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Therapeutic Considerations in Epilepsy: Clinical Insights into Drug Therapies

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Abstract

Nowadays, the majority of seizure patients have lost confidence in themselves and are worried about their self-image, so they attempt to conceal their illness from others. Once a decision to treat epilepsy has been made, it is necessary to have a thorough knowledge of the choice of drug, toxic effects, mode of action with each antiepileptic drug. However, by determining the serum concentration and manipulating it within the therapeutic range it should be possible to find a regimen that adequately controls seizures without introducing unnecessary toxic effects. Since valproic acid is also a first-line treatment for epilepsy, it is now the most effective medication used. Over time, these medications are taken regularly.

Keywords: Epilepsy, Seizures, Medication, Effectiveness, Anticonvulsants.

INTRODUCTION

Although 1% of the population has epilepsy, most people are afraid of it and don't really understand it. A patient's confidence and self-image may suffer after receiving an epilepsy diagnosis. Few persons with epilepsy are willing to speak publicly about their disease, and there is little financial or social support available for those who suffer from the ailment. Removing one's driver's license is considered a psychological setback in North America, and epilepsy patients find it challenging to continue working or participating in social activities when they are unable to drive. Controlling epilepsy is so obviously crucial for psychological well-being [1].

The patient with epilepsy may also be treated for reasons that are solely medical. Certain types of epilepsy, such as generalized tonic-clonic seizures, may be fatal or cause brain damage, and recurrent seizures can affect cognitive function. Untreated seizures have a propensity to worsen over time, and status epilepticus poses a high mortality risk (up to 20%). There is a chance of harm from certain types of epilepsy, such as complex partial seizures and absence seizures, which can temporarily impair cognitive or motor function. Some people think that a patient can only be diagnosed with epilepsy if they have experienced many seizures. However, waiting for a second seizure before beginning anticonvulsant medication can be challenging because the patient's quality of life may significantly worsen after the second seizure [2-4].

Medications for Epilepsy and Goals of Therapy

An optimal approach to treating epilepsy would manage seizures without compromising cognitive function, arousal, motor abilities, or emotional state. It has proven challenging to develop a specific medicinal treatment for seizures that does not damage all neurons and certain other cells in the body since seizures are caused by abnormal firing of populations of neurons. Even surgical intervention eliminates far more neurons than those that might be responsible for convulsions. Effective seizure control is useless if the patient cannot carry out daily tasks at home, school, or the workplace. There are situations when managing epilepsy requires balancing the medication's harmful side effects with seizure control [2].

Selection of Drugs

The disease and the medication's effectiveness in treating it will determine which drug is best. Table 1

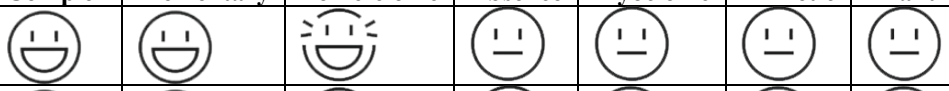
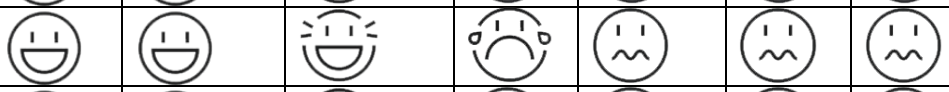
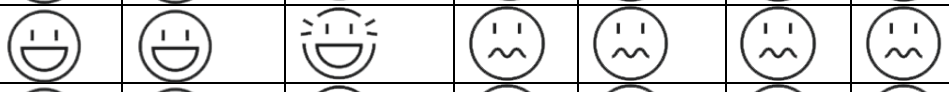
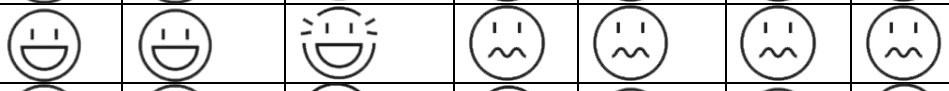
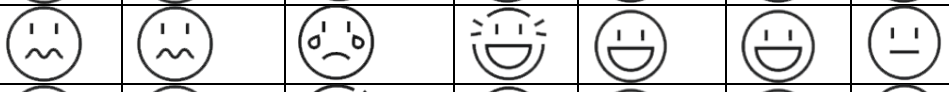
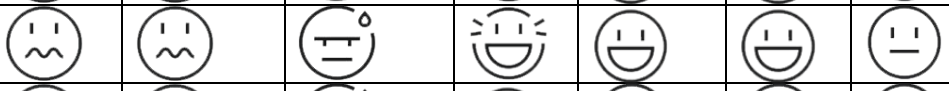
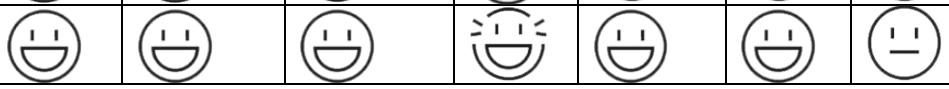
contains the essential data required to prescribe anticonvulsants for epilepsy. The treatment needs for each type of epilepsy, however, vary (Table 2), and certain anticonvulsants, such as phenytoin for absence seizures, may have the unintended effect of decreasing seizure control. While several studies have been carried out to compare the effectiveness of anticonvulsants, several of these studies have significant methodological flaws. Patients were not randomized to treatment regimens in certain previous research. In other investigations, the number of patients was insufficient to lower the type ii error to a level that was acceptable when comparing two active medications [1, 4-8].

Few studies have shown that there are likely not much of an efficacious difference between carbamazepine and phenytoin [8-10]. For significant generalized and partial seizures, phenytoin, phenobarbital, and carbamazepine are therefore equally effective. Primidone, which is largely converted to phenobarbital, may have some benefits over phenobarbital, but this is unknown [11].

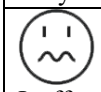
Table 1: Anticonvulsants dosage and pharmacokinetic information

Dose						
Usual daily total						
Drug	Adult, Mg	Child, Mg/kg	Initial	Daily No.	Approximate half-life, H	Remarks
Phenobarbital	60-210	Infant:8 Older:3-5	1/3	1	48-144	Cheap; may aggravate abnormal behaviour
Primidone	500-1500	10-25	1/4	4	3-12	Expensive; appears to have no advantage over phenobarbital
Carbamazepine	600-1200	20-30	Low	3	Short term therapy:12-30 Long term therapy:7-12	Expensive
Ethosuximide	750-2000	20-30	Full	1	Adult:48-72 Child	Expensive; may need to give 8 caspsules a day
Clonazepam	1.5-20	0.01-0.2	1/10	3	18-50	Seems to lose effect after 1 month
Diazepam	6-30	0.01-1.0	-	-	24-48	Ineffective orally, poorly absorbed intramuscularly
Valproic acid	60/kg	20-30	1/3	4		

Table 2: Effects of anticonvulsants on seizures

Drugs	**Partial seizures**		**Generalized seizures**				
	Complex	**Elementary**	**Tonic-clonic**	**Absence**	**Myoclonic**	**Akinetic**	**Infantile spasms**
Phenobarbital							
Phenytoin							
Carbamazepine							
Primidone							
Ethosuximide							
Trimethadione							
Clonazepam							
Valproic acid							

*seizures made worse in some patients and better in others.

 Very effective	 Effective	 Moderately effective	 Somewhat effective
 Ineffective	 Aggravates somewhat	 Aggravates	 Aggravates greatly

Drug of Choice for Seizures

- **Valproic acid:** Valproic acid is suggested as monotherapy and adjunctive therapy for complex partial seizures, which originate in a specific region of the brain, and has demonstrated efficacy in treating both partial and generalized seizures. Either alone or in conjunction with other seizure types, these seizures can happen. Additionally, the medication can be used as an adjuvant therapy for patients with several seizure types, including absence seizures, as well as for patients with simple and complex absence seizures. Although the exact processes by which valproate prevents seizures are unknown, its effectiveness in treating epilepsy may be associated with higher levels of GABA in the brain. it has proven challenging to link the higher GABA concentrations to valproate's antiseizure effects thus far. Once valproic acid is converted into a form absorbed by the body, it is known as valproate [12-14].

- **Carbamazepine:** It is recommended to take carbamazepine as an anticonvulsant medication. Studies that enrolled patients with
  (i). generalized tonic-clonic seizures (grand mal)
  (ii). mixed-seizure patterns, including the latter two types or other partial or generalized seizures.
  (iii). partial seizures with complex symptomatology revealed evidence supporting its effectiveness as an antiepileptic drug. Carbamazepine does not seem to be able to manage absence (petit mal) seizures.

  It seems that carbamazepine works by inhibiting post-tetanic potentiation and lowering polysynaptic responses. Although the exact mode of action of the medication is still unknown, use-dependent blockage of voltage-sensitive sodium channels may be the source of its anticonvulsant effects[15,16].

- **Phenytoin:** Phenytoin is recommended for the prevention and treatment of seizures that develop during or after neurosurgery, as well as for the control of complex partial seizures (psychomotor, temporal lobe) and generalized tonic-clonic seizures (grand mal). The medicine appears to primarily act on the motor cortex, where it prevents seizure activity from spreading. Phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of lowering membrane sodium gradient; this action includes diminishing post-tetanic potentiation at synapses. This effect may be achieved by encouraging sodium efflux from neurons [17].

- **Oxcarbazepine:** Oxcarbazepine is used as additional therapy for children 2 years of age and older, as well as for adults and children 2 to 16 years of age with partial seizures. It can be used as monotherapy for adults and children 4 to 16 years of age with partial seizures. The 10-mono-hydroxy metabolite of the drug is the main mechanism of action (mhd). Unknown is the exact mechanism via which mhd and oxcarbazepine prevent seizures. Preclinical data had shown that they cause voltage-sensitive sodium channels to be blocked, which stabilizes hyperexcited neural membranes, prevents recurrent neuronal firing, and reduces synaptic impulse propagation [18].

- **Ethosuximide:** Ethosuximide is recommended for the treatment of absence epilepsy (petit mal). In absence seizures, it reduces the paroxysmal three-cycles-per-second (3-hz) spike-and-wave activity linked to lapses in consciousness. The frequency of epileptiform attacks is reportedly decreased by motor cortex depression and a rise in the central nervous system's threshold for convulsive stimulation. The medication works by modifying the thalamic t-type calcium currents, which prevents the coordinated firing of neurons linked to spike-and-wave discharges [19, 20].

- **Phenobarbital:** Phenobarbital is often used to treat seizures that occur in neonates and in the first year of life. It is effective for both generalized tonic–clonic seizures and partial seizures in patients of all ages. The medication decreases neurotransmitter release from nerve terminals, most likely by its action on calcium channels, and potentiates inhibitory neurotransmission by lengthening the period that GABA-mediated chloride channels remain open. Additionally, phenobarbital decreases excitatory neurotransmission by lessening glutamate's effects[20-23].

- **Primidone:** Primidone raises electroshock or chemo shock seizure thresholds and may change seizure patterns in experimental animals; its antiseizure mechanism is unknown. It is indicated for controlling psychomotor, focal epileptic, and grand mal seizures as well as grand mal seizures that have not responded to another antiepileptic drug [24].

- **Clonazepam:** Clonazepam, a derivative of benzodiazepines, is helpful either by itself or in conjunction with other therapies for myoclonic

seizures, akinetic seizures, and lennox-gastaut syndrome (petit mal form). Clonazepam may be helpful in people with absence (petit mal) seizures who have not responded to succinimides. Although the exact method by which clonazepam prevents seizures and calms anxiety is unclear, it is thought to be connected to its capacity to increase GABA's activity, the primary inhibitory neurotransmitter in the central nervous system [24].

Toxic Effects

There are three categories of anticonvulsant toxic effects: acute, chronic, and serum related concentration:

- **Acute**

Acute toxic effects from carbamazepine include drowsiness, upset stomach, skin eruptions, and blood dyscrasias. If the patient is not at risk of status epilepticus, in case it might be necessary to use a loading dose, gastric upset, which can be caused by any of the anticonvulsants, may be lowered by beginning treatment with a low dose of one medication and gradually increasing the dose until the serum concentration is within the therapeutic range. This action can also lessen sedation; however, an alternative method is to administer an anticonvulsant with a long half-life in a single dose at bedtime (Table 1). The drowsy side effects of anticonvulsants typically cause tolerance to develop, though certain motor skills impairments or lack of focus may linger. Children on phenobarbital may experience paradoxical enthusiasm to the point where a prescription change is required. Antiepileptic medications all have the potential to cause skin outbreaks. Stevens-Johnson syndrome can occur from phenytoin with or without a history of morbilliform rash. Phenobarbital, phenytoin, carbamazepine, and primidone are examples of enzyme-inducing medications that may cause a porphyria attack in individuals who have risk factors for the condition [25-28].

- **Chronic**

A thorough review has been conducted on the topic of chronic toxic effects. Due to the toxic effects of anticonvulsants on every part of the body, close observation is required to avoid or minimize disease and mortality. Early treatment beginning, which exposes developing tissue, long-term therapy, the use of several medications, poor diet, and alterations in metabolism are risk factors. In patients with brain damage, chronic toxic effects on the central nervous system may be particularly difficult to identify. Before starting therapy and on a frequent basis once it has begun, appropriate studies of the systems that are likely to be affected should be conducted [29].

- **Serum related concentration**

The third category of risk factors are those related to the serum concentration of different drugs.

Nystagmus is often brought on by phenytoin above a serum concentration of 20 mg/l, however it can also happen at lower concentrations and even go away at very high quantities. Serum concentrations over 30 mg/l often cause ataxia; concentrations over 40 mg/l, may cause drowsiness, irritability, and slurred speech; and serum concentrations over 50 mg/l may cause coma. Concentrations of phenytoin and other anticonvulsants over the therapeutic range might cause movement problems, especially in patients who are mentally retarded. Exceeding a serum concentration of 35 mg/l, phenobarbital can cause ataxia and slowness. Serum values exceeding 65 mg/l have been known to cause coma. Regular usage of phenobarbital, however, may enable the patient to cope with much greater levels—up to 160 mg/l—without experiencing unconsciousness. When carbamazepine concentrations exceed 6 mg/l, vertigo, sleepiness, and diplopia may occur. Nystagmus is not a reliable marker of carbamazepine toxicity because it can happen at low serum concentrations. Correlating hazardous effects with ethosuximide, clonazepam, and valproic acid serum concentrations is challenging [27, 30-34].

CONCLUSION

Mostly seizure patients these days lost self-confidence and have a concern of loss self-image therefore they try to hide their sickness from people. Nowadays, most effective medicine that is being utilized is valproic acid since it is also a first line treatment for epilepsy. These drugs are taken consistently throughout time. After the patient has been seizure-free for four to five years, we can stop the medicine. If stopped early it can also show the reoccurrence of the disease in the patient.

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