INJ INTERNATIONAL NEUROUROLOGY JOURNAL

Therapeutics of Epilepsy: A Review

Usha Adiga *[1], Nandit PB [2]
[1]Professor, NITTE (Deemed to be University), KS Hegde Medical Academy (KSHEMA), Dept of Biochemistry, Mangalore, India 575018
[2]Zonal Medical Advisor, Rivaara Lab Pvt Ltd, Bangalore, India

Abstract

Antiepileptic drugs (AEDs) play a crucial role in the management of epilepsy, a neurological disorder characterized by recurrent and unprovoked seizures. The rationale for using AEDs lies in their ability to modulate the excessive and synchronous electrical activity in the brain that underlies seizures. These medications aim to prevent the spread of abnormal electrical discharges, thus reducing the frequency and severity of seizures and enhancing the individual's quality of life.

AEDs can be classified into several distinct classes based on their mechanisms of action. The first-generation AEDs, including phenobarbital and phenytoin, primarily target voltage-gated ion channels, particularly sodium channels, to dampen neuronal excitability. While effective, these drugs are associated with significant side effects and limited efficacy in certain seizure types. Second-generation AEDs, such as lamotrigine and levetiracetam, offer a broader range of mechanisms, including modulation of calcium channels, enhancement of inhibitory neurotransmission, and reduction of glutamate release. These drugs tend to have a more favorable side effect profile and are often preferred for their versatility.

The third-generation AEDs continue to expand the therapeutic options by targeting novel mechanisms, like the sodium channel blocker lacosamide and the potassium channel opener ezogabine. Additionally, some AEDs exhibit multiple mechanisms of action, exemplified by valproate, which influences GABA levels and ion channels. The diversity of AED mechanisms enables clinicians to tailor treatments to individual patients, optimizing seizure control while minimizing adverse effects.

In recent years, personalized medicine has gained prominence, allowing for a more precise selection of AEDs based on a patient's specific seizure type, underlying etiology, and potential drug interactions. The rational use of AEDs involves considering efficacy, safety, tolerability, and patient-specific factors to devise a comprehensive treatment plan. While these medications can significantly improve seizure management, it's important for healthcare providers to continuously monitor their patients, adjust doses if necessary, and explore new therapies as they emerge, ensuring the best possible outcomes for individuals with epilepsy..

Key words: epilepsy, antiepileptics, mechanism of action, personalized medicine

Introduction

Knowing antiepileptic drugs (AEDs) offers several significant benefits for healthcare professionals, researchers.For healthcare professionals, understanding AEDs enables them to provide more effective and personalized care to patients with epilepsy. They can make informed decisions about drug selection, dosing, and management, leading to better seizure control and enhanced quality of life for their patients.Knowledge of AEDs helps healthcare providers anticipate and manage potential adverse effects and drug interactions. This proactive approach minimizes the risks associated with AED therapy, ensuring that patients receive the most suitable and safest treatment options.Learning about the different classes of AEDs allows healthcare professionals to choose the most appropriate medication based on the patient's seizure type, comorbidities, and individual characteristics. This tailored approach improves treatment outcomes and reduces trial-and-error prescribing.Researchers studying antiepileptic drugs contribute to the development of new therapies and the refinement of existing treatments. In-depth knowledge of AED mechanisms and their effects on neural circuits can lead to the discovery of novel drug targets and more effective therapeutic approaches.Understanding antiepileptics fosters collaboration between various healthcare disciplines, such as neurology, pharmacy, and psychology. Collaborative efforts result in comprehensive and holistic care for patients with epilepsy, addressing both medical and psychosocial aspects.Individuals with epilepsy and their caregivers benefit from understanding the medications used to manage the condition. Education about AEDs promotes treatment adherence, empowers

ISSN:2093-4777 | E-ISSN:2093-6931
DOI: 10.5123/inj.2023.4.inj16
Vol. 27 Iss. 4 (2023)

patients to actively participate in their healthcare decisions, and reduces anxiety related to medication use.Epilepsy is a prevalent neurological disorder worldwide, and gaining knowledge about AEDs contributes to improved global health outcomes. Healthcare professionals equipped with expertise in antiepileptic drugs can positively influence epilepsy management and treatment access in underserved regions.Proficiency in AEDs can open up career opportunities in various healthcare settings, such as epilepsy clinics, research institutions, pharmaceutical companies, and regulatory agencies. Professionals with expertise in antiepileptic drugs are well positioned to contribute to advancements in epilepsy care.

In conclusion, learning about antiepileptic drugs provides a range of benefits that span from improved patient care and safety to fostering innovation and collaboration within the medical community. It empowers healthcare professionals, researchers, and individuals affected by epilepsy to make informed decisions and contribute to the advancement of epilepsy treatment and care.The aim of the review is to summarise the antiepileptics.

Antiseizure Drugs

History of Antiseizure drug:

The first antiseizure drug used was bromide, used in the late 19th century. The first synthetic organic agent recognized as having antiseizure activity was Phenobarbital. Its use was restricted to generalized tonic-clonic seizures and at a lower degree of partial seizures. It does not affect absence seizures. Merritt and Putnam discovered that diphenylhydantoin (phenytoin) suppressed seizures in the absence of sedative effects[1].

Phenobarbital chemical structure was related in most drugs introduced before 1965; these include the hydantoins and the succinimides. Between 1965 and 1990, the chemically distinct structures of the benzodiazepines, carbamazepine, and branched-chain carboxylic acid (sodium valproate) were introduced. Later by the 1990s lamotrigine, gabapentin, topiramate, tiagabine, and levetiracetam were introduced.

The treatment of epilepsy is usually initiated with monotherapy of anti-epileptic drugs, and the dosage is increased if recurrent seizures are observed. If the seizures are not controlled with the initial agent at adequate plasma concentrations, the substitution of a second drug is preferred to the concurrent administration. However, multiple drug therapy may be required, mainly when two or more seizures occur in the same patient[1]

Currently used anti-epileptic drugs are antiseizure agents, but whether they prevent epileptogenesis is uncertain. Anti-epileptic drugs can be classified based on their mechanism of action

- Drugs that decrease in neuronal excitability by delaying the recovery of inactivated Na^+ channels:
  - Phenytoin, Carbamazepine, Lamotrigine, Topiramate
- Drugs that reduce the low threshold calcium currents (T-current) in the thalamic neurons
  - Ethosuximide
- Drugs having an action similar to both phenytoin and ethosuximide
  - Sodium valproate, Zonisamide
- Drugs that enhance inhibition through GABA:
  - Acting through GABA related receptors
    - Barbiturates, Benzodiazepines
  - By releasing GABA from neuronal endings
    - Gabapentin
  - By inhibiting GABA transaminase
    - Sodium valproate, Vigabatrin
  - By inhibiting neuronal reuptake of GABA
    - Tiagabine
- Drugs that decrease the release of the excitatory neurotransmitter glutamate
  - Lamotrigine
- Miscellaneous
  - Levetiracetam, Acetazolamide.

Barbiturates:

Barbiturates usually have antiseizure activity, only some barbiturates such as phenobarbitone have a maximal antiseizure effect. Phenobarbitone was the first efficacious anti-epileptic introduced in 1912. Barbiturates have an aromatic (phenyl) ring at position-5 that exhibits anticonvulsant action. Primidone is a deoxyphenobarbitol. It

is metabolized to phenobarbital and phenylethyl malonamide, and all these agents play a crucial role in anticonvulsant actions.

Phenobarbital binds to the channel modulatory site on the GABA receptor and enhances the GABA-mediated inhibitory effects by increasing the duration of the Cl^- channel opening. It also inhibits glutamate-mediated excitatory effects by blocking the AMPA receptor. The increase in GABA-mediated inhibition and the decrease in glutamate-mediated excitation are observed with therapeutic doses of phenobarbitone and primidone. At higher doses, however, they block L-type Ca^{2+} channels and use-dependent Na^+ channels[1,2]

Phenobarbital is metabolized by the liver and is a potent enzyme inducer for CYP2A, CYP2B, CYP2C, CYP3A, and CYP6A isoforms of cytochrome P-450 and also for glucuronyl transferase enzyme. The plasma half-life of phenobarbital is around 100hrs. Once a steady-state is reached, there is a minimal fluctuation in plasma level for 24hrs.

Phenobarbital and primidone are effective against partial seizures and generalized tonic-clonic seizures but are less effective than phenytoin and carbamazepine. Though both are enzyme inducers, they competitively inhibit each other's metabolism[1,2]

PHENYTOIN:

Phenytoin is effective against all types of focal and tonic-clonic seizures but not absence seizures. Phenytoin exerts antiseizure activity without causing general depression of the CNS. In toxic doses, it may produce excitatory signs and, at lethal levels, a type of decerebrate rigidity[1,2]

Phenytoin prevents the repetitive firing of action potentials evoked by a sustained depolarization of spinal cord neurons, which is conducted by prolonging the recovery rate of voltage-activated Na^+ channels from the inactivated state. Phenytoin also inhibits the presynaptic release of glutamate (excitatory neurotransmitter), facilitates GABA (inhibitory neurotransmitter) release, and reduces Ca^{++} influx. Therapeutic concentrations of phenytoin do not affect resting membrane potential, and standard synaptic transmission is not altered. At concentrations 5-10 fold higher, multiple effects of phenytoin are evident, including reduction of spontaneous activity and enhancement of response to GABA. These effects may underlie some unwanted toxicity associated with high levels of phenytoin[1,2]

Prolonged use might cause gum hypertrophy, hirsutism, hypersensitivity reactions, megaloblastic anemia, osteomalacia, and if used in pregnancy, can cause fetal hydantoin syndrome. Phenytoin is a potent inducer of CYP2C8/9, CYP3A4/5 isoenzymes, and it competitively inhibits CYP2C9/19[2]

Phenytoin is a prime drug for GTCS and partial seizures, but now in the present scenario, phenytoin is used only when better tolerated newer drugs cannot be used[1,2].

BENZODIAZEPINES:

These are primarily used as sedative antianxiety drugs. Diazepam and lorazepam have a well-defined role in the management of status epilepticus. Clobazam is used in various seizure phenotypes and treatment of Lennox-Gastaut syndrome in patients aged two years or old[1,2].

Benzodiazepines potentiate GABA-induced Cl^- influx to produce sedation, and the exact mechanism has been held responsible for the anticonvulsant property. Still, the sites of action in the brain may be different. Clobazam potentiates GABA-mediated neurotransmission in the same fashion as other benzodiazepines at GABA receptors[1,2].

Clonazepam is useful in the therapy of absence seizures and myoclonic seizures in children. However, tolerance to its antiseizure effects is usually after 1-6 months of the administration. Diazepam is an effective agent for the treatment of status epilepticus. Clorazepate is effective in combination with certain other drugs in the treatment of focal seizures. Clobazam is used in various seizure phenotypes and is also used to treat Lennox-Gastaut syndrome in patients aged two years or older[1,2].

CARBAMAZEPINE AND OXCARBAZEPINE:

It is chemically related to imipramine, introduced in the 1960s for trigeminal neuralgia, but soon became a first-line drug for partial seizures and GTCS. Carbamazepine is structurally related to tricyclic antidepressants, while oxcarbazepine is a keto analog of carbamazepine. The therapeutic profile of oxcarbazepine is similar to carbamazepine, while its toxicity profile is better than carbamazepine. Oxcarbazepine is a mild enzyme inducer, and the chances of drug interaction are less compared to carbamazepine.

Like phenytoin, carbamazepine blocks the use-dependent Na^+ channels and inhibits the high-frequency repetitive firing of the neurons in the brain at therapeutic doses.

Carbamazepine is also effective in treating manic depressive psychosis. Carbamazepine can produce therapeutic responses in patients with bipolar disorder. Carbamazepine also has antidiuretic effects[1,2]

SUCCINIMIDES:
Ethosuximide is a primary agent for the treatment of generalized seizures. Ethosuximide reduces low threshold T-type Ca^{++} currents in thalamic neurons. Inhibition of T-type currents is likely the mechanism by which ethosuximide inhibits absence seizures. Ethosuximide is the drug of choice in the absence of seizures. The primary action appears to be exerted on the thalamocortical system, which is involved in the generation of absence seizures. It is used in the treatment of petit mal seizures[2].

LAMOTRIGINE:
Lamotrigine suppresses sustained rapid firing of neurons and produces a voltage and use-dependent inactivation of sodium channels. It appears likely that lamotrigine also inhibits voltage-gated Ca^{2+} channels, particularly the N and P/Q type channels, which would account for its efficacy in primary generalized seizures in childhood, including absence attacks. Lamotrigine also decreases the synaptic release of glutamate [2].

TOPIRAMATE:
Topiramate blocks repetitive firing of cultured spinal cord neurons, as do phenytoin and carbamazepine. Its mechanism of action, therefore, is likely to involve the blocking of voltage-gated sodium channels. Topiramate also appears to potentiate the inhibitory effect of GABA, acting at a site different from the benzodiazepine or barbiturate sites[2].

GABAPENTIN AND PREGABALIN:
Gabapentin is an analog of GABA that is effective against partial seizures. Pregabalin is another GABA analog closely related to gabapentin. This drug has been approved for both antiseizure activities and its analgesic properties[2].

VIGABATRIN:
Vigabatrin is an irreversible inhibitor of GABA aminotransferase (GABA-T), the enzyme responsible for GABA degradation. Vigabatrin produces a sustained increase in the extracellular concentration of GABA in the brain. It is effective in a wide range of seizure models[2].

TIAGABINE:
Tiagabine is an inhibitor of GABA uptake in both neurons and glia. It prolongs the inhibitory action of synaptically released GABA, but its most significant effect may be the potentiation of tonic inhibition[2].

LEVETIRACETAM:
Levetiracetam binds selectively to the synaptic vesicular protein SV_2A. The function of this protein is not understood, but levetiracetam likely modifies the synaptic release of glutamate and GABA through action on vesicular function[2].

ZONISAMIDE:
Zonisamide is a sulfonamide derivative. Its primary site of action appears to be the sodium channel; it may also act on voltage-gated calcium channels. The drug is effective against partial and generalized tonic-clonic seizures and may also be helpful against infantile spasms and certain myoclonias[2].

SODIUM VALPROATE:
Sodium valproate was first identified and synthesized in 1882, but its anticonvulsant activity was discovered

serendipitously by Pierre Eymard. Sodium valproate (2-propylvaleric acid, 2-propylpentanoic acid, or n-dipropylacetic acid) was derived from valeric acid (naturally obtained from the flower of *Valeriana officinalis*).

Sodium valproate is a branched short-chain fatty acid that forms a clear liquid at room temperature and has a half-life of 9-16hrs. This finding was published in 1963, and it is considered a milestone in the history of anti-epileptic treatment. Sodium valproate is an eight-carbon branched-chain carboxylic acid resembling the properties of a weak acid (pKa 4.95). Sodium valproate is commonly prescribed worldwide as a broad-spectrum anti-epileptic drug with specific indications for many forms of epilepsy and many types of seizures, affecting both children and adults [3].

Chemically sodium valproate is sodium dipropyl acetate. It is a branched short-chain aliphatic carboxylic acid derived from naturally occurring valeric acid with a broad spectrum anticonvulsant action. It is more potent in blocking PTZ seizures than in modifying maximal electroshock. Sodium valproate (2-propylpentanoic acid) is a widely used anti-epileptic drug. Fatty acid-binding proteins can absorb sodium valproate, and the effective dose of Sodium valproate depends on the polymorphisms of the fatty acid-binding protein [4].

The mechanism of Sodium valproate has been theorized due to the increased level of GABA by inhibition of GABA transaminase enzyme and by increased activity of GABA synthetase enzyme. Impairment of GABAergic inhibitory activity can lead to convulsions, making the control of this pathway a target for anti-epileptic drugs. GABA is formed from α-ketoglutarate through the tricarboxylic acid (TCA) cycle and metabolized to succinate semialdehyde (SSA) by GABA transaminase (ABAT) and then to succinate by succinate semialdehyde dehydrogenase (ALDH5A1). α-ketoglutarate can also be converted to succinyl CoA through the action of α-ketoglutarate dehydrogenase (OGDH), shunting it away from GABA formation. In-vivo and in-vitro studies have shown that sodium valproate inhibits GABA transaminase and succinate semialdehyde dehydrogenase enzymes, both involved in the GABA degradation pathway[5].

Sodium valproate also blocks the sodium channels and stabilizes the neuronal membrane, which inhibits the generation of the repetitive action potential. Sodium valproate reduces the low threshold calcium currents (T-currents) in the thalamic neurons at clinically relevant concentrations that are slightly higher than those that limit sustained repetitive firing. This effect of T-type currents may contribute to the effectiveness of valproate against focal and tonic-clonic seizures and absence seizures, respectively [5].

Sodium valproate is also a potent inhibitor of histone deacetylase (HDAC), potentially increasing the expression of genes involved in apoptosis and antitumor action. Therefore valproic acid has also been proposed to be a potential antitumor agent [6].

Sodium valproate is available in formulations like syrup, suppositories, tablets, or locale injection: the different formulations can affect the molecule's bioavailability and rate of absorption. Classically age or weight does not influence sodium valproate concentration [7]. Sodium valproate is highly protein-bound (87-95%) resulting in low clearance (6-20 ml/h/kg). Sodium valproate is absorbed rapidly and completely after oral administration. Valproate drug undergoes hepatic metabolism (95%) with less than 5% excreted unchanged in the urine. The metabolism of Sodium valproate has drawn attention since the 1970s. Glucuronide conjugation (50%) and β-oxidation (40%) are the prominent metabolic pathways. In comparison, CYP-mediated oxidation (10%) is a minor pathway. Glucuronide conjugation has been confirmed as the major metabolic pathway.

Sodium valproate has almost complete bioavailability for all formulations. Tmax value of sodium valproate is 1–2 hours for conventional tablets and solutions, 3–6 hours for enteric-coated tablets, and 10–12 hours for sustained-release tablets. The drug's half-life is about 11–20 hours, but shorter 6–12 hours values are observed in patients receiving enzyme-inducing co-medication. Usually, sodium valproate has a relatively shorter half-life; sampling time concerning dose ingestion is essential for interpreting the drug concentration. Ideally, samples for sodium valproate measurements should be collected before the morning dose as trough samples[8].

Adverse effects:

Severe reactions: Sodium valproate has multiple serious adverse reactions such as hepatotoxicity, acute pancreatitis, thrombocytopenia, pancytopenia, hallucinations, psychosis, Stevens-Johnson syndrome, anaphylaxis, hyponatremia, hyperammonemia, myelosuppression, aplastic anemia, polycystic ovarian syndrome, encephalopathy, and coma. Abrupt discontinuation of the drug can cause withdrawal seizures [5].

Common reaction: Patients using sodium valproate have reported common reactions like drowsiness, headache, dizziness, abdominal pain, nausea, vomiting, weight gain, thrombocytopenia, diarrhea, tremors, alopecia, insomnia, depression, rash, nervousness, appetite changes, elevation in ALT and AST values, tinnitus, blurred vision, myalgia, and dyspnea[5].

Contra indications: Sodium valproate is contraindicated in patients with significant hepatic and renal impairment, hypersensitivity to drug components, urea cycle disorders, abnormal mitochondrial disorders, and pregnancy (for migraine headache prophylaxis use of sodium valproate). Also, sodium valproate use requires caution in patients under two years old because the metabolic enzymes get functional only after one year of birth, organic brain disorders, head injury, mental retardation with seizure disorders, congenital metabolic disorders, hereditary mitochondrial disorders, multiple anticonvulsant treatments, and bleeding risk [5].

General principles for initiating anti-epileptic drugs:
The decision to start anti-epileptic treatment primarily depends on the risk of seizure recurrence. Recurrence seizure attack risk of 60% or more is often considered the cut-off for initiating an anti-epileptic drug. Clinical diagnosis of epilepsy is met when a child has two or more unprovoked seizures or if the predicted risk of recurrence of seizure is 60% or severity of seizure is more after the first seizure attack[9]. Factors leading to increased recurrence of seizures after a first seizure include the presence of an abnormal neurologic examination, abnormal brain MRI, abnormal EEG, and history of nocturnal seizures[9]. Abnormal EEG and seizures related to slight brain injury predict an increased risk for recurrence in children. Early initiation of anti-epileptic treatment after the first seizure attack has been shown to delay the second seizure. However, the long-term prognosis is unchanged irrespective of whether treatment is started early or delayed until a second seizure.

Therapeutic Drug Monitoring in Epilepsy (TDM):
TDM was initiated for several anti-epileptic drugs to establish optimal therapy regimens for individual patients. This approach provides clinicians a valuable tool to understand further why patients do not respond satisfactorily to a particular treatment dose. TDM helps to study the variation in pharmacokinetics between individuals and the factors responsible for variation in drug response.

Individualization of dosage during anti-epileptic drug therapy is necessary. Hence identification of the optimal dose on purely clinical examination can be difficult because of many reasons:

- Since anti-epileptic treatment is prophylactic and seizures occur at irregular intervals, it is often challenging to determine rapidly whether the prescribed dosage will be sufficient to produce long-term seizure control.
- Clinical symptoms and signs of toxicity may be subtle or difficult to differentiate from the manifestations of underlying disorders.
- There are no direct laboratory markers for clinical efficacy or the most common manifestations of AED toxicity, such as adverse CNS effects.

TDM seeks to optimize patient outcomes by managing their medication regimen with information on the concentration of AEDs in serum; hence TDM is essential during the therapy of AED [10]. Therapeutic levels of some antiepileptic drugs are mentioned in (Table 1)

Table 1: Therapeutic levels of antiepileptic drugs.

Antiepileptic drug	Therapeutic plasma concentration
Phenytoin	10 - 20 mcg/ml
Phenobarbitone	10 - 40 mcg/ml
Carbamazepine	4-12 mcg/ml
Ethosuximide	40-100 mcg/ml
Sodium valproate	50-100 mcg/ml

Epilepsy is a chronic neurological disorder that is characterized by an enduring predisposition to generate epileptic seizures[11]. Epilepsy is one of the most common neurological disorders affecting individuals of any ethnicity and age. In industrialized countries, 3-4% of people will develop epilepsy during their lifetime. Higher risk is observed in resource-poor countries[12]. Epilepsy is diagnosed mainly on clinical grounds and supporting

investigations, including electroencephalography (EEG) and neuroimaging, primarily magnetic resonance imaging (MRI).

Pharmacogenetics refers to the science about how genetic variations affect the drug metabolism, drug targets, or disease pathways leading to a varying response to the drug about its efficacy or adverse effect. The concept of "individualized medicine" is evolving. There has been a paradigm shift from the concept of "one drug fits all" to "right drug for the right patient at the right dose and time" Inter-individual genetic variations lead to significant heterogeneity of disease pathogenesis and clinical phenotype, as well as to the variability in drug response in terms of efficacy and safety[13]. The challenge in today's generation is to translate accumulating genetic data research into advances in clinical care and to improve the life quality of epileptic children [13].

It has been observed that genetic factors account for about 40% of the etiological cause of epilepsy, and it has been estimated that the risk of epilepsy for offspring and siblings of patients with epilepsy of any cause to be about 2% to 5%[14-16]. With recent advances in genetic testing modalities, multiple gene mutations have been discovered to be the cause of a broad spectrum of genetic epilepsies.

Genetic testing in pediatric epilepsy is an important issue. The results from genetic testing usually are so low that it is not justifiable to do such testing unless there is familial history or if there is drug resistance or developmental delay, or any abnormal neurologic examination observed. In such conditions, genetic testing is justifiable because the yield is relatively high [17].

Genetic testing often leads to searching for underlying etiology. In some situations, finding the underlying etiology may help in the choice of therapy, such as in the case of Dravet syndrome, the avoidance of the use of valproate in patients with polymerase G mutations to avoid the risk of hepatotoxicity, and the diagnosis of glucose transporter deficiency in rare patients with normal cerebrospinal fluid glucose levels, leading to initiation of the ketogenic diet[18].

Genetic diagnosis begins and ends with phenotypic assessment. Epilepsy phenotyping involves a holistic understanding of the child, including the family history with at least a three-generation pedigree, neuro-radiologic findings, and congenital malformations and comorbidities outside the child's nervous system neuro-developmental trajectory and its relationship to the age of epilepsy onset. The epilepsy phenotype includes the evolution of the EEG background over time, seizure types, seizure patterns, and triggers or the context of seizures[19,20]

With regards to epilepsy, Genotype-phenotype correlation is always not clear with drug concentration and clinical outcome. Variable expressivity, genetic heterogeneity, and phenocopies are natural features of most epileptic disorders. However, newly developed tools like Mass-array systems, next-generation sequencing, whole-exome sequencing have permitted us to identify an increasing number of genes and genetic regions, mainly coding for ion channels, neurotransmitters, neurotransmitter receptors, cell adhesion molecules, neurotrophic factors, and factors that are essential for the absorption, distribution, metabolism, and excretion of particular drug molecules. If a mutation is seen, that can predispose or even be the underlying cause of various epileptic disorders[21,22]

Despite the increased availability of newer antiepileptic drugs, the exact mechanism for drug resistance is not studied yet. Several hypothetical studies have been conducted to explain drug resistance epilepsy. The target hypothesis and transporter hypothesis are the most cited ones. There are no studies that can provide a full pathophysiological background of the drug resistance phenomenon[23].

Conclusion

In conclusion, delving into the realm of antiepileptic drugs (AEDs) brings forth a cascade of advantages. It empowers healthcare professionals to optimize patient care, researchers to innovate and uncover new horizons, patients to engage actively in their well-being, and global health efforts to make strides in managing epilepsy. The multifaceted benefits of AED knowledge ripple through medical practice, research, education, and beyond, ultimately leading to improved lives for those touched by epilepsy.

References

1. Brunton LL, Chabner B, Knollmann BC, editors. Goodman & Gilman's the pharmacological basis of therapeutics. New York, NY, USA: McGraw-Hill Education; 2018.
2. Katzung GB, Masters SB, Trevor AJ. *Basic and Clinical Pharmacology,* Fourteenth Edition, Mc Graw Hill Publication, 2018.
3. Puranik YG, Thorn CF, Lamba JK, Leeder JS, Wensong, Birnbaum BK et al. Valproic acid pathway: Pharmacokinetics and Pharmacodynamics. Pharmacogenet Genomics. 2013;23(4):236-241.
4. Bradbury CA, Khanim FL, Hayden R, Bunce CM, White DA, Drayson MT, et al. Histone deacetylases in acute myeloid leukemia show a distinctive pattern of expression that changes selectively in response to deacetylase inhibitors. Leukemia. 2005; 19:1751–1759
5. T. May and B. Rambeck. Serum concentrations of valproic acid: influence of dose and comedication, Therapeutic Drug Monitoring, 1985;7:387-90.
6. Krishnaswamy S, Hao Q, Al-Rohaimi A, Hesse LM, von Moltke LL, Greenblatt DJ. UDP glucuronosyl transferase (UGT) 1A6 pharmacogenetics: II. Functional impact of the three most common nonsynonymous UGT1A6 polymorphisms (S7A, T181A, and R184S). Journal of Pharmacology and Experimental Therapeutics. 2005;313:1340-6.
7. Allain EP, Rouleau M, Lévesque E, Guillemette C. Emerging roles for UDP-glucuronosyltransferases in drug resistance and cancer progression. British journal of cancer. 2020;122:1277-87.
8. Iyanagi T, Haniu M, Sogawa K, Fujii-Kuriyama Y, Watanabe S, Shively JE, Anan KF. Cloning and characterization of cDNA encoding 3-methylcholanthrene inducible rat mRNA for UDP-glucuronosyltransferase. Journal of Biological Chemistry. 1986;261:15607-14.
9. Moosa. Antiepileptic drug treatment of Epilepsy in children. Continuum Journal. 2019:25:381-407.
10. Mackenzie PI, Bock KW, Burchell B, Guillemette C, Ikushiro S-i, Iyanagi T, et al. 'Nomenclature update for the mammalian UDP glycosyltransferase (UGT) gene superfamily,' *Pharmacogenetics and Genomics. 2005;*15:677-685
11. Gregory PA, Lewinsky RH, Gardner-Stephen DA, Mackenzie PI. Regulation of UDP glucuronosyltransferases in the gastrointestinal tract. Toxicology and applied pharmacology. 2004;199:354-63.
12. Bousman C, Al Maruf A, Müller DJ. Towards the integration of pharmacogenetics in psychiatry: a minimum, evidence-based genetic testing panel. Current opinion in psychiatry. 2019;32(1):7-15.
13. Cuéllar-Barboza AB, McElroy SL, Veldic M, Singh B, Kung S, Romo-Nava F, et al., Potential pharmacogenomic targets in bipolar disorder: considerations for current testing and the development of decision support tools to individualize treatment selection. International Journal of Bipolar Disorders. 2020;8:1-7.
14. Perucca P, Scheffer IE, Kiley M. The management of epilepsy in children and adults. Med J Aust. 2018;208(5):226-233.
15. Beghi E, Hesdorffer D. Prevalence of epilepsy – an unknown quantity. Epilepsia 2014;55:963-67.
16. Maagdenberg H, Vijverberg SJ, Bierings MB, Carleton BC, Arets HG, de Boer A, et al. Pharmacogenomics in pediatric patients: towards personalized medicine. Pediatric Drugs 2016;18:251-60.
17. Peljto AL, Barker-Cummings C, Vasoli VM, Leibson CL, Hauser WA, Buchhalter JR, et al. Familial risk of epilepsy: a population-based study. Brain. 2014 Mar;137(3):795-805.
18. Guerrini R, Noebels J. How can advances in epilepsy genetics lead to better treatments and cures? Adv Exp Med Biol 2014;813:309–17.
19. Winawer MR, Shinnar S. Genetic epidemiology of epilepsy or what do we tell families? Epilepsia 2005;46(Suppl 10):24–30.
20. Hani AJ, Mikati HM, Mikati MA. Genetics of Pediatric Epilepsy. Pediatr Clin N Am 2015;62:703-22.
21. Ream MA, Mikati MA. Clinical utility of genetic testing in pediatric drug-resistant epilepsy: a pilot study. Epilepsy Behav 2014;37:241–8.
22. Klein KM, Yendle SC, Harvey AS, Antony JH, Wallace G, Bienvenu T, et al. A distinctive seizure type in patients with CDKL5 mutations: Hypermotor-tonic-spasms sequence. Neurology. 2011;76(16):1436-8.
23. Helbig I, Tayoun AA. Understanding genotypes and phenotypes in epileptic encephalopathies. Mol Syndromol. 2016;7:172–81.

.