond [85]. The period of infancy is characterized by peak hippocampal and cortical regional development, as well as myelinogenesis, dendritogenesis, and synaptogenesis in the brain, and changes in these processes underlie the deficits in spatial learning and memory processes [86]. Many of the human studies on cognition and behavior have focused on infants, preschool, and school-age children. There is a developmental component to the relation between poor seizure control and mental performance. The presence of epilepsy and its treatment during a period of maximal white-matter growth could affect the development of white matter. The studies examined the effects of electroconvulsion-induced seizures in rats at various developmental stages that revealed that seizures in early development selectively impaired myelin accumulation in proportion to their effect on brain growth [87]. It was found that some myelin specific lipids (such as cerebroside and proteolipid protein) were reduced by about 11–13% in immature epileptic rats [88]. Executive functions, mainly under frontal lobe control, seem to be particularly vulnerable to epileptic EEG activity during the period of maturation; their disruption possibly interferes with the normal development of learning processes [89]. Adults rats experiencing kainic acid (KA)-induced seizures on specific days during early postnatal development revealed the presence of a long-term loss of hippocampal plasticity, as manifested by a reduced capacity in long-term potentiation (LTP), which has been suggested to underlie memory formation, reduced susceptibility to kindling, and impaired special learning. Seizure activity incrementally causes an indiscriminate and widespread induction of LTP, consuming and reducing the overall hippocampal plasticity available for information processing [90].

Clinical and Research Implications

Many evidences suggest that chronic epilepsy is associated with a cumulative neurobiological burden, which is detrimental to both cognition and QOL. Epilepsy *per se* and its related variables may induce or exacerbate an underlying cognitive impairment. Even static cognitive impairment in children and adolescents with epilepsy may have lifespan implications. Research in the general population has shown that a lower childhood intelligence level at age 11 is associated with the risk of adverse cognitive outcome decades later [91]. The nature, timing, and course of cognitive progression with epilepsy are of considerable concern and have important clinical and research implications as follows:

(1) Comprehensive pretreatment evaluation and judicious management of all factors that contribute to cognition, behavior, and educational problems in epilepsy are essential for optimal outcome.
(2) Neurocognitive deficits in children born to mothers with epilepsy may be subtle and may not be identified for years following delivery. In particular, disorders of higher cortical function (such as memory, attention, speech and language, abstract thinking, and executive control) may not manifest themselves until the child reaches grade school [41]. Some learning deficits may not be apparent until the teenage years. Relying solely on IQ is insensitive for assessing cognition. Children of mothers with epilepsy who appear to be functioning within the normal range may reveal specific impairments with careful sensitive neuropsychological tests that require appropriate professional input [47]. This highlights the importance of early identification and proper evaluation. Subtle neurocognitive deficits may induce long-term consequences and significantly reduce the child's likelihood of achieving success in school and eventually reduce employment opportunities.
(3) It has been suggested that the first year of life is a critical period for the subsequent development of intellectual abilities. The development of epilepsy in the first year of life is associated with a high incidence of intellectual impairment (82.4%) [7]. This also highlights the importance of early identification and treatment in this population.
(4) A child with history of seizure presenting with recent-onset impairment in learning needs a very immediate careful evaluation and management.
(5) Old individuals with chronic epilepsy are exposed to additional risk factors that are associated with abnormal cognition, in which many of these risk factors present as early as midlife. It is important to systematically identify and treat known modifiable risk

factors in order to protect and promote cognition in older persons with chronic epilepsy [92].

Cognitive States with Antiepileptic Medications

It is expected that AEDs could improve patients' cognitive functions by controlling the number of overt and subtle epileptic activities as well as by improving the psychosocial environment, which provides additional benefit to cognition. However, the deleterious effect of AEDs on cognition is well documented in epileptic patients and volunteer studies. AEDs of little negative impact on cognition in normal subjects may have detrimental cognitive effects in patients with epilepsy [21,27]. Some patient groups may be at particular risk (e.g., fetus, children, and elderly) [16,39,40,49,93]. These effects sometimes arise even in the therapeutic ranges of the drug. Some parents reported differences in child cognition and behavior after starting therapy such as slowness in response and the child being less talkative or difficulty to control. The major cognitive effects of AEDs are impaired attention, vigilance, and psychomotor speed, but secondary effects on other cognitive functions can be seen. Even in patients who do not report cognitive changes, neuropsychological tests have shown significant impairments [21].

Differential cognitive effects are seen with various AEDs. Carbamazepine (CBZ) [94,95], phenytoin (PHT) [96,97], and valproate (VPA) [26] can adversely affect cognition to a similar extent, which appears to be less than that of barbiturates (PB) and benzodiazepines (BZ) [97,98]. The limited studies done to detect the effect of new AEDs on cognition revealed that new AEDs such as gabapentin (GBP) [99], lamotrigine (LTG) [28], zonisamide (ZNS) [100], and levetiracetam (LEV) [101] have fewer effects on cognition than do older drugs. Topirmate (TPM) reported to have the worst effect on cognition [102]. However, even their modest effects can be clinically significant and impact the patient's QOL. Increased doses of AEDs, rapid initiation, and polytherapy entail an increased risk. In general, the cognitive effects of AEDs are less than the sum total of other factors and are usually reversible. Conversion of polytherapy to monotherapy may consequently improve cognitive functioning [103].

The cognitive states with antiepileptic medications will be discussed within the context of (1) the differential effect of conventional and new antiepileptic medications on cognition, (2) the pathophysiologic mechanisms of cognitive alteration due to AEDs, and (3) the vulnerability of immature brains to the cognitive adverse consequences of AED.

The Differential Effect of Antiepileptic Medications on Cognition

Phenobarbital (PB) and Benzodiazepine (BZ)

Animal and human studies confirmed the deleterious effect of PB and BZ on cognition compared with other conventional and new AEDs [97,98]. The offspring of pregnant mice treated with PB demonstrated more hyperactivity, less rapid habituation, impaired performance in operant behavior [104], impaired performance in repeated acquisition task [8], and a conditioned avoidance task [105], compared with control offspring. Adult rats exposed to PB demonstrated deficits in hippocampal 8-arm maze, spontaneous alternations, and water maze performance [106]. PB and BZ are known to impair cognition in healthy volunteers and patients with epilepsy [21]. Children on PB demonstrated low IQ, which was improved with discontinuation of PB [107]. In the largest prospective study done by Shapiro et al. [97] on a large number of children exposed to PB monotherapy *in utero* (the number of children exposed to PB with mothers of epilepsy was 35, whereas 4,705 of exposed children had mothers without epilepsy) demonstrated that the latter group did not differ from control children with respect to IQ measured at 4 years of age. The study done by Reinisch et al. [98] on 114 male offspring demonstrated that the effect of PB exposure occurred if maternal treatment lasted for at least 10 days during pregnancy. The authors reported reduced verbal IQ scores (~7 IQ points) in two cohorts of men exposed *in utero.* In the study of Farwell et al. [107], the long-term cognitive effects of early postnatal PB exposure was investigated in a randomized, placebo-controlled, blinded study with 217 toddler-aged children having febrile seizures, in which they were randomized to receive either PB (4–5 mg/kg/day) or placebo. The children were examined at age 7, several years after discontinuation of PB; 64% of these children were examined with the Wide Range Achievement Test (WRAT-R) and the Stanford–Binet Intelligence Scale. Compared with the placebo group, PB-exposed children were found to have significantly impaired performance in WRAT-R reading scores but not in the Stanford–Binet Scale. The IQ impairment was most marked after exposure in the third trimester. A high prevalence of developmental delay and irreversible cognitive dysfunction has been identified in children exposed to PB *in utero* [98,108]. Sulzbacher et al. [25] demonstrated that the deleterious effect of long-term use of PB remained several years after drug discontinuation when children were tested for cognition 3–5 years later. This suggests the persistent complex effect of PB on developmental

maturation in addition to interfering with acquired cognitive function.

Phenytoin (PHT)

Several studies provide information about the beneficial effect of PHT on cognition. In support: (1) PHT was reported to prevent stress and corticosterone-induced reductions in CA3 apical dendritic length and branch point numbers [108], (2) PHT may reverse stress-induced impairment of spatial learning and hippocampal atrophy [109], (3) PHT could keep lLTP, an important component of memory, from being inhibited by stress [110], (4) *in vivo*, PHT decreased the dimension of cerebral infarct in animals with bilateral or unilateral carotid occlusion [111], and (5) recently, PHT was found to be associated with increased hippocampal volume in patients with posttraumatic stress disorder (PTSD) assessed by MRI, and this was associated with improvement in hippocampal-based verbal declarative memory function [112].

In contrast, animal and human studies revealed that PHT has shown mild adverse effect on cognition [89,113]. The limited animal studies revealed that PHT resulted in reduced brain weight, impaired startle responses, hyperactivity, altered neuronal membranes in the hippocampus, delayed neurodevelopment, and impaired special memory and motor coordination when given to rats' mothers during pregnancy. The AED-induced dysfunction in rats is related to both the dose and the duration of PHT exposure [114]. Hanson et al. [96] and Shapiro et al. [97] reported that reduced IQ results were (five points lower than that of control children of mothers without epilepsy) for a different cohort on cognition and PHT.

Carbamazepine (CBZ) and Oxcarbazepine (OCBZ)

Several studies demonstrated that CBZ does not compromise and even improves the learning performance of nonepileptic animals in different learning and memory tasks [32,115]. Rostock et al. [115] reported that administration of low doses of CBZ was able to reverse amnesia induced by electroconvulsive shock as well as improve learning during an active avoidance test treated with repeated doses with ethanol. Preclinical studies revealed that CBZ improved memory in passive avoidance tests, T-maze, and Y-maze [116], decreased light discrimination task performance and Y-maze performance in epileptic animals [117], and improved memory, as demonstrated by Morris test after 7–14 days of treatment [118]. *In utero* studies revealed that CBZ monotherapy with serum maternal levels within the reference ranges did not impair intelligence of the exposed children [119]. Most patients treated for a long time with CBZ do not reveal cognitive or memory impairment or compromise procedural memory, provided that the drug concentration is within the therapeutic window. It even improved concentration, mental manipulation, adaptive abilities, discriminative memory, thought of thinking, speed of thinking, and learning in individuals with epilepsy [32].

In contrast, CBZ utilization may be associated with mild cognitive dysfunction including excessive sedation, compromise in attention, concentration, visual motor coordination, and psychomotor slowing [120]. A small risk in learning and memory has been registered especially with high serum concentrations of the drug. Some children are at high risk for developing cognitive side effects due to CBZ [94]. EEG slowing associated with CBZ might be significantly related to the magnitude of cognitive decline on later IQ subset performance [95].

OCBZ is an analog of CBZ, with a comparable anticonvulsant efficacy, but has a better cognitive profile compared with CBZ [121,122]. It shows both neuropsychological impairment and EEG slowing in healthy volunteers [121], but of less magnitude compared with CBZ.

Valproate (VPA)

Although studies revealed that use of VPA is associated with improvement of intellect, alertness, attention, immediate recall, visuosptial functions, cooperation, and better school performance [123]; however, studies in healthy volunteers revealed that VPA may produce a modest but statistically significant cognitive disruption [21]. Previous behavioral studies demonstrated that prenatal VPA exposure decreases locomotor activity and increases swimming maze errors in rats tested by the 8-arm radial maze and passive avoidance test [124]. The studies revealed that children exposed to VPA *in utero* had learning difficulties, behavioral problems, and an increased need for special education [26]. In one large prospective study, increased memory deficits, reduced verbal IQ by 8–15 points, and an excess of additional needs were reported in children exposed to VPA prenatally [41].

Topiramate (TPM)

TPM receives greatest concern among the new AEDs due to its documented worst cognitive profile [125]. Its cognitive adverse events are reported in 10–20% of the subjects [126,127]. The symptoms of cognitive deficits associated with TPM include concentration/attention difficulty, confusion, abnormal thinking, slow thoughts, dull thinking, mental slowing, blunted mental reactions, word-finding difficulties, difficulty calculating and memory

impairment, and decreased cognition. The greatest changes were found in verbal IQ, verbal fluency, verbal learning, and digit span [102]. Martin et al. [27] observed that among healthy young adults, the negative effects of TPM on measures of attention, word fluency, verbal memory, and psychomotor speed were greater than those with LTG and GBP when tested 3 hours after large initial doses, and its effect persisted for 2- and 4-week intervals. Leonard et al. [128] found that motor tasks were affected by TPM, as observed by bimanual sequential tapping. This is one of the motor measures that requires the most cognitive processing, as patients must tap in a different specific sequential order with the two hands simultaneously. The task involves attention, perception, and the capacity to monitor and coordinate out-of-phase movement. Functional MRI and cognitive testing revealed disruption of information processing in the prefrontal cortex and more heterogeneous patterns of cortical activation with TPM [129]. Whether TPM side effects are dose dependent and whether they critically depend on the speed of drug titration are matters of debate [129,130]. It has been suggested that low starting dose, slow upward drug titration, and reduction of polytherapy will control seizures as well as produce tolerance to the drug, with minimal cognitive side effects [102,103,131]. In the longitudinal study done by Thompson et al. [102], the authors demonstrated deterioration in verbal IQ, verbal fluency, and verbal learning following introduction of higher doses of TPM (150–600 mg/day) as adjunctive therapy in patients with epilepsy, with improvement in verbal fluency, verbal learning, and digit span occurring when TPM was reduced or withdrawn. Lee et al. [131] observed improvement in both verbal and nonverbal fluency scores by $\geq$70% after TPM discontinuation. Reife et al. [127] observed psychomotor slowing with lower dosage (200 mg/day) of TPM and language disturbances with higher doses. Kockelmann et al. [130] and Huppertz et al. [132] reported significant improvement in performance on tests of verbal fluency, verbal working memory, spatial short-term memory, and attentional functions after withdrawal of TPM.

In contrast, recent animal studies indicated the neuroprotective effect of TPM on cognition. Zhao and colleagues [133] administered TPM or saline chronically during and following a series of 25 neonatal seizures. After completion of the TPM treatment, rats treated with TPM performed better in the water maze than rats treated with saline. Koh et al. [134] used a ''two-hit'' rodent seizure model to study the therapeutic efficacy of a post-seizure treatment with TPM in reversing the perinatal hypoxia on later KA seizure-induced neuronal damage. The authors observed that repeated administration of TPM given for 48 hours after hypoxia-induced seizures prevented the increased hippocampal neuronal injury induced by KA.

Zonisamide (ZNS)

Studies on the effect of ZNS were limited and controversial. Weatherly et al. [135] reported little cognitive decline in some patients with epilepsy on ZNS as add-on therapy. Recently, Park et al. [100], in a prospective randomized and open-labeled study, observed that after 1 year of starting treatment with ZNS (received as monotherapy in a dose of 100, 200, 300, and 400 mg/day), although ZNS decreased seizure frequency and EEG abnormalities; mood changes and cognitive deficits were observed in 15% and 47% of patients, respectively, and were dose related. Cognitive performance was worse on delayed word recall, Trail-Making Test part B, and verbal fluency.

Gabapentin (GBP)

The good neurophysiological profile of GBP has been observed in animal and human studies. Cilio et al. [136] observed that treatment of KA-induced SE in P35 rats with twice daily doses of GBP resulted in a reduced incidence of spontaneous recurrent seizures, reduced SE-associated hyperactivity, and the absence of performance difference in the water maze compared with saline-treated animals. GBP has a proven good neuropsychological profile, with little or no cognitive impairment in healthy volunteers and patients with epilepsy. Even enhancement of cognition has been reported with utilization of GBP [27,137]. In contrast to CBZ, GBP causes slowing of EEG but does not associate with cognitive effect. The amount of EEG slowing with GBP is less than that with CBZ [138]. However, the possibility of a cumulative cognitive effect from GBP cannot be excluded. GBP may also promote an improved mood and a sense of well-being independent of seizure reduction, and hence improvement of cognitive functions [99,130]. Dimond et al. [139] demonstrated increases in ratings of QOL and well-being when patients were switched to this drug. Harden et al. [99] demonstrated significant reduction in depressive scores on a dysthymia rating scale in patients receiving GBP independent of seizure reduction.

Tiagabine (TGB)

Earlier trials that assessed the cognitive effects of TGB as adjunctive therapy showed that patients receiving TGB at a dose range of 16.0–67.6 mg/day did not experience a decline in cognitive function during an initial titration or extension phase [140]. Dodrill et al. [141] demonstrated a more favorable cognitive profile than with TPM and

improvement in cognition when TGB was combined with PHT. Äikiä et al. [142] suggested that TGB has a modest cognitive profile, which is similar to CBZ.

Vigabatrin (GVG)

The cognitive profile of GVG (γ-vinyl or γ-butyric acid [GABA]) is reportedly good [143]. Some attributed this to its psychotropic effects, such as its utility in treating PTSD [144].

Lamotrigine (LTG)

LTG is proved by some studies to have a good neuropsychological profile, with no effect on cognition in healthy volunteers and patients with epilepsy. [28,145,146]. Pressler et al. [28] in their double-blind, placebo-controlled, cross-over study studied a group of children with well-controlled or mild epilepsy randomly assigned to either LTG followed by placebo or placebo followed by LTG as add-on therapy for a period of 9 weeks for each treatment phase and cross-over period of 5 weeks. The authors found that compared with the placebo group, epileptic children on LTG exhibited no clinically significant difference in continuous performance, binary choice reaction time, verbal and nonverbal recognition, computerized visual searching task, verbal and spatial delayed recognition, and verbal and nonverbal working memory. The author concluded that LTG does not affect cognition. Blum et al. [147] found a better performance with LTG than with TPM when assessing a group of adults having partial epilepsy for cognition using screening Contextualized Writing Assessment (CoWA), Stroop color-word interference, and symbol-digit modalities tests. The beneficial effect of LTG on cognition has been also confirmed with disorders other than epilepsy. Kaye et al. [148] assessed cognition in a group of patients with bipolar I disorder when LTG (200 mg/day) was utilized for 12 weeks, whether or not they were receiving concomitant VPA, antidepressants, or antipsychotics. The authors observed an improvement on self-rated cognitive function scores utilizing self-rated Medical Outcomes Study Cognitive (MOS-Cog) Scale.

Levetiracetam (LEV)

LEV appeared safe and efficacious. LEV does not impair cognitive function in healthy volunteers [120] or patients with epilepsy [101]. Recently, a general subjective and objective cognitive improvement has been noted with LEV in patients with epilepsy. Mandelbaum et al. [149] in their retrospective study done on a group of children with intractable epilepsy (before and after 1 year of LEV administration) observed good-to-excellent seizure control (50–100% reduction) in patients with focal, generalized, and mixed seizures, and this efficacy was independent of cognitive status. Recent studies compared the effect of LEV and TPM as monotherapy [150,151]. In two groups of patients with focal epilepsy, Gomer et al. [150] found that patients on LEV manifested no change in cognitive performance after drug titration, whereas TPM worsened cognitive speed and verbal fluency as well as short-term memory. Helmstaedter and Witt [29] observed cognitive improvement in 58% of 401 patients after introducing LEV as monotherapy or add-on therapy. Zhou et al. [152] evaluated the effect of LEV, as an add-on treatment, on cognitive function and QOL in patients with refractory partial seizures. Their study comprised two phases: (1) a short-term phase (randomized, double-blind, placebo-controlled design) for 8-week baseline period, 4-week titration interval, and 12-week period at the maximum LEV dose (1500 mg twice daily), and (2) a long-term phase (an open-label study) in which the maximum LEV dose was administered for another 24 weeks. After the short-term LEV treatment, performance time on the Wisconsin Card Sorting Test (WCST) and Delayed Logic Memory were significantly improved for the patient but not the control group. Subscale scores on the quality of life in epilepsy-31 (QOLIE-31), including scores on Cognitive Functioning and Social Function, were also improved only for the LEV group. At the end of the long-term phase, these improvements were maintained, and both groups performed better in more areas, as measured by the Trail-Making Test, WCST, and Delayed Visual Memory in the neuropsychological battery and the QOLIE-31 subscales.

The Known and Hypothesized Pathophysiologic Mechanisms of Cognitive Alterations Due to AEDs

In general, the mechanisms of AEDs are to reduce neuronal irritability and increase postsynaptic inhibition or alter synchronization of neural networks to decrease excessive neuronal excitability associated with seizure development and secondary spread of epileptic activity to the surrounding normal brain. AEDs modulate brain activity through their action on voltage-dependent ion channels (sodium or Na^+ and low threshold [T-type] calcium or Ca^{2+} channels) and inhibitory (GABA) and excitatory neurotransmitters and their receptors [153]. Slowed motor and psychomotor speeds and poor attention and memory processing are common side effects of Na^+ channel blockade [154,155], increasing GABAergic inhibitory activity [156], and decreasing neuronal excitability [156]. Table 1 summarizes cognitive deficits

Table 1 Cognitive deficits with AEDs and the suggested mechanisms of their causation

Antiepileptic drugs	Effect on cognition	Mechanism of cognitive impairment
Phenobarbital (PB)	Deleterious negative effect	Direct binding to $GABA_A$/benzodiazepine receptor complexes (GBRs). *In utero* exposure results in widespread neurodegeneration and apoptosis.
Benzodiazepine (BZ)	Deleterious negative effect	Direct binding to GABA/Cl^- channel complex, potent GABA agonists. *In utero* exposure results in widespread neurodegeneration and apoptosis.
Phenytoin (PHT)	Mild negative effect	Sodium channel blockade and control of excitatory synaptic transmission. *In utero* exposure results in neurodegeneration and apoptosis.
Carbamazepine (CBZ)	Mild negative effect	Sodium channel blockade and control excitatory synaptic transmission. No detected effect with *in utero* exposure.
Oxcarbazepine (OCBZ)	Modest negative effect	Its excessive activation of ionotropic glutamate receptors, causing neurodegeneration.
Valproate (VPA)	Modest negative effect	(1) Indirect modulation of GABA neurotransmissions, (2) an enhancement of $GABA_A$ receptor-mediated hyperpolarizing responses will inhibit the activation of NMDA receptors and impairment of LTP and LTD, and (3) VPA has sodium channels blockade activity. *In utero* exposure results in defective neuronal migration.
Gabapentin (GBP)	Little or negligible negative effect	Indirect modulation of GABA neurotransmission. GBP enhances the levels of GABA in the brain and decreases brain glutamate concentration. Its actions include modulation of GABA-synthesizing enzyme, glutamic acid decarboxylase (GAD) and glutamate-synthesizing enzyme, and branched-chain amino acid transaminase.
Vigabatrin (GVG)	Little negative effect	Indirect modulation of GABA neurotransmission. GVG is an AED that elevates brain GABA several folds by irreversibly inhibiting the GABA-metabolizing enzyme, GABA transaminase. *In utero* exposure results in defective neuronal migration.
Topiramate (TPM)	Deleterious negative effect	(1) Increasing GABAergic inhibitory activity on the brain, (2) its inhibitory effect on carbonic anhydrase isoenzymes II and IV, causing increased Mg^{++}-dependent tonic inhibition of NMDA receptors and apoptosis, (3) it has negative modulatory effect on the AMPA/KA subtype of glutamate receptors, and (4) TPM has sodium channel blockage activity. No negative effect has been observed with *in utero* exposure.
Lamotrigine (LTG)	Negligible negative effect	Unknown. No negative effect has been observed with *in utero* exposure.
Tiagabine (TGB)	Negligible negative effect	Indirect modulation of GABA neurotransmission. TGB is selective GABA reuptake inhibitor. It increases synaptic GABA availability via selective inhibition of the GABA transporter-1 (GAT-1).
Levetiracetam (LEV)	Negligible negative effect	Unknown.
Zonisamide (ZNS)	Mild negative effect	Unknown but could be due to its blockage effect on voltage-sensitive Na^+ channels and modulatory effect on GABA-mediated inhibition.

with AEDs and the suggested mechanisms of their causation.

Mechanisms of Deleterious Effect of AEDs on Cognition

In general, the deleterious effect of AEDs on cognition could be attributed to: (1) Na^+ channel blockade, (2) enhanced GABAergic activity, and (3) decrement in glutamate-mediated excitation.

Na^+ channel blockade decreases the release of neurotransmitters including excitatory neurotransmitters and contravenes depolarization by interfering with the propagation of action potentials, that is, limitation of sustained repetitive firing and stabilizing neuronal membranes [154]. In hippocampal neurons, intracellular increased Na^+ increases the probability to open NMDA receptors and thus might control excitatory synaptic transmission [155]. The cognitive side effects of some AEDs have been attributed to their Na^+ channels blockade activity including PHT, CBZ and OCBZ, and VPA [154,156].

Increasing GABAergic brain activity by AEDs results in the re-establishment of the background level of inhibition and helps in the return of the nervous system to its normal balance between excitation and inhibition. Drugs that increase the extracellular levels of brain GABA or mimic GABA transmission are widely used in the treatment of epilepsy in children and adults including

PB, BZ, VPA, GBP, TPM, ZNS, and GVG [153,156]. In general, the mechanisms of enhancing GABA-mediated inhibition are: (1) direct modulation of GABAergic neurotransmission induced by allosteric modulation of GABA receptors through direct binding to the receptors and changing its shape or configuration, hence increasing GABAergic inhibitory neurotransmission and inhibitory postsynaptic potential. PB directly binds to $GABA_A$/benzodiazepine receptor complexes (GBRs), whereas BZ has a unique receptor site on GABA/Cl^- channel complex, and these are potent GABA agonists; and (2) indirect modulation of GABAergic neurotransmission by enhancing synthesis and/or decreasing reuptake of GABA. Drugs that mediate indirect modulation of GABAergic neurotransmission include VPA, GBP, GVG, TGB, TPM, and ZNS. VPA does not directly interact with GABA receptors but increases brain levels of GABA, possibly by enhancing glutamate decarboxylase or inhibiting GABA transaminase [157–159]. GBP is a structural analog of the inhibitory neurotransmitter GABA. Nuclear Magnetic Resonance (NMR) spectroscopy indicates that GBP enhances the levels of GABA in the brain and decreases brain glutamate concentration. Its actions include modulation of GABA-synthesizing enzyme, glutamic acid decarboxylase (GAD) and glutamate-synthesizing enzyme, and branched-chain amino acid transaminase [160]. GVG is an AED that elevates brain GABA several folds by irreversibly inhibiting the GABA-metabolizing enzyme, GABA transaminase [161]. TGB is selective GABA reuptake inhibitor. It induces its effect by increasing synaptic GABA availability via selective inhibition of the GABA transporter-1 (GAT-1) [162]. TPM rapidly raises brain GABA levels [163]. Mental slowing, memory impairment, inattention, and language dysfunction are suggested to be due to increasing GABAergic activity in the prefrontal cortex [164]. Drugs that directly increase GABAergic inhibitory neurotransmission and inhibitory postsynaptic potential such as PB and BZ produce significant disruption of short-term memory and attention [8]. Indirect modulation of GABA neurotransmissions have modest (e.g., VPA) or even little effect on cognition than direct GABA modulation, that is, GBP, GVG, TGB, and LEV have a good neuropsychological profile or little or negligible effect on cognition.

Decrement in glutamate-mediated excitation such as by antagonizing the response mediated by NMDA or α-amino-3-hydroxy-5-methyl-4 isoxazol propionic acid (AMPA)/KA subtype of glutamate receptors is believed to underlie the mechanism of some AEDs as TPM [157, 158]. Slowed motor and psychomotor speeds and poor attention and memory processing are adverse effects of reduced neuronal excitability as well as increased GABAergic inhibitory activity on the brain.

Some AEDs can cause cognitive deficits through multiple mechanisms. VPA modest effect on cognition has been attributed to: (1) indirect modulation of GABA neurotransmissions; (2) an enhancement of $GABA_A$ receptor-mediated hyperpolarizing responses caused by VPA, which will inhibit the activation of NMDA receptors in a dose-related manner [158,165,166]. Its suppressive effect on synaptic response mediated by NMDA receptors may contribute to the impairment of LTP and LTD caused by VPA [167]. Lee et al. [30] reported that VPA suppresses the expression of LTP in the CA1 region of the hippocampal slices. Gean et al. [167] reported that in rat amygdaloid slices, VPA suppresses the response mediated by NMDA receptors in a dose-related manner; and (3) VPA reduces repetitive neuronal firing via blockade of voltage-dependent Na^+ channels [159].

Several mechanisms have been suggested to explain the adverse effect of TPM on cognition. TPM increases cortical GABA notably in the frontal lobes. GABAergic dysfunction in the prefrontal cortex could lead to mental slowing, and subsequent spread of this dysfunction to the dorsolateral areas including Broca's area could underlie impairments of language production with TPM [163]. Clinical studies demonstrated that TPM adverse effects on cognition including impaired concentration and memory, slowed thinking, and word-finding difficulties have been attributed to its inhibitory effect on carbonic anhydrase isoenzymes II and IV, causing increased magnesium-dependent tonic inhibition of NMDA receptors and apoptosis [168]. TPM also has negative modulatory effect on the AMPA/KA subtype of glutamate receptors [157,163]. In addition, TPM blocks Na^+ channels [169].

No studies were done to explore the mechanisms of cognitive deficits observed with ZNS; however, one can speculate that its blockage effect on voltage-sensitive Na^+ channels and modulatory effect on GABA-mediated neurotransmission inhibition may explain the cognitive impairment elicited by ZNS [155].

Mechanisms of the Beneficial Effect of AEDs on Cognition

In general, the beneficial effects of AEDs on cognition could be due to: (1) reduction of seizure activity; (2) modulating effect on neurotransmitters, lowering excitotoxicity associated with a reduction in glutamate release from presynaptic terminals and preventing anoxic depolarization capacities; (3) inhibition of Ca^{2+}-mediated cellular functions (protein phosphorylation and neurotransmitter release) and Ca^{2+}-dependent depolarization; (4) scavenging of free radicals; and (5) their psychotrophic effect.

Drugs that mediate indirect modulation of GABAergic neurotransmission (such as VPA, GBP, GVG, TGB, and

ZNS) by enhanced synthesis and/or decreased reuptake of GABA has modest (VPA)-to-little or negligible effect (GBP, GVG, TGB, and ZNS) on cognition compared with drugs mediating direct modulating effect such as PB and BZ [153,156].

PHT has effect on glutamatergic function that affects brain structure. PHT arrests Ca^{2+}-mediated cellular functions and Ca^{2+}-dependent depolarization, both associated with neuronal death. It blocks cellular responses to excitatory amino acids. PHT antagonizes glutamate-induced excitation of cerebrocortical neurons and blocks the effect of glutamate at NMDA receptors [110–112,170].

CBZ affords significant protection against glutamate neurotoxicity in hippocampal cell cultures and reduces NMDA-mediated brain injury. It inhibits KA-induced Ca^{2+} ion elevation [171]. Ambrósio et al. [171] suggested that, at concentrations that do not cause toxicity, CBZ has a neuroprotective effect on KA-induced toxicity in hippocampal neurons, which is essentially mediated by the activation of AMPA receptors. CBZ increases brain acetylcholine level in the hippocampal structure and simultaneously reduces choline level. The role of cholinergic function in memory and related cognitive processes is well known. Deterioration of cholinergic neurons in the medial septal nucleus that project to the hippocampus, amygdale, and cortex (e.g., critical memory areas) was demonstrated in rat models of epilepsy [172]. In support, acetylcholine esterase inhibitors are shown to improve memory functioning in diverse neurological conditions [173]. The hippocampus, a cerebral structure highly involved in learning and memory, is a target for abundant cholinergic innervation and hippocampal nicotinic acetylcholine receptors that modulate synaptic plasticity via mechanisms involved in LTP [174]. The normothymic effect of CBZ may be related to its impact on the neurotransmitter systems (GABAergic, serotoninergic, noradrenergic, or adenosine) and may additionally demonstrate G-protein- or inositol phosphate-modulating effects [175].

Although, no studies were done to explore the mechanisms of beneficial effect of LTG on cognition; however, the neuroprotective effect of LTG could be attributed to lowering excitotoxicity mainly in the hilus and the CA3 subfield of the hippocampus as well as the piriform cortex [175,176].

The possible mechanisms underlying mechanisms by which LEV improves cognitive function and QOL remain unknown. LEV is postulated to inhibit seizure activity through a totally different mechanism. LEV seems to partially inhibit N-type high-voltage-activated Ca^{2+} currents and reduces the Ca^{2+} release from intraneuronal stores. It also reverses inhibition of GABA- and glycine-gated currents induced by negative allosteric modulators and effects voltage-gated potassium channel conductance. LEV also has a specific stereoselective binding site in the CNS at the synaptic vesicle protein 2A (SV2A) [177]. LEV can reduce neuronal necrosis and maintain LTP in the hippocampus [178], which may also contribute to its effects on cognition. Piracetam and its derivative LEV belong to the pyrrolidine class; drugs in this class can protect against brain insults and have low toxicity [179]. They might enhance the efficacy of higher integration mechanisms in the brain and improve mental function such as learning and memory while protecting against seizures. Piracetam seems to improve learning, memory, and attention [180] and has been used to treat age-related cognitive disturbances and aphasia [181]. Hence, it is reasonable to assume that LEV may also influence the metabolism of some frontal areas, leading to improved cognitive function [101].

ZNS decreases secretion of excitatory amino acids and reduces postanoxic depolarization as well as scavenges free radicals including hydroxyl and nitric oxide radicals, and these effects could attribute to its neuroprotective effect against cognitive impairment [182].

The Vulnerability of Immature Brain to the Cognitive Adverse Consequences of AED

The effects of *in utero* exposure to AEDs are increasingly being investigated and differential drug risk is considered for both anatomic and cognitive outcomes. Although information on the role of fetal and postnatal exposure to AEDs is limited in humans, there is a growing body of information from animals, suggesting that AEDs may have substantial effects on brain development. The pathophysiologic mechanisms responsible for these deficits remain largely unknown; however, there is evidence that AEDs can adversely effect neuronal proliferation and migration and increase apoptosis [183–187].

Normally, neuroblast migration is influenced by crucially promoting signals (motility, acceleratory, and stop signals) from GABA and glutamate neurotransmittors that act on several receptors subtypes ($GABA_A$, $GABA_B$, and NMDA). Neuronal migration may be influenced not only by genetic alterations but also by drug intake. $GABA_A$ agonists are frequently used as sedatives and anticonvulsants in mothers with epilepsy or their offspring. Neuronal migration can adversely be affected by AEDs [183]. Manent and colleagues [183] reported occurrence of hippocampal and cortical dysplasias in rat pups exposed to GVG and VPA *in utero*. The authors found that prenatal exposure to GVG (200 mg/kg/day), and VPA (100 mg/kg/day) from embryonic days 14–19 (in doses that are similar to those used clinically) resulted in neuronal migration defect and neuronal death

observed postnatally in the form of hippocampal and cortical dysplasias. These effects were not found with CBZ (20 mg/kg/day).

There may be a relationship between AED-induced apoptosis and cognitive function. The recent discovery of neuronal apoptosis following *in utero* AED exposure in animals during a period that corresponds to the third trimester and early infancy in humans raises further concerns. Utilization of PB in rat pups results in significant decreases in brain weight and DNA, RNA, protein, and cholesterol concentrations and reduced neuronal number [104,184]. Chronic exposure of cultured mouse spinal cord neurons to PB leads to reduced cell survival and decreased length and number of dendrite branches. Brain concentrations of dopamine and norepinephrine were reduced and the uptake of dopamine, norepinephrine, serotonin, and GABA into synaptosomal preparations of brain tissue was greater for offspring of pregnant mice treated with PB [185]. The studies demonstrate that PHT, PB, BZ, GVG, and VPA cause widespread apoptotic neurodegeneration in the developing rat brain at plasma concentrations relevant for seizure control in humans. In these studies, the drugs were administered to the fetus or rat pup during a period of intense synaptogenesis [186,187]. Jevtovic-Todorovic and colleagues [188] observed widespread apoptotic neurodegeneration and impaired LTP in hippocampal slices obtained from 7-day-old infant rats when they were administered midazolam, nitrous oxide, and isoflurane for a period of 3 weeks. Persistent deficits in memory and learning were demonstrated when the rats were tested subsequently during the Morris water maze or the radial arm maze. In contrast, similar apoptotic effects were not seen at therapeutic dosages for CBZ, LEV, LTG, or TPM in monotherapy dosages [189–191]. However, preliminary results suggest that CBZ, LTG, and TPM, but not LEV, may potentiate cell death when given in combination with proapoptotic agents such as other AEDs.

The apoptotic effect of some AEDs appears to result from reduced neurotrophins and protein kinases, which are important for neuronal survival. Postnatal VPA exposure suppresses the synthesis of the neurotrophins, brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), and reduces the levels of survival-promoting proteins in the brain, which reflected an imbalance between neuroprotective and neurodestructive mechanisms in the brain [186]. Lee et al. [30] found that VPA suppressed protein kinase C (PKC) activity in both membrane and cytosol compartments in hippocampal slices. PKC is highly enriched in the brain and plays a major role in regulating both pre- and postsynaptic aspects of neurotransmission, including neuronal excitability, neurotransmitter release, and long-term alterations in gene expression and plasticity. PKC is critical for the induction of LTP and LTD [192]. There is also evidence from laboratory studies that blockage of NMDA receptors can increase neuronal apoptosis, resulting in chronic behavioral, structural, and molecular effects. Harris et al. [193] studied the long-term consequences of NK-801 (0.5 mg/kg), NMDA antagonist, in a group of rats treated postnatally day 7. The authors observed reduced volume and neuronal number within the hippocampus and altered hippocampal NMDA receptor (NR1 subunit). The same treated adult rats with MK-801 developed prepulse inhibition deficits and increased locomotor activity. The same mechanism for neuronal apoptosis can be applied for AEDs that cause decrement in glutamate-mediated excitation by antagonizing the response mediated by NMDA or AMPA/KA subtype of glutamate receptors as with TPM [157]. Blocking NDMA receptors leads to an excessive release of glutamate in the cerebral cortex [194] and functional interaction of GABAergic (inhibitory) interneurons and glutamatergic (excitatory) neurons in local circuits. Activation of GABAergic interneurons via NMDA receptors exerts an inhibitory tone on the major excitatory neurons [195]. Blockade of NMDA receptors disrupts GABAergic neurodevelopment in medial prefrontal cortex [196].

Clinical and Research Recommendations

AEDs are the major therapeutic modality for control of seizures. Optimal therapy should result not only in complete seizure control but also in improving the patients' neuropsychological profile, maximizing school performance for children, and improving QOL for children, adults, and their families. This information has important clinical and research implications as follows:

(1) Provided that treatment decision may have lifelong implications, the neurologists should be aware that the ultimate therapeutic goal is not only to control seizures but also to consider the long-term adverse consequences of epilepsy on cognition and behavior. The cognitive and behavioral effects of AEDs are one of the factors to be considered in the selection of appropriate drug therapy for an individual patient. The lack of cognitive side effects related to an AED should be relevant for treatment decisions. LTG has been widely advocated for the treatment of women with epilepsy during pregnancy, but there is little evidence concerning neurodevelopmental outcomes. CBZ might be considered as an alternative, but it is contraindicated in myoclonic and absence seizures. Women on VPA should be advised to gradually withdraw VPA and switch to one of the known

safe AEDs during pregnancy. However, if there is no optimal seizure control with the alternative drugs, then alternative combination of low-dose VPA with the additional drug might be acceptable.

(2) AED levels should be properly selected and monitored more closely than usual during pregnancy. Pharmacokinetic changes demand monitoring of free levels of highly protein-bound AEDs to avoid confusion with increased seizures (or symptoms of toxicity) despite therapeutic total serum drug levels. The levels should be monitored at least in each trimester and for 2–3 months following delivery. If dose is increased during pregnancy, medication dose tapering should be anticipated in the postpartum period to avoid medication toxicity.

(3) As most neuropsychological drug effects have been incompletely described, the need for establishing neuropsychological profile of AEDs or special objective methods to determine their behavioral and cognitive consequences is important to maximize long-term treatment effectiveness. A recent American Academy of Neurology (AAN) and Child Neurology Society (CNS) practice guidelines stated that behavioral and cognitive side effects need to be better evaluated, especially for new AEDs, and individual risks as well as group differences assessed on tests of cognition [197]. Further investigations of mediating factors such as serum concentrations, co-medication, and other potential risk factors are needed to enable appropriate targeting of treatment with the effective AED.

(4) The argument stated that "the optimal treatment for epilepsy is not only to control seizures but also to reduce the risk or consequences of cognitive impairments and behavioral abnormalities as much as possible," also has to be made for decisions about epilepsy surgery. Preliminary findings indicate that postsurgical training improves memory deficits and encourage further research. Epilepsy surgery is an option for patients intractable for medical treatment with focal seizures that arise from noneloquent brain regions. Because the epileptogenic tissue that is resected is dysfunctional, seizures are reduced and the use of AEDs is reduced, thus the risk of significant cognitive decline is generally reduced. However, the risks of functional impairment due to tissue ablation need to be weighted carefully against the benefits of surgery on seizure control and overall functional state. Damage of functional tissue, low mental reserve capacity, and poor seizure outcome increase the risk for postsurgical memory impairment, whereas functional release due to seizure freedom counteracts negative impact. Patients older than 40 years may be at an increased risk of memory impairment postoperatively. Risk for verbal memory decline occurs with left anterior termporal lobectomy (ATL), whereas visuospatial memory impairment occurs with right ATL [22].

(5) Multidisciplinary management strategies must aim far beyond mere seizure control including detailed psychological evaluation and appropriate management. It is important to address the psychosocial difficulties associated with epilepsy. Proper neuropsychological assessment of the child will help the school personnel in planning the academic strategies. Strategies such as social skills training, educational, speech and language interventions, and psychopharmacotherapy are necessary. It is important to indicate epilepsy-specific optimistic orientation and the potential activities for overcoming stigma and increasing education and awareness related to epilepsy in community-based research studies [198,199].

(6) Although animal studies can provide valuable information regarding mechanisms of AED-induced developmental pathology, they do not provide insight into cortical functions unique to humans, such as speech and language. Even the results from some animal studies are controversial, which has been attributed to the difference in animal species, age when treatment commenced, duration of treatment, dosage, and outcome measures. Additional animal testings are necessary to explore the effects of AEDs on brain development *in utero* or postnatally. Large cohort and controlled prospective studies are necessary and should include a sufficient number of women and children exposed to newer AEDs. This demands provision of adequate information and counseling about drug treatment during childbearing years through epilepsy services programs.

(7) The basic mechanisms underlying AED-induced cognitive/behavioral teratogenesis need to be delineated through prospective clinical studies. Demonstrations in animals that AEDs can induce neuronal apoptosis in developing brains raise concern that similar adverse effects may occur in children exposed *in utero* or in the neonatal period.

Conflict of Interest

The author has no conflict of interest.

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