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A Systematic Review on Cognitive and Behavioral Effects of Anti-Epileptic Drugs in Epilepsy Patients

Amritha, Dilshana Kp, Thara Baby, Vineetha S, Tamil Selvan.T, Keerthi S, Gopika Cs

Department Of Pharmacy Practice, Nehru College Of Pharmacy, Thiruvilwamala, Pampady, Thrissur, Kerala 680588 India.

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ABSTRACT

IMPORTANCE: Antiepileptic medications (AEDs) reduce neuronal excitability or increase inhibitory neurotransmission, which might have a negative impact on cognitive function. While it is evident that long-term AED treatment can cause cognitive damage in epileptic patients, methodological issues make it difficult to determine the impact of AEDs on cognition over shorter time frames, even up to a year. Similar to this, when the drug level is within the therapeutic concentration and in monotherapy, cognitive adverse effects are discovered to be mild. Drugs used to treat epilepsy act by reducing neuronal excitability, which may have the unintended side effect of impairing cognitive function. The information regarding cognitive and behavioral side effects linked to anti-epileptic medications is the main topic of this review. **OBJECTIVE:** The objective of this article is to provide a detailed and systematic knowledge on the cognitive and behavioral adverse effects associated with various anti-epileptic drugs (AEDs). **METHODS:** A vigorous, maximum sensitive and online search of the literature was performed in published articles in the last 10 years (JUNE 2010–JUNE 2024). The databases searched were MEDLINE (via PubMed), Scopus, Web of Science Data Bases and Cochrane Library. **CONCLUSION:** Cognition comprises a broad range of functions, such as attention, intelligence, visual memory, and fine motor dexterity. Cognitive side effects are observed as a result of such global action that are usually fairly modest in monotherapy. The most prevalent of the cognitive side effects observed in an AED therapy are sedation, somnolence, distractibility, insomnia, and dizziness. Sedation, in particular, is associated with most of the common AED therapies. Based on a number of studies, the different types of antiepileptic drugs having different mechanism of action are shown to have various side effects, out of which behavioral and cognitive side effects are one among them.

KEYWORDS: Cognition, Behavioral Effects, AEDs, BAEs/BSEs, Epilepsy

INTRODUCTION

The long-term effects of epilepsy have a significant impact on the patient's life. It is the most prevalent neurological condition that need ongoing medical attention. There are about 50 million epileptics in the world. In one's lifetime, one in twenty-one males and one in twenty-eight women will have epilepsy [1][3].

The Greek term epilambanein, which means "to be seized," is the source of the English word epilepsy. The Greek word **"EPILEPSY"** means **"TO SEIZE, POSSESS, ORAFFLICT"** and was first used in antiquity [5].

From brief attention deficits or jerks to severe and protracted convulsions, convulsions can take many different forms. Seizures can also occur more frequently—from less than once a year to multiple times a day. Not all seizures are indicative of epilepsy; 10% of people worldwide experience only one seizure. Two or more seizures are described as epilepsy [6].

MANAGEMENT OF EPILEPTIC SEIZURES-ANTI-EPILEPTIC DRUGS

Anti-epileptic medications are typically used to treat epilepsies. Epilepsy treatment is a challenging and intricate procedure. AEDs impair neuronal excitability or increase inhibitory neurotransmission, which has a deleterious effect on cognition [3].

Antiepileptic medications mainly function by preventing seizures from starting or progressing. Numerous mechanisms are involved, such as the blocking of voltage-gated Ca++ channels, the blocking of Na+-dependent channels, the facilitation of potassium channel opening, the reduction of glutamate activity, the enhancement of GABA receptor function, the elevation of GABA availability, and the control of synaptic vesicle contents release [3].

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Patients receive either monotherapy (one AED) or polytherapy (two or more AEDs). Affected individuals have a higher prevalence of neuropsychological impairment than the general population due to the illness itself and the use of AEDs to treat it, which may have some detrimental effects on cognition and behavior [5]. Anticonvulsant drugs are the cornerstone of treatment for epileptic seizures. When taken for an extended period of time, these anti-epileptic medications may also impair the patient's cognitive abilities [2].

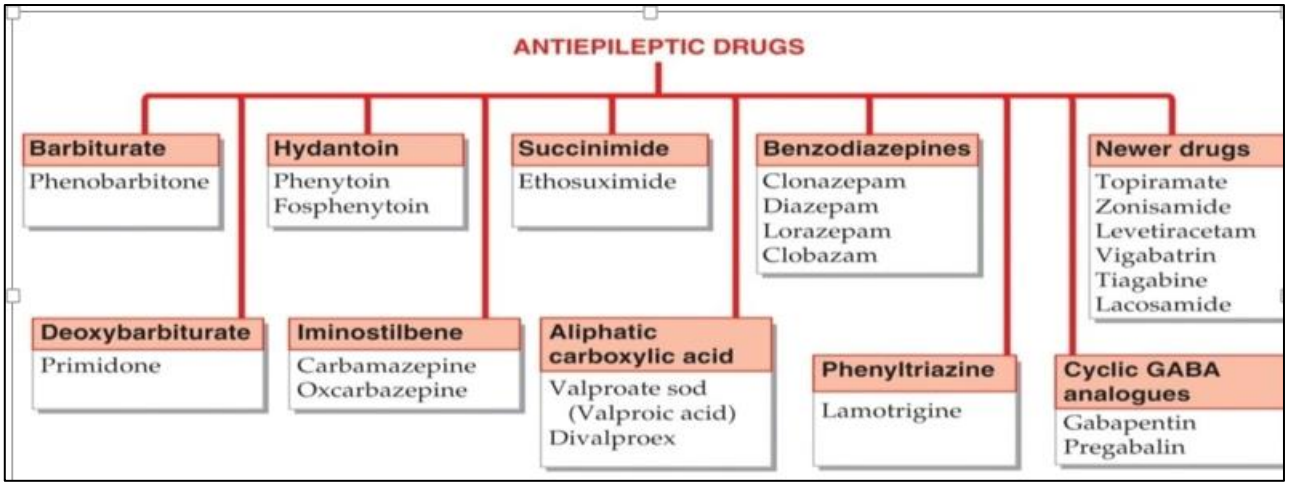

FIG 1: Classification of Anti-Epileptic Drugs

Treatments for each form of epilepsy vary and are often determined by the length and nature of the individual's seizures.

Table 1 shows choice of Anti-Seizure Drugs used in various types of seizures.

Table 1: Choice of Anti-Seizure Drugs based on Types of Seizures [11]

TYPES OF SEIZURES	FIRST LINE DRUGS	SECOND LINEDRUGS	ALTERNATE/ADD ON DRUGS
Generalized Tonic-Clonic/Simple Partial	Carbamazepine Phenytoin	Valproate Phenobarbitone	Lamotrigine, Gabapentin, Levetiracetam,
Complex Partial Seizures	Carbamazepine Valproate Phenytoin	Gabapentin Lamotrigine Levetiracetam	Clobazam Zonisamide Topiramate
Absence	valproate	Ethosuccimide Lamotrigine	Clobazam Clonazepam
Myoclonic	Valproate	Lamotrigine Topiramate	Levetiracetam Clonazepam
Atonic	Valproate	Clonazepam Clobazam	Lamotrigine
Febrile Seizures	Diazepam	-	-
Status Epilepticus	Lorazepam (i.v) Diazepam (i.v)	Fosphenytoin (i.v) Phenobarbitone(i.v, i.m)	Gen.Anesthetics

WHAT IS COGNITION AND COGNITIVE EFFECTS?

Cognition can be defined as an individual's ability to think, or more precisely, to use information about and from the environment in an adaptive manner. Cognitive impairment is common in epilepsy patients. A number of factors can negatively impact cognition in people with epilepsy, including the cause of the seizures, cerebral lesions acquired prior to the onset of seizures, the type of seizure, the age at which epilepsy first manifests, the frequency, duration, and severity of the seizures, intraictal and interictal physiologic dysfunction, structural brain damage from repeated or prolonged seizures, hereditary factors, psychosocial factors, and side effects from epilepsy treatment, such as antiepileptic medications (AEDs) and epilepsy surgery [9].

Epilepsy patients undergoing anti-epileptic drug therapy often experience cognitive impairments. AEDs primarily impact attention, vigilance, and psychomotor speed, with possible secondary effects on other cognitive functions. [8].

EpiTrack, is a new 15-minute screening tool developed to detect dysfunctions of attention and executive control caused by epileptic disorders or antiepileptic drugs, and to track cognitive performance parallel to changes in medical therapy [10].

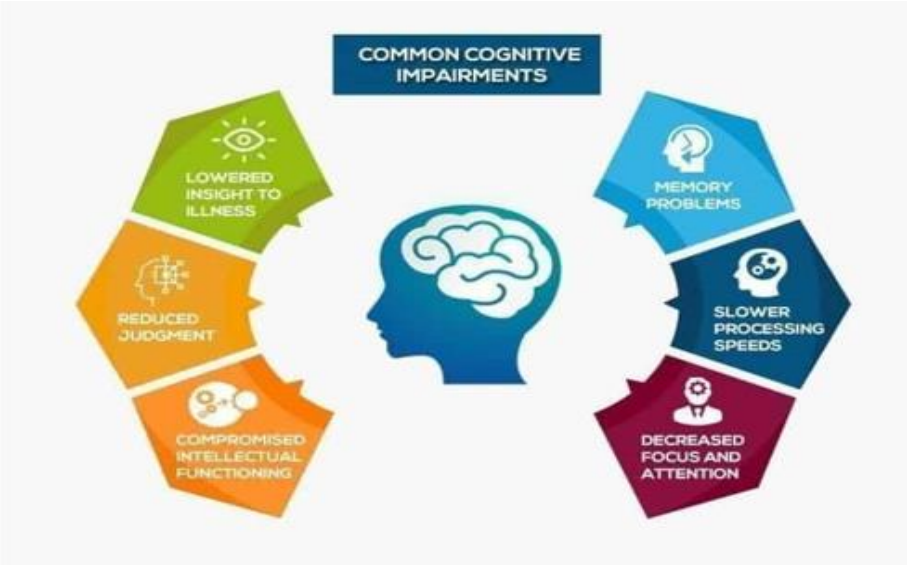

Fig 2 Factors Contributing to Cognitive Impairment in Epilepsy Patients

WHAT ARE BEHAVIORAL ADVERSE EFFECTS?

Behavioral AEs can be associated with poorer seizure control, mental retardation, or previous behavioral problems. Some reports indicate that the occurrence of BAEs can be related to medication dose, titration, or duration of intake. High starting dose and faster titration are risk factors.

Depending on the stage of life, AEDs may have different behavioral consequences. AEDs that elicit behavioral effects include sodium valproate, Levetiracetam, gabapentin, phenobarbital, and Vigabatrin. Older medications that cause anxiety, hyperactivity include Primidone and phenobarbital [20]. Anti-epilepsy medications (AEDs) may have behavioral side effects in addition to cognitive ones.

These effects might include everything from hyperactivity and irritation to beneficial psychotropic effects on mood. Anxiety, depression, mood swings, irritability, confusion, psychosis, sleep disturbances including insomnia, agitation, aggression, suicidal thoughts, hyperactivity, etc. are examples of behavioral adverse effects [21].

Depression, anxiety/agitation, and aggressiveness are common behavioral anxiety disorders (BAEs) In children, and they are more common in individuals with partial epilepsy. Changes in appetite, drowsiness, and difficulty concentrating might also be seen. Depression, agitation, aggression, hyperactivity, sleepiness, anxiety, lethargy, confusion, and psychosis are examples of BAEs in adults [22].

Most AEDs cause some degree of adverse drug reactions. Behavioral side effects (BSEs) associated with AEDs is often overlooked, but is a significant consideration. Agitation, aggression, psychosis, behavioral disorders, hyperactivity, and restlessness are some AED-related BSEs. Depression as a BAE deserves particular attention, given the possibility of suicide risk [19].

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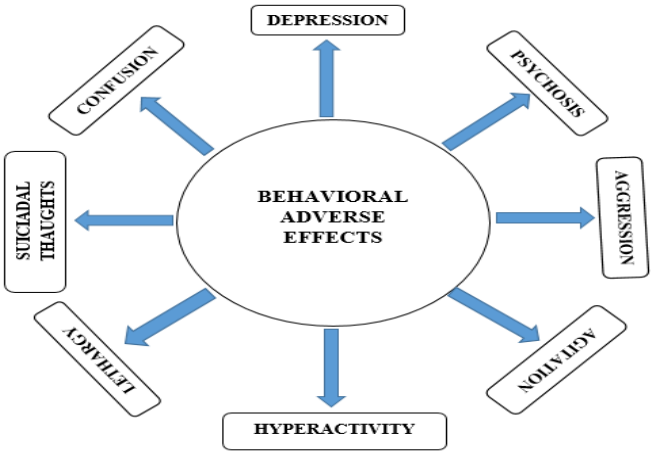

FIG 3: Image Showing Behavioral Adverse Effects in Epilepsy Patient

METHODS

LITERATURE SEARCH: A vigorous, maximum sensitive and online search of the literature was performed using the PubMed, Scopus, PsycINFO, MEDLINE and Web of Science Data Bases. The search strategy was limited to published articles in the last 10 years (JUNE 2014–JUNE 2024) to include the most recent, up-to- date data that reflect the current clinical practice in English. The search terms used were, "Anti-Epileptic Drugs", "Cognitive Side Effects", "Behavioral Effects", "Anti-Epileptic Medication", "Cognition in Epilepsy", ". Behavioral Side Effects" combined with Boolean operators "AND" and "OR" as appropriate.

STUDY SELECTION: Initial screening of titles and abstracts of the retrieved articles were independently screened by two reviewers to assess their relevance to the review topic. The first stage of screening was performed based on the titles and abstracts. Eligible studies were screened based on the full text in the second stage.

DATA EXTRACTION: Data extraction was performed by two reviewers using a standardized data extraction. Extracted data included the details such as study characteristics, participant characteristics, anti-epileptic drugs investigated, cognitive and neuropsychological outcomes measured and the key findings related to the side effects.

DATA SYNTHESIS: The findings from the synthesized data were performed to find out the cognitive and behavioral adverse effects of various anti-epileptic drugs.

RESULTS

Newer Anti-Epileptic Drugs

Topiramate

Topiramate (TPM) is a sulfamate-substituted monosaccharide that has multiple mechanisms of action. Studies conducted suggest that *Topiramate* have reported significant memory impairment in patients with epilepsy. The impairments were characterized by short term memory deficits, difficulties in verbal memory [11].

Sodium Valproate

Sodium valproate is a GABA receptor analogue which is used to treat epilepsy. Various studies conducted suggests that sodium valproate have reported significant memory impairment in patients with epilepsy. The impairments were characterized by short term memory deficits, difficulties in verbal memory, and in working memory. Sometimes it may also cause BSEs such as sleepiness and aggression followed by hyperactivity [11].

Levetiracetam

Studies conducted suggests that the newer anti- epileptic drugs such as *Levetiracetam* newer anti-epileptic drugs show side effects such as aggregation, followed by headache, hyperactivity reaction, sometimes it may also cause psychosis for prolonged use of time [12].

Zonisamide

Studies conducted suggests that the newer anti-epileptic drug *Zonisamide* shows cognitive effects such as Memory and attention problems and long lasting impact on cognitive function has been reported in patients taking Zonisamide [12].

Tiagabine

TGB is a γ-aminobutyric acid (GABA) uptake inhibitor that is structurally related to nipecotic acid but has an improved ability to cross the blood–brain barrier. A number of studies were conducted shows that there were no cognitive effects of monotherapy with TGB at a low or high dose, but there was some evidence for mood effects of add-on treatment with TGB at higher dosing, possibly related to titration speed [14].

Gabapentin

Gabapentin is a novel AED, currently used as add-on therapy in patients with partial seizures. Gabapentin probably involves action such as potentiation of GABA-mediated inhibition and possibly in activation of sodium channels. Studies conducted suggest that gabapentin shows neuropsychological side effects among which Drowsiness was more often found in higher dosing (2,400 mg) [11].

Older Anti-Epileptic Drugs

Carbamazepine, Mysoline (Primidone) And Phenobarbital.

Studies conducted suggest that the older AEDs such as carbamazepine, Primidone and Phenobarbital can cause cognitive effects such as Memory Loss and Confusion for prolonged use of time [11] [12].

Phenytoin

Studies conducted suggest that the older AEDs such as Phenytoin has been implicated in declines in concentration, memory, visuo motor functions and mental speed. These effects may be of dose related, sometimes it may also affect attention and motor functions [16].

Vigabatrin

Studies conducted reported that Vigabatrin shows impaired performance relating to motor speed and design learning in adolescents and adults with partial epilepsy sometimes it also affects memory functions as motor memory and visual memory [17].

Clobazam

Studies conducted suggest that the older AEDs such as Clobazam can cause behavioral effects such as aggregation, agitation and attention problems for prolonged use of times [15].

Phenobarbital and Phenytoin

Studies conducted suggest that drugs such as Phenobarbital and Phenytoin may cause an increase in suicidal thoughts and sometimes may cause depressive behavior on prolonged use of time which may be of dose related [16].

CONCLUSION

Cognition comprises a broad range of functions, such as attention, intelligence, visual memory, and fine motor dexterity. Cognitive side effects are observed as a result of such global action that are usually fairly modest in monotherapy. The most prevalent of the cognitive side effects observed in an AED therapy are sedation, somnolence, distractibility, insomnia, and dizziness. Sedation, in particular, is associated with most of the common AED therapies. Based on a number of studies, the different types of antiepileptic drugs having different mechanism of action are shown to have various side effects, out of which neuropsychological side effects are one among them.

Behavioral AEs can be associated with poorer seizure control, mental retardation, or previous behavioral problems. Some reports indicate that the occurrence of BAEs can be related to medication dose, titration, or duration of intake. High starting dose and faster titration are risk factors.

Various studies conducted suggested that each Anti-epileptic drugs have different side effects. Studies conducted suggest that AEDs shows cognitive as well as behavioral adverse effects followed by neuropsychological side effects.

The use of antiepileptic drugs (AEDs) may impair cognitive function because they decrease neuronal excitability or enhance inhibitory neurotransmission. While it is clear that individuals with epilepsy who get long-term AED medication may suffer cognitive damage, methodological problems make it challenging to assess the effects of AEDs on cognition during shorter time periods, even up to a year. Similarly, modest cognitive adverse effects are found in monotherapy when the medication level is within the therapeutic concentration. Epilepsy medications work by decreasing neural excitability, which may unintentionally affect cognitive function.

Despite the difficulties of having epilepsy, many people are able to enjoy happy lives with proper management and a few lifestyle changes, such getting adequate sleep. Seizures can be less frequent by following a nutritious diet, avoiding drugs and alcohol, and keeping an eye on blood pressure. With proper management, help-seeking, and required accommodations, many individuals with epilepsy can have meaningful, fulfilling lives.

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To accomplish great things, we must not only act, but also dream; not only plan, but also believe. Believe in our self and may the impossible be the smaller word.

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