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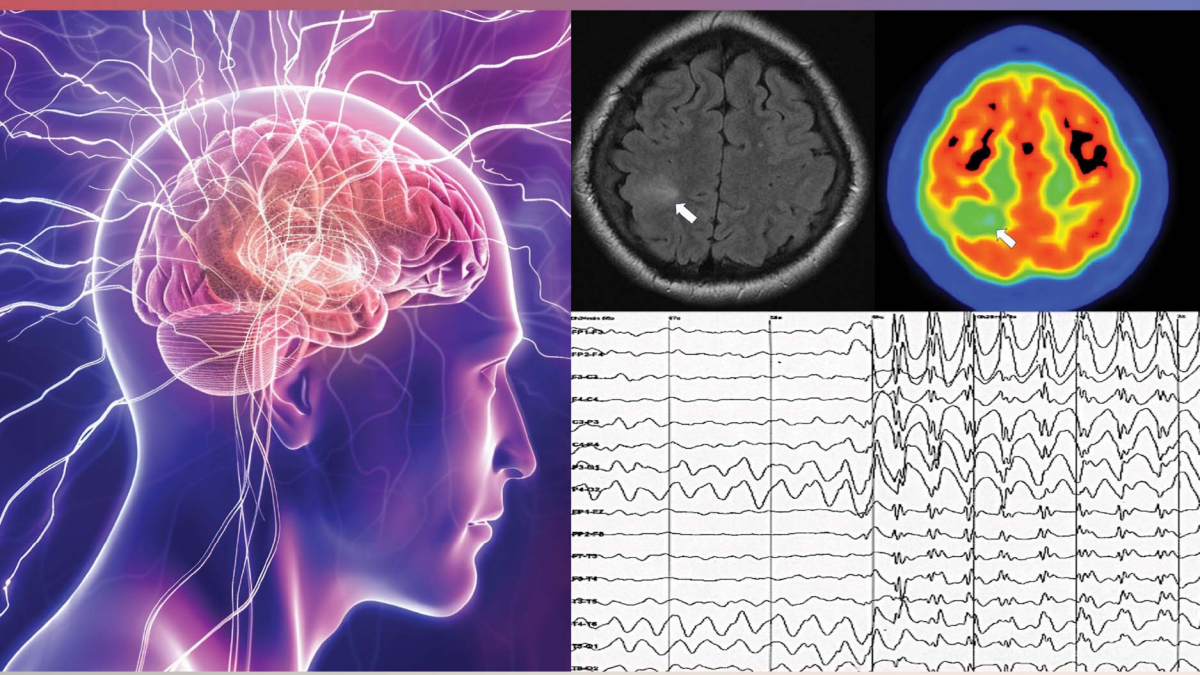
EPILEPSY DEMYSTIFIED

A Clinical Toolkit for Residents and Physicians



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13

Antiseizure Medications: Balancing Efficacy, Safety, and Tolerability

INTRODUCTION

The cornerstone of management of seizures are "antiseizure medications". Former term "antiepileptic drugs" is a misnomer as these drugs do not prevent epileptogenesis pathways, however, control occurrence of seizures. The main objective of antiseizure pharmacotherapy with antiseizure medications (ASMs) for epilepsy is to balance the maximum benefit achieved from the drugs with the adverse effects these drugs impose to the patient.[1]

ANTISEIZURE MEDICATIONS

Antiseizure medications can be classified into various classes based on:

- Generations of drugs in which they were made available
- Mechanism of action
- Drugs depending on types of seizures
- Chemical basis or pharmacological formulation

CLASSIFICATION[1-4]

Generational Classification

With the advent of antiseizure medications in 1912 where phenobarbitone was first used as antiseizure drug in Poland, a few more drugs got added into the list. These drugs were called as the *first generation ASMs.* Then phenytoin was introduced in 1940 which was followed by number of drugs including ethosuximide, carbamazepine, and valproate which were discovered in year 1958, 1974, and 1978, respectively. So, the first generational ASMs are the drugs which came into use in between 1912 and 1978. These are clinically effective but carry more adverse effects in general when they are compared with the newer generations.[2]

Similarly, *second generation ASMs* are relatively newer to the first generational ones. These were discovered between 1989 and 2004 and include medicines namely levetiracetam, lamotrigine, oxcarbazepine, pregabalin,

gabapentin, topiramate, felbamate, tiagabine, vigabatrin, stiripentol, zonisamide, and rufinamide. These drugs are relatively safer and carry lesser adverse effects when these are compared with the first generation ASMs.[2]

The drugs post 2004 are newer and emerging and are termed as *third generation ASMs.* These include drugs such as lacosamide, eslicarbazepine, perampanel, ganaxolone, cenobamate, and cannabidiol. These drugs were developed between 2004 and 2022 and many more are still under development.[2-4]

Mechanism of Action

Antiseizure medications can act on various ion channels or alter neurotransmitter binding to the receptors. The main drug target sites are:

- Sodium channel
- Calcium channel
- Potassium channel
- Synaptic vesicle associated protein
- AMPA receptor
- GABA-glutamate receptors, channels, and metabolism
- Cannabinoid receptors
- Multiple mechanisms of action

Figure 13.1 summarizes the mechanism of action of various ASMs.

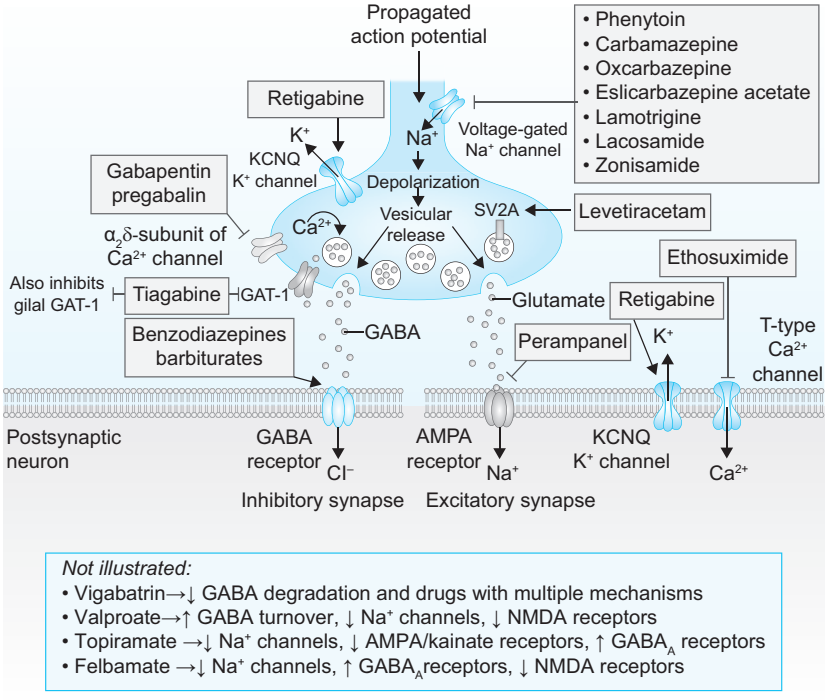

FIG. 13.1: Mechanism of action of antiseizure medications.

Source: Adapted from Shih JJ, Tatum WO, Rudzinski LA. New drug classes for the treatment of partial onset epilepsy: focus on perampanel. Ther Clin Risk Manag. 2013;9:285-93.

Type of Seizures

- *Drugs for focal seizures:* Carbamazepine, lamotrigine, levetiracetam, phenytoin, oxcarbazepine, zonisamide, topiramate, and lacosamide.
- *Drugs for generalized tonic-clonic seizures*:
  - Drugs for absence seizures: Valproate, ethosuximide, and lamotrigine.
  - Drugs for myoclonic seizures: Levetiracetam and valproate.

Based on Pharmacological Composition

The following are various classes of ASMs according to their formulation:

- *Barbiturate group*: Phenobarbitone
- *Deoxybarbiturate group*: Primidone
- *Hydantoin group*: Phenytoin and fosphenytoin
- *Iminostilbene group*: Carbamazepine, oxcarbazepine, and eslicarbazepine
- *Succinimide group*: Ethosuximide
- *Aliphatic carboxylic acid group*: Valproate sodium and divalproex
- *Benzodiazepines*: Diazepam, clonazepam, lorazepam, and clobazam
- *Phenyltriazine group*: Lamotrigine
- *GABA analogs*: Gabapentin and pregabalin
- *Others:* Levetiracetam, brivaracetam, topiramate, zonisamide, lacosamide, vigabatrin, and tiagabine

ANTISEIZURE MEDICATIONS: DOSAGE (PER KG)

Table 13.1 summarizes the doses for routinely used ASMs.

TABLE 13.1: Weight-based dosage of antiseizure medications.

Drug	Starting dose (Adults)	Range of daily maintenance dose	Dose frequency
Sodium valproate	400–600 mg/day	• *Adults*: 500–3,000 mg • *Children*: 10–40 mg/kg	Twice or thrice daily
Ethosuximide	500 mg/day	• *Adults*: 500–1,500 mg • *Children*: 10–15 mg/kg	Once daily
Phenytoin	200–300 mg/day	• *Adults*: 100–400 mg • *Children*: 5–15 mg/kg	Once, twice or thrice daily
Carbamazepine	200 mg/day	• *Adults*: 400–1,800 mg • *Children*: 10–30 mg/kg	Twice or thrice daily
Clonazepam	1 mg/day	• *Adults*: 1–10 mg • *Children*: 0.01–0.3 mg/kg	Once or twice daily
Phenobarbitone	30 mg/day	• *Adults*: 30–240 mg • *Children*: 2–6 mg/kg	Once or twice daily

Continued

Continued

Drug	Starting dose (Adults)	Range of daily maintenance dose	Dose frequency
Lacosamide	50–100 mg/day	• *6–30 kg*: 1 mg/kg PO/IV BID; Increase up to 6–12 mg/kg/day • *30–50 kg*: 1 mg/kg PO/IV BID; Increase up to 4–8 mg/kg/day • *>50 kg*: 50 mg PO/IV BID; Increased till 300–400 mg/day	Twice daily
Lamotrigine	12.5 mg/day	• *With enzyme inducing ASM and no valproic acid (age 2–12 years)*: 0.6 mg/kg/day q12h × 2 weeks then 1.2 mg/kg/day q12h × 2 weeks then at 5 weeks increase by 1.2 mg/kg q1–2 weeks to maintenance dose of 5–15 mg/kg/day q1–2 hours • *With valproic acid (age 2–12 years)*: 0.15 mg/kg/day q12h × 2 weeks then 0.3 mg/kg/day q12h × 2 weeks then at 5 weeks increase by 0.3 mg/kg q1–2 weeks to maintenance dose of 1–5 mg/kg/day q1–2 hour (not >200 mg/day)	Once daily
Perampanel	2 mg/day	2–8 mg/day	Once daily
Clobazam	5 mg/day	• *<30 kg*: 5 mg/day (maximum 20 mg/day) • *>30 kg*: 5 mg q12h (maximum 40 mg/day)	Once or twice daily
Levetiracetam	1,000–1,500 mg/day	• *Adults*: 1,000–1,500 mg • *Children*: 10–15 mg/kg	Twice daily
Brivaracetam	100–150 mg/day	• *Adults*: 100–150 mg • *Children*: 1–1.5 mg/kg	Twice daily

Pharmacokinetics of Commonly Used ASMs

Table 13.2 summarizes pharmacokinetics of commonly used ASMs.

ANTISEIZURE MEDICATION TREATMENT: SIDE EFFECTS

Antiseizure medications like other drugs are not without side effects. Following **Table 13.3** summarizes the dose related as well as idiosyncratic side effects:

TABLE 13.2: Pharmacokinetics of commonly used ASMs.

Pharmacokinetic properties	Sodium valproate	Ethosuximide	Sodium phenytoin	Carbamazepine	Phenobarbitone	Clonazepam
Time for peak level	1–4 hours	1–4 hours	4–12 hours	4–8 hours	1–3 hours	1–6 hours
Elimination half-life in adults	9–21 hours	40–70 hours	9–140 hours	10–30 hours	20–40 hours	50–160 hours
Time for steady state	4 days	7–14 days	7–21 days	Up to 10 days	Up to 14 days	Up to 30 days
Plasma protein binding	90%	Negligible binding	85–90%	75%	85%	45%
Major metabolite	Oxidation products	2 (1-hydroxyethyl) 2-methylsuccinimide	5-(p-hydroxyphenyl) 5-phenylhydantoin	10,11 epoxide	7-aminoclonazepam	Parahydroxyphenobarbitone

TABLE 13.3: Side effects of commonly used antiseizure medications (ASMs).

Drug	Dose related	Idiosyncratic
Clonazepam	• Sedation • Fatigue • Dizziness • Ataxia • Irritability • Hypersalivation • Bronchorrhea • Psychosis	• Rash • Thrombocytopenia
Ethosuximide	• Anorexia • Nausea • Vomiting • Agitation • Drowsiness headache • Lethargy	• Rash • Erythema multiforme • Stevens–Johnson syndrome • Agranulocytosis • Aplastic anemia
Carbamazepine	• Vertigo • Nausea • Diplopia • Headache • Drowsiness • Neutropenia • Hyponatremia • Cardiac arrhythmia	• Skin rash • Aplastic anemia • Stevens–Johnson syndrome • Lupus like syndrome • Thrombocytopenia • Teratogenicity
Valproate	• Weight gain • Tremor • Alopecia • Anorexia • Dyspepsia • Vomiting • Edema • Drowsiness • Hyperammonemia	• Hepatotoxicity • Pancreatitis • Thrombocytopenia • Stupor • Encephalopathy • Teratogenicity
Phenytoin	• Ataxia • Nystagmus • Depression • Drowsiness • Headache • Megaloblastic anemia • Osteomalacia neonatal hemorrhage	• Acne • Gum hypertrophy • Coarse facies • Hirsutism • Rash • Stevens–Johnson syndrome • Blood dyscrasias • Pseudolymphoma • Dupuytren's contracture • Hepatotoxicity • Teratogenicity

Continued

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Drug	Dose related	Idiosyncratic
Phenobarbitone	• Drowsiness • Fatigue • Depression • Hyperkinesia • Distractibility • Irritability • Poor memory • Megaloblastic anemia • Neonatal hemorrhage • Osteomalacia	• Maculopapular rash • Exfoliation • Toxic epidermal necrolysis • Teratogenicity • Hepatotoxicity

ANTISEIZURE MEDICATION TREATMENT: DRUG INTERACTIONS

Changes in plasma concentration of an ASM when a new ASM is added is shown in **Table 13.4**.

Table 13.5 shows changes in plasma concentration of ASM when an another drug is introduced along with ASM.

ANTISEIZURE MEDICATION TREATMENT: INITIATION AND REGULATION[1-4]

- Start therapy with drug of choice.
- *Choice of treatment depends upon various factors*:
  - Patient related
  - Drug related
  - Drug–drug interactions
  - Previous trial of drug successful or not
  - Type of seizures, epilepsy, and epilepsy syndromes
  - Cost effectiveness
- Reports clearly favor monotherapy and avoidance of polytherapy. In about 80% of the adult patients, seizure can be controlled by a drug. Addition of a second drug helps about 20% of those who failed to response to monotherapy.
- Single drug treatment is simpler. Improves patient compliance, reduces immediate and long-term side effects and avoids drug interaction.
- Initial dose of most anticonvulsants is one-third or one-fourth of the maintenance dose. Phenytoin can be started with full dose.
- Slowly increase to reach full dose over 3 weeks.
- Measure lowest plasma levels during steady state, if facility is available. Monotherapy should be strived for. Once a drug has been introduced,

TABLE 13.4: Drug interactions among commonly used ASMs.

Drugs	CBZ	VPA	PHT	PB
CBZ	——	⇩	⇧⇩	——
VPA	⇧	——	⇧⇩	⇧
PHT	⇩	——	——	⇧
PB	⇩	——	⇧⇩	——

(CBZ: carbamazepine; PB: phenobarbitone; PHT: phenytoin; VPA: valproate; ⇧ : increase; ⇩ : decrease)

TABLE 13.5: Drug interactions of commonly used ASMs with other drugs.

Drug	PHT	CBZ	VPA	PB
Analgesics/Antipyretics				
Aspirin	Increase	-	Increase	-
Ibuprofen	Increase	-	-	-
Gastrointestinal drugs				
Ranitidine	Increase	-	-	-
Cimetidine	Increase	Increase	-	-
Cardiovascular drugs				
Diltiazem	-	Increase	-	-
Nifedipine	Increase	-	-	-
Verapamil	-	Increase	-	-
Antimicrobials drugs				
Erythromycin	-	Increase	-	-
Isoniazid	Increase	Increase	-	-
Rifampicin	Decrease	-	-	-
Psychotropic drugs				
Chlorpromazine	Increase	-	Increase	-
Imipramine	Increase	-	-	-

(CBZ: carbamazepine; PB: phenobarbitone; PHT: phenytoin; VPA: valproate)

its dose should be increased slowly and progressively until either seizure control is achieved, or clinical side effects appear. Allow the drug to achieve a steady state before increasing its dose.

- If seizure occurs despite an adequate dose, a second drug of choice should be tried while withdrawing the first drug slowly over the period of 2–4 weeks. Should the second drug fail, a third drug of choice should be tried while withdrawing the second drug.

- If at least three drugs are properly tried without control of seizures, the combination of drugs should be used.
- The goal of drug therapy is to control or eradicate the seizures with the minimum of side effects. Regular medications or drug compliance is very important.

Important note: It is important to note that combination of drugs of same class with similar mechanism of action need to be avoided as they can just cause more side effects than the benefits. Hence, ASMs with different mechanism of action are added in a combination therapy for better clinical outcomes.

Preferred combinations of ASMs:
- Combinations of ASMs with minimal or no hepatic metabolism
- Weak or no enzyme inducing properties along with ASMs with no or minimal hepatic metabolism

Combinations to be avoided:
- ASMs which are hepatic enzyme inducers along with other ASMs enzyme induction properties
- ASMs which cause hepatic enzyme induction include—phenytoin, phenobarbitone, primidone, carbamazepine, oxcarbazepine, eslicarbazepine, topiramate, etc.
- ASMs which are nonenzyme inducers include—clobazam, valproate, levetiracetam, brivaracetam, gabapentin, pregabalin, tiagabine, etc.

CONCLUSION

Antiseizure medications form the cornerstone of epilepsy management. Advances in pharmacology have expanded treatment options, allowing more individualized therapy with improved safety profiles. Understanding drug mechanisms, indications, and adverse effects is crucial for optimizing treatment outcomes.

KEY POINTS

- ASMs control seizures but do not cure epilepsy.
- Drugs can be classified by generation, mechanism, or seizure type.
- Newer ASMs have improved tolerability.
- Rational drug selection is essential for seizure control.
- Monitoring for adverse effects and drug interactions is important.

Note: Most of the seizures can be controlled by monotherapy. A specialist's opinion should be sought in patients with uncontrolled seizures on polytherapy.

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EPILEPSY DEMYSTIFIED

A Clinical Toolkit for Residents and Physicians

Epilepsy Demystified: A Clinical Toolkit for Residents and Physicians is a practical, clinically focused guide designed to simplify the complexities of epilepsy care. Bridging the gap between theory and bedside practice, this book offers a structured and evidence-based approach to the diagnosis and management of seizure disorders. Covering key areas such as seizure classification, EEG interpretation, neuroimaging, pharmacotherapy, and surgical options, it equips clinicians with essential tools for real-world decision-making. Special emphasis is placed on epilepsy mimics, status epilepticus, drug-resistant epilepsy, and care across diverse patient populations. With insights into genetics, emerging therapies, and psychosocial aspects, this book serves as a concise yet comprehensive resource for residents, physicians, and neurologists striving for excellence in epilepsy management.

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