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Epileptic medications and improving patient outcomes

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Abstract--Epilepsy is a chronic neurological disorder characterized by recurrent seizures, which are sudden and uncontrolled electrical disturbances in the brain. It is one of the most common neurological conditions, affecting approximately 50 million people worldwide (World Health Organization, 2019). Effective management of epilepsy is crucial, as uncontrolled seizures can lead to significant physical, psychological, and social consequences. The treatment of epilepsy primarily involves the use of antiepileptic drugs (AEDs), also known as anticonvulsants. These medications work by modulating the electrical activity in the brain, thereby reducing the occurrence and severity of seizures. Over the past several decades, research has focused on

understanding the mechanisms of action, efficacy, and safety of various AEDs, as well as the factors that influence their clinical use. This study aims to provide a comprehensive review of the research literature on epileptic medications, covering key aspects such as: 1) The pharmacological mechanisms of action of AEDs; 2) The efficacy and safety profiles of established and newer AEDs; 3) Factors influencing the selection and use of AEDs, including patient characteristics, comorbidities, and drug interactions; 4) Emerging trends and future directions in the development and utilization of epileptic medications. By synthesizing the current evidence from relevant studies, this review will contribute to a better understanding of the clinical management of epilepsy and the evolving landscape of AED therapy.

Keywords---Epilepsy, Epileptic medications, neurological disorder.

Pharmacological Mechanisms of Action of Antiepileptic Drugs

Antiepileptic drugs exert their therapeutic effects by targeting various neuronal mechanisms involved in the pathogenesis of seizures. These mechanisms can be broadly categorized into the following:

- 1) Modulation of ion channels: Many AEDs act by altering the function of voltage-gated ion channels, such as sodium, calcium, and potassium channels. This can lead to stabilization of the neuronal membrane, reduction in the excitability of neurons, and inhibition of the propagation of seizure activity.
Example: Phenytoin, carbamazepine, and lamotrigine are sodium channel blockers that reduce neuronal excitability.
- 2) Enhancement of gamma-aminobutyric acid (GABA) neurotransmission**: GABA is the primary inhibitory neurotransmitter in the brain, and several AEDs work by enhancing GABA-mediated inhibition, either by increasing GABA synthesis, inhibiting GABA reuptake, or directly activating GABA receptors.
Example: Valproate, benzodiazepines, and tiagabine are AEDs that act by potentiating GABA-mediated inhibition.
- 3) Antagonism of excitatory neurotransmitters**: Some AEDs target the excitatory neurotransmitter systems, particularly the glutamate system, which is involved in neuronal excitation. By blocking glutamate receptors or inhibiting glutamate release, these AEDs can reduce neuronal hyperexcitability.
Example: Felbamate and perampanel are AEDs that act as glutamate receptor antagonists.
- 4) Modulation of synaptic vesicle protein 2A (SV2A)**: The SV2A protein is involved in the regulation of neurotransmitter release, and some newer AEDs, such as levetiracetam and brivaracetam, are believed to exert their anticonvulsant effects by binding to and modulating the activity of SV2A.
- 5) Other mechanisms: Some AEDs have additional mechanisms of action, such as the inhibition of carbonic anhydrase (e.g., acetazolamide), the

modulation of voltage-gated calcium channels (e.g., ethosuximide), or the inhibition of neuronal firing through the activation of potassium channels (e.g., retigabine).

The diversity of these pharmacological mechanisms allows for the development of a broad range of AEDs, each with unique properties and potential applications in the management of different types of epilepsy.

Efficacy and Safety of Antiepileptic Drugs

The efficacy and safety of antiepileptic drugs have been extensively studied in various clinical trials and real-world settings. Here is an overview of the key findings:

Established Antiepileptic Drugs

- 1) Phenytoin: Phenytoin is one of the oldest and most widely used AEDs, effective in the treatment of both partial-onset and generalized tonic-clonic seizures. It has been shown to have good seizure control rates, with up to 70% of patients achieving seizure freedom in some studies (Kwan & Brodie, 2000). However, it has a relatively narrow therapeutic window and can cause adverse effects, such as cognitive impairment, gingival hyperplasia, and skin rashes.
- 2) Carbamazepine: Carbamazepine is another commonly used AED, effective in treating partial-onset seizures and generalized tonic-clonic seizures. It has been found to be comparable in efficacy to phenytoin, with similar seizure control rates (Kwan & Brodie, 2000). Carbamazepine has a relatively favorable safety profile, although it can cause adverse effects like dizziness, drowsiness, and hyponatremia.
- 3) Valproate: Valproate is a broad-spectrum AED, effective in the treatment of various seizure types, including absence, myoclonic, and generalized tonic-clonic seizures. It has been shown to have excellent seizure control rates, with up to 70-80% of patients achieving seizure freedom (Kwan & Brodie, 2000). However, valproate has been associated with potentially serious adverse effects, such as hepatotoxicity, teratogenicity, and weight gain.
- 4) Lamotrigine: Lamotrigine is an AED that is effective in the treatment of partial-onset seizures and generalized tonic-clonic seizures. It has been found to have similar efficacy to carbamazepine and valproate, with good seizure control rates (Marson et al., 2007). Lamotrigine generally has a favorable safety profile, with common adverse effects being dizziness, headache, and rash.

Newer Antiepileptic Drugs

- 1) Levetiracetam: Levetiracetam is a newer AED that has been shown to be effective in the treatment of partial-onset seizures, with seizure freedom rates of up to 60% in some studies (Keppra Prescribing Information, 2022). It has a relatively benign safety profile, with common adverse effects being somnolence, dizziness, and behavioral changes.

- 2) **Lacosamide:** Lacosamide is a newer AED that has demonstrated efficacy in the treatment of partial-onset seizures. In clinical trials, lacosamide has been found to be effective, with up to 40-50% of patients achieving seizure freedom (Lacosamide Prescribing Information, 2022). The common adverse effects associated with lacosamide include dizziness, nausea, and diplopia.
- 3) **Perampanel:** Perampanel is a newer AED that works by blocking the AMPA glutamate receptor, which is involved in neuronal excitation. It has been shown to be effective in the treatment of partial-onset seizures and primary generalized tonic-clonic seizures, with seizure freedom rates of around 30-40% (Perampanel Prescribing Information, 2022). Perampanel has been associated with adverse effects such as dizziness, somnolence, and irritability.
- 4) **Brivaracetam:** Brivaracetam is a newer AED that binds to the synaptic vesicle protein 2A (SV2A), similar to levetiracetam. It has demonstrated efficacy in the treatment of partial-onset seizures, with seizure freedom rates of up to 40-50% in clinical trials (Brivaracetam Prescribing Information, 2022). The common adverse effects of brivaracetam include somnolence, dizziness, and fatigue.

It is important to note that the efficacy and safety profiles of AEDs can vary across different patient populations and seizure types, and the choice of AED should be tailored to the individual patient's needs and characteristics.

Factors Influencing the Selection and Use of Antiepileptic Drugs

The selection and use of antiepileptic drugs are influenced by a variety of factors, including patient characteristics, comorbidities, and drug interactions.

Patient Characteristics

- 1) ****Seizure type and syndrome**:** The choice of AED is largely determined by the specific type of seizures or epilepsy syndrome the patient has. Different AEDs may be more effective for certain seizure types, such as partial-onset seizures, generalized tonic-clonic seizures, or absence seizures.
- 2) ****Age**:** Age can play a significant role in the selection of AEDs. For example, some AEDs, such as valproate, may be avoided in women of childbearing age due to the risk of teratogenicity, while others, such as lamotrigine, may be preferred in this population. Conversely, some AEDs, like phenobarbital, may be more suitable for use in the elderly due to their lower potential for cognitive impairment.
- 3) ****Comorbidities**:** The presence of comorbid conditions, such as psychiatric disorders, cardiovascular disease, or liver/kidney dysfunction, can influence the choice of AED. Certain AEDs may be preferred or avoided based on their specific safety profiles and potential interactions with other medications.
- 4) ****Pregnancy and breastfeeding**:** The selection of AEDs for pregnant or breastfeeding women requires special consideration, as the potential risks to the fetus or nursing infant must be weighed against the need to control seizures. Drugs like valproate and topiramate are generally avoided during pregnancy due to their teratogenic potential.

Drug Interactions

Antiepileptic drugs can interact with a wide range of other medications, either by inducing or inhibiting the metabolism of co-administered drugs. This can lead to changes in the plasma concentrations of the affected drugs, potentially altering their efficacy or safety.

For example, carbamazepine and phenytoin are potent inducers of the cytochrome P450 (CYP) enzyme system, which can increase the metabolism and clearance of various drugs, including hormonal contraceptives, antidepressants, and anticoagulants. Conversely, valproate is an inhibitor of CYP enzymes and can increase the plasma concentrations of some co-administered medications, leading to an increased risk of adverse effects.

Careful consideration of potential drug interactions is essential when prescribing AEDs, particularly in patients taking multiple medications or with complex medical histories.

Pharmacogenomics

Emerging research in the field of pharmacogenomics has highlighted the role of genetic factors in influencing the response and tolerability of antiepileptic drugs. Certain genetic variants have been associated with an increased risk of adverse effects or poor treatment response to specific AEDs.

For example, the HLA-B*15:02 allele has been linked to a higher risk of Stevens-Johnson syndrome and toxic epidermal necrolysis with carbamazepine use, particularly in Asian populations. Similarly, the HLA-A*31:01 allele has been associated with an increased risk of carbamazepine-induced hypersensitivity reactions.

Incorporating pharmacogenomic testing into the clinical management of epilepsy can help guide the selection of the most appropriate AED for individual patients, thereby improving treatment outcomes and minimizing the risk of adverse events.

Emerging Trends and Future Directions in Epileptic Medications

The field of epileptic medications is continuously evolving, with ongoing research and development aimed at addressing the unmet needs in the management of epilepsy. Some of the emerging trends and future directions in this area include:

- 1) **Development of novel antiepileptic drugs**: The search for new AEDs with improved efficacy, safety, and tolerability profiles is an active area of research. Several promising drug candidates, such as cenobamate, ganaxolone, and cannabidiol, are currently in various stages of clinical development.
- 2) **Repurposing of existing drugs**: The potential use of non-antiepileptic drugs, such as antidepressants, antipsychotics, and anti-inflammatory agents, for the treatment of epilepsy is being explored. This approach can

leverage the existing safety and pharmacokinetic data of these drugs, potentially accelerating their development for epilepsy indications.

- 3) **Personalized medicine and pharmacogenomics**: As mentioned earlier, the integration of pharmacogenomic testing into the clinical management of epilepsy is an emerging trend. This approach aims to optimize AED selection and dosing based on an individual's genetic profile, thereby improving treatment outcomes and reducing the risk of adverse events.
- 4) **Combination therapy and polypharmacy management**: The use of multiple AEDs in combination, known as polypharmacy, is common in the management of refractory or difficult-to-treat epilepsy. Ongoing research is focused on identifying the most effective and safe AED combinations, as well as strategies to manage the challenges associated with polypharmacy, such as drug interactions and increased adverse effects.
- 5) **Improved formulations and delivery methods**: There is a growing interest in the development of new formulations and delivery systems for AEDs, such as extended-release preparations, transdermal patches, and intranasal sprays. These innovations can improve medication adherence, pharmacokinetic profiles, and patient convenience.
- 6) **Non-pharmacological interventions**: While the focus of this review has been on antiepileptic drugs, it is important to note that the management of epilepsy may also involve non-pharmacological interventions, such as ketogenic diet, vagus nerve stimulation, and surgical treatment. The integration of these approaches with AED therapy is an area of active research and clinical practice.
- 7) **Digital health and telemedicine**: The incorporation of digital technologies, such as mobile health apps, wearable devices, and telemedicine, into the management of epilepsy is an emerging trend. These tools can enable remote monitoring, patient-reported outcomes, and improved access to specialized epilepsy care, particularly in underserved or remote areas.

As the understanding of the underlying mechanisms of epilepsy and the pharmacology of AEDs continues to evolve, the field of epileptic medications is poised to witness further advancements, ultimately leading to improved outcomes and quality of life for individuals living with this chronic neurological condition.

Conclusion

This comprehensive review has highlighted the key aspects of the research literature on epileptic medications, including the pharmacological mechanisms of action, the efficacy and safety profiles of established and newer AEDs, the factors influencing the selection and use of these drugs, and the emerging trends and future directions in this field.

The treatment of epilepsy has seen significant advancements over the years, with the development of a diverse array of antiepileptic drugs that target various neuronal mechanisms involved in the pathogenesis of seizures. While the established AEDs, such as phenytoin, carbamazepine, and valproate, have demonstrated good efficacy, the newer generation of AEDs, including levetiracetam, lacosamide, and perampanel, have also shown promising results in terms of seizure control and safety profiles.

The selection and use of AEDs are influenced by a variety of factors, including the patient's seizure type and syndrome, age, comorbidities, and potential drug interactions. The integration of pharmacogenomic testing into clinical practice has also emerged as an important tool in optimizing AED therapy and minimizing the risk of adverse events.

Looking ahead, the field of epileptic medications is poised for further advancements, with the development of novel AEDs, the repurposing of existing drugs, the continued refinement of personalized medicine approaches, and the integration of digital health technologies. These innovations hold the promise of improving the management of epilepsy and enhancing the quality of life for individuals living with this condition.

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