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REVIEW ARTICLE

Antiepileptic Drugs in Patients with Aggression and Epilepsy

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ABSTRACT

In the United States, the prevalence and incidence of epilepsy are about 5 to 8.4 per 1000 and 35.5 to 71 per 100,000 persons per year, respectively. Epilepsy management is a personalized and multifactorial medical approach; it is based on the type of epilepsy syndrome, severity and frequency of epileptic seizures, antiepileptic drug's (AED) side effects, drug-drug interactions, disease-related psychosocial problems, and the overall lifestyle of the patient. Aggressive behavior is a major side effect of many AEDs. It deteriorates patients' health. In this study, we reviewed different mechanisms of aggression in patients with or without epilepsy, and eventually, we introduced medications that potentially managed both.

INTRODUCTION

According to the Institute of Medicine, the incidence and prevalence of epilepsy in the United States are 35.5 to 71 per 100,000 and 5 to 8.4 per 1000 persons per year or approximately 1% of the population, respectively (1). Over the past 20 years, more than 15 different antiepileptic drugs (AEDs) with more unique characteristics and mechanism of action have been introduced in the US drug market.[2] Despite the availability of new medications, more than 30% of the patients are refractory to treatment. This demands for new strategies so that the medical requirements for managing epilepsy can be fulfilled. Epilepsy management is an individualized and multifactorial medical approach.

Traditionally, seizures are classified into (2) main categories: focal (partial) and generalized. Although the initiation of AEDs is not often required in individuals with a single reversible provoked seizure, it is required in individuals who are at the risk of recurrent seizures. Different factors considered for the initiation of AEDs in individuals with epilepsy are as follows: type of epilepsy, patients' comorbid medical conditions, concomitant medications, side effects of AEDs, patients' lifestyle, their psychosocioeconomic conditions, and their gender.(3) Long-term video-EEG monitoring (LTM) is used to diagnose the type of epilepsy syndrome.(4)

Epilepsy has been frequently associated with aggressive behavior. Baseline pathology, side effects of AEDs, or preictal, ictal, and postictal states may be one of the reasons for such aggressive behavior. The prevalence of psychoses in epilepsy is in the range of 2% to 7%. Both epilepsy itself and the AEDs are contributing factors for the aggressive behavior in patients with epilepsy. Here, we review different studies describing the underlying mechanism of aggression, epilepsy, and the common pathophysiology of their coexistence. In addition, we review different AEDs with potential effectiveness on both epilepsy and aggression.(5)

NEUROBIOLOGY MECHANISMS COMMON TO AGGRESSION AND EPILEPSY

Studies on aggression have shown different underlying mechanisms of aggression because of dysregulation in neurotransmitters and structural changes in the brain, leading to a seizure. To address both issues-neurotransmitter dysregulation and brain's structural changes-AEDs are prescribed as a common treatment method.

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Studies on violent and aggressive behavior have revealed that the reduction of the orbitofrontal cortex gray matter (dorsal and ventral prefrontal cortices), the amygdala, hippocampus, anterior cingulate, hypothalamus, frontal lobes, limbic system, and thalamus may be the underlying factors behind some aggressive behaviors.(6) On the other hand, epileptic seizures can cause changes in subcortical structures such as the thalamus and brain stem, leading to ictal behavioral manifestation.(7)

Studies have hypothesized that impulsive behavior and aggression are suppressed by signals originating in the prefrontal cortex (PFC), which inhibit other areas of the brain involved in the aggressive behavior such as the amygdala, anterior cingulate, thalamus, and hypothalamus. Any structural changes or damages to PFC lead to the downregulation of the inhibitory effect of PFC and firing of thalamus and hypothalamus, which eventually trigger the adrenal response (Figure 1).

AEDs lead to the dysregulation of neurotransmitters leading to epilepsy and aggression. Monoamines and other neuroactive compounds are targeted by AEDs, thereby influencing the initiation of seizure. Some of them have been listed below:

Serotonin

Serotonin modulates the orbital frontal cortex and anterior cingulate cortex by affecting 5-HT2 receptors in these regions, leading to the suppression of impulsive aggression.(8) There are 2 different serotonin receptor subtypes that have shown different mechanisms of action. Antagonists of the 5-HT2A receptors reduce aggression as opposed to the agonists of the 5-HT2C receptors that reduce aggression.(9) Studies have shown that selective serotonin reuptake inhibitors have both antiaggressive and anticonvulsant effects on animal models of epilepsy.(10) Agonists of the 5-HT1A receptors are anticonvulsant, whereas the antagonists of 5-HT2C receptors cause rare fatal epilepsy in mice. Agonists of the 5-HT1A/1B receptors demonstrate antiaggressive effect.(11-13)

Dopamine

Dopamine plays a significant role in epileptogenesis and aggression, depending on the types of receptors that are involved. The nonselective D1/D2 agonists have anticonvulsant properties, whereas D1/D2 antagonists have a proconvulsant effect. Also, dopamine is a part of the initiation circuit of aggression.(1-164)

Noradrenaline

Noradrenaline (NA) is an antiepileptic neurotransmitter that works through alpha-1 (α1)- and alpha-2 (α2)-adrenoceptors. The α2-adrenoreceptor antagonists provoke epilepsy, whereas their agonists suppress it. The increased or decreased level of NA is associated with aggression. Clonidine works as an α2-adrenoceptor agonist that decreases NA neuronal activity and decreases aggression.(17)

Gamma-Aminobutyric Acid

There are no clear data supporting whether or not the gamma-aminobutyric acid (GABA) level is decreased or increased in aggression, and whether enhancing GABA is anti- or proaggressive. In addition, GABA receptors play an inhibitory role in epilepsy; however, it can vary between different types of epilepsy syndromes.

Glutamate

Glutamate works through its excitatory *N*-methyl-D-aspartate receptor (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptors. The expression of glutamate (NMDA, AMPA, and kainite receptors) leads to epileptogenesis. The NMDA antagonists have shown proconvulsant action at very high doses and anticonvulsant properties at low doses, whereas AMPA antagonists have anticonvulsant activity. Animal models have shown the dose-dependent effect of NMDA antagonists on aggression as they act as proaggression agents at a low dose and as antiaggression agents at a high dose.(18-21)

TARGETED DRUGS

There are debates regarding what would be the best option to target both epilepsy and aggression in patients. Based on the available evidence, we can say that some AEDs seem to be associated with a higher risk of aggression than others, including clobazam (8%), clonazepam (no report), levetiracetam (1%-10%), perampanel (1%-10%), phenobarbital, tiagabine (2%-5%), topiramate (1%-10%), vigabatrin (1%-10%), lacosamide (1%-10%), and zonisamide (>10%). Many AEDs such as valproic acid (1%-10%), topiramate (1%-10%), gabapentin (1%-10%), lamotrigine, carbamazepine, oxcarbazepine, lamotrigine, and maybe pregabalin (0.1%-1%), and phenytoin (no reported aggression) are also used to treat aggression. Before listing the different AEDs and their anti- or proaggressive actions, we should mention about 3 phenomena that are involved with this combination. They are as follows:

1. Enhancing GABA with paradoxical proaggressive effect: The GABA system with both inhibitory and excitatory effects can be imbalanced in epilepsy. Although GABA displays antiaggressive actions, in some regions of the epileptic brain, it can act as a proaggressive agent.(22)
2. Dose-dependent opposite effect of NMDA receptor antagonists: This effect is dose dependent and related to the region where epilepsy occurs in the brain.(23)
3. Forced normalization: The relationship between aggression and epilepsy has been observed over many years. There is a hypothesis that the better the seizures are controlled, the worse psychiatric status of the patient will be. Although this observation and hypothesis have not been well explained and well studied, different aspects of this correlation have been considered. Is worsening of the psychiatric symptoms because of the side effect of AEDs? Is it a pathophysiologic progression of the disease? Or is it really a result of seizure suppression?(24)

Valproic Acid

Valproate (VPA) blocks the voltage-dependent sodium channel and inhibits the cytochrome P450 (CYP) system and uridine diphosphate-glucuronyltransferase (UGT)-glucuronidation. VPA-related hyperammonemic encephalopathy (VHE) causes lethargy and increased seizures. VPA has some inhibitory effects on the NMDA and AMPA receptors that can decrease aggression. In different trials, VPA has reported aggression with the incidence of 1% to 10%, but it is also considered as a mood stabilizer.

Topiramate

Topiramate blocks the voltage-dependent sodium channel, enhances the activity of GABA at a nonbenzodiazepine site on GABA(A) receptors, and antagonizes an NMDA-glutamate receptor. It also weakly inhibits carbonic anhydrase in the central nervous system.[25,26] Impaired cognition and expressive language are the side effects of topiramate. This results in aggression, which is as common as 1% to 10% of the patients using this drug, with the aggression tendency being more in children than in adults. Topiramate has not yet been proven as an antiaggression agent, and the use of this drug as an antiaggression agent is very controversial.

Lamotrigine

Lamotrigine blocks the repetitive firing of neurons by inactivating voltage-dependent sodium channels and diminishes the release of these excitatory neurotransmitters. It is used in the adjunctive treatment of focal seizures in adults and children as young as 2 years old, as well as for adjunctive therapy for primary generalized tonic-clonic seizures and Lennox-Gastaut syndrome.[26] The level of drugs increases when they interact with VPA. Even though there are reports of aggressive behavior (1%-10%) because of the side effect, this medicine is considered as a mood stabilizer and an antiaggressive.

Carbamazepine

Carbamazepine can be used to treat focal and generalized seizures. It binds to voltage-dependent sodium channels, which leads to the inhibition of action potential. It is a CYP 450 inducer. It can cause fluid retention (SIADH) and Stevens-Johnson syndrome mostly in Asian with the HLA-B*1502 allele. Carbamazepine has autoinduction during the first 2-3 months and therefore levels should be monitored frequently due to the autoinduction. And if needed the dosage should be increased until achieving more stable level and dosage after the period of autoinduction. Carbamazepine acts as an antiaggressive agent with a very low incidence of aggression as a side effect (0.01%-0.1%).

Oxcarbazepine

Oxcarbazepine is used as first-line treatment for focal and secondarily generalized tonic-clonic seizures. It also minimally affects the CYP system. It has antiaggressive effects and a very low rate of aggression (1-2%) as a side effect.

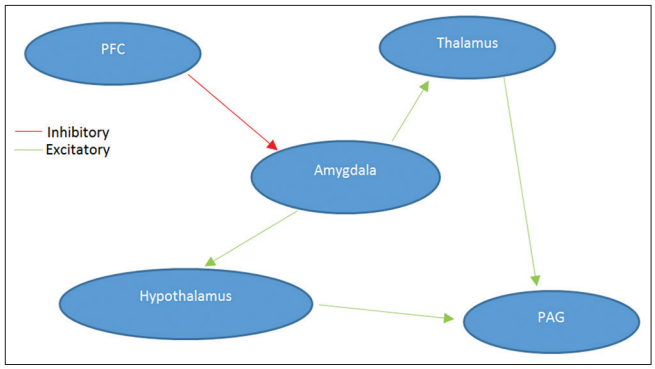

Figure 1. Aggression Circuit. PFC indicates prefrontal cortex; PAG, periaqueductal gray

Phenytoin

It is used for focal and generalized seizures, status epilepticus, and as a second-line agent for patients with mixed seizures. It blocks voltage-dependent sodium channels and inhibits calcium-calmodulin protein phosphorylation. Phenytoin is an inducer of CYP and UGT-glucuronidation. Phenytoin can cause a small decrease in irritability.

Eslicarbazepine

Its mechanism of action is similar to that of carbamazepine and oxcarbazepine; it blocks voltage-gated sodium channels and is an inducer of CYP3A4 and uridine diphosphate-glucuronosyltransferase (UGT) 1A1 and a moderate inhibitor of CYP2C19. It can be used in epilepsy and aggression, with a very uncommon incidence of aggression as a side effect (0.1%-1%).

CONCLUSION

Since aggression is the side effect of many AEDs, treatment of epilepsy can be very challenging in patients with cognitive and behavioral comorbidities. Levetiracetam, perampanel, gabapentin, topiramate, zonisamide, and phenobarbital have the highest incidence rate of aggression in the profile and should be avoided in patients with this morbidity. Dosing should be very slow and gradual. Furthermore, there are AEDs that can be considered as better options in patients with epilepsy and aggression such as oxcarbazepine, carbamazepine, eslicarbazepine, lamotrigine, and valproic acid.

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