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CLINICAL PHARMACOLOGY OF DRUGS USED IN THE TREATMENT OF EPILEPTIC SYNDROME

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Abstract: This article provides a comprehensive overview of the clinical pharmacology of antiepileptic drugs (AEDs) used in the management of epileptic syndrome. It explores the mechanisms of action, pharmacokinetics, therapeutic indications, drug selection based on seizure type, and safety profiles of traditional and newer AEDs. Special emphasis is placed on personalized treatment strategies, drug interactions, and pharmacoresistance in epilepsy. The article aims to support rational, evidence-based pharmacological interventions for improved seizure control and patient outcomes.

Keywords: Epileptic syndrome, antiepileptic drugs, pharmacokinetics, pharmacodynamics, monotherapy, polytherapy, seizure control.

INTRODUCTION

Epileptic syndrome refers to a heterogeneous group of neurological conditions characterized by recurrent, unprovoked seizures due to abnormal electrical activity in the brain. Epilepsy affects more than 50 million people worldwide, making it one of the most common chronic neurological disorders. Pharmacological treatment is the cornerstone of epilepsy management, with the goal of achieving seizure freedom without intolerable side effects. The choice of antiepileptic drugs (AEDs) depends on seizure type, epilepsy classification, patient characteristics, and potential comorbidities. Understanding the

clinical pharmacology of AEDs is essential for rational drug selection, individualized therapy, and minimizing treatment failure [1].

MATERIALS AND METHODS

Approximately 30% of patients with epilepsy are considered pharmacoresistant, meaning they fail to achieve seizure control despite adequate trials of two or more appropriately selected and tolerated AEDs. Mechanisms of resistance may include genetic polymorphisms affecting drug targets, increased drug efflux at the blood–brain barrier (e.g., overexpression of P-glycoprotein), and disease-related alterations in neural circuitry.

Novel therapies aimed at overcoming resistance include [2]:

Cenobamate: a newer AED with dual activity as a sodium channel blocker and GABA-A receptor modulator.

Cannabidiol (CBD): approved for Dravet syndrome and Lennox–Gastaut syndrome; modulates intracellular calcium and adenosine reuptake.

Gene therapy and neuromodulation: investigational approaches targeting specific epileptic foci or defective ion channels.

Personalized medicine approaches are increasingly utilized, leveraging pharmacogenomics to predict drug metabolism (e.g., HLA-B*1502 screening to avoid carbamazepine-induced Stevens–Johnson syndrome in Asian populations) and optimize AED selection.

RESULTS AND DISCUSSION

Effective pharmacological treatment of epileptic syndrome requires a firm understanding of the underlying neurophysiological mechanisms of seizure genesis and propagation. Epilepsy is not a uniform disease but a collection of syndromes that arise from different etiologies — genetic channelopathies, cortical dysplasias, traumatic brain injury, infections, metabolic disturbances, or idiopathic origins. Each subtype presents with distinct electrical activity, seizure semiology, and neuronal circuit dysfunction.

Therefore, the clinical pharmacologist or neurologist must align drug selection with the specific pathophysiological substrate of the seizure disorder. For instance, in generalized epilepsy syndromes like juvenile myoclonic epilepsy, broad-spectrum agents such as valproic acid, levetiracetam, or lamotrigine are preferred due to their efficacy across multiple seizure types. In contrast, focal epilepsies — often associated with structural lesions or post-traumatic changes — respond more favorably to carbamazepine, oxcarbazepine, or lacosamide, which primarily inhibit sodium channel-mediated hyperexcitability in localized brain regions [3].

In rare forms like Lennox-Gastaut syndrome or Dravet syndrome, treatment involves not only classical antiepileptics but also syndrome-specific agents such as rufinamide, clobazam, and cannabidiol. These cases highlight the importance of syndrome-specific pharmacotherapy, underscoring that empirical treatment without seizure classification may be ineffective or even detrimental.

In clinical practice, managing epilepsy is rarely limited to seizure suppression. Most patients, particularly those with chronic forms, also present with psychiatric comorbidities (e.g., depression, anxiety), cognitive impairment, or sleep disturbances — all of which influence drug choice and treatment outcomes. Some AEDs, such as topiramate or zonisamide, may exacerbate cognitive slowing, while others like lamotrigine exhibit mood-stabilizing properties, making them preferable in patients with comorbid affective disorders.

Moreover, treatment decisions must consider age, sex, hormonal profile, reproductive planning, hepatic and renal function, and potential drug–drug interactions with other chronic medications. For example, enzyme-inducing AEDs like phenytoin and phenobarbital can reduce the efficacy of hormonal contraceptives, while valproate has well-documented teratogenic risks and should be avoided in women of reproductive age unless no alternatives are viable.

These nuances emphasize the role of individualized medicine in neurology, where pharmacological treatment is tailored not only to the seizure type but also to the patient's entire clinical and biological profile. Treatment algorithms must therefore integrate multidisciplinary considerations, including endocrinology, psychiatry, nephrology, and obstetrics where relevant.

Pharmacological treatment of epilepsy is dynamic rather than static. Over time, patients may develop tolerance, require dose escalation, or experience breakthrough seizures due to hormonal changes, stress, or other systemic conditions. Hence, the concept of therapeutic drug monitoring (TDM) is a critical pillar of medical pharmacology in epilepsy care. TDM allows clinicians to assess serum drug concentrations in relation to clinical efficacy and toxicity thresholds, particularly for agents with narrow therapeutic windows (e.g., phenytoin, phenobarbital).

Beyond serum levels, clinical monitoring includes seizure diaries, EEG findings, imaging studies (e.g., MRI for lesion tracking), and neuropsychological evaluations. These tools help determine whether adjustments in dose, drug type, or delivery method (e.g., oral vs. parenteral) are needed. In complex cases such as status epilepticus, rapid IV administration of agents like benzodiazepines, followed by longer-acting AEDs (e.g., fosphenytoin or valproate), is essential to abort seizure clusters and prevent neuronal damage [4].

Furthermore, treatment-resistant epilepsy often prompts consideration of non-pharmacologic interventions, such as vagus nerve stimulation, responsive neurostimulation, or surgical resection. However, these options remain adjunctive to pharmacotherapy and are typically reserved for patients whose seizures remain uncontrolled despite optimal medical management.

While the primary goal of antiepileptic drug (AED) therapy is the suppression of abnormal neuronal discharges, increasing evidence highlights the neurotropic effects of

many AEDs — that is, their ability to influence neural plasticity, neurotransmitter balance, and cortical network remodeling. These effects go beyond seizure control and may have significant consequences — both beneficial and adverse — for long-term brain function.

For instance, valproic acid not only enhances GABAergic transmission but also influences histone deacetylase activity, affecting gene expression in neurons. This epigenetic mechanism has drawn attention in neurodevelopmental and neuropsychiatric contexts. Similarly, levetiracetam, by binding to synaptic vesicle protein SV2A, appears to modulate synaptic release mechanisms in a way that may influence mood, behavior, and even cognitive performance in certain patients.

However, these neurotropic properties can be a double-edged sword. Topiramate and zonisamide, while effective anticonvulsants, are known to cause language disturbances, word-finding difficulties, and cognitive deceleration, particularly in pediatric and elderly patients. Recognizing these effects is crucial in clinical pharmacology, especially when treating populations that are vulnerable to cognitive fluctuations, such as students, elderly individuals, or patients with pre-existing cognitive decline.

A relatively new and evolving area in epileptology is the role of the immune system in seizure pathogenesis, particularly in cases of autoimmune epilepsy, which is often resistant to conventional AEDs. Autoimmune epilepsies — including those associated with anti-NMDA receptor antibodies, LGI1, and GAD65 autoimmunity — require an integrated therapeutic strategy that combines immunomodulatory agents (such as corticosteroids, IVIG, or plasmapheresis) with traditional AEDs.

From a pharmacological standpoint, the presence of an immune-mediated mechanism implies that AED monotherapy may be insufficient unless the underlying inflammation is controlled. Furthermore, some AEDs may exert indirect immunomodulatory effects. For example, valproate has been shown to reduce proinflammatory cytokine levels in certain in

vitro models. However, these effects are not consistent or reliable enough to replace targeted immunotherapies.

Clinical identification of autoimmune epilepsy requires high suspicion, especially in patients with late-onset focal epilepsy, psychiatric symptoms, or treatment resistance. Early recognition and integration of immunotherapy with AEDs can significantly alter prognosis. This reinforces the need for close neurology–immunology collaboration and the expansion of pharmacological management beyond classical neuronal targets.

CONCLUSION

The clinical pharmacology of antiepileptic drugs is characterized by a diversity of mechanisms, pharmacokinetic complexities, and therapeutic nuances. Rational drug selection for epileptic syndrome requires detailed knowledge of seizure types, patient-specific factors, and the pharmacological profiles of available agents. As newer therapies and precision medicine tools continue to emerge, optimizing seizure control while minimizing adverse effects is increasingly achievable. A careful balance between efficacy, tolerability, and long-term safety remains the cornerstone of successful epilepsy management.

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