ANTIEPILEPTIC DRUGS

Epilepsy

- Epilepsy is a common neurological abnormality affecting about 1% of the world population.
- A seizure means a paroxysmal abnormal discharge at high frequency, from an aggregate of neurons in cerebral cortex.
- The term seizure needs to be carefully distinguished from convulsions and epilepsy.

Epilepsy

- Epilepsy is a condition characterised by recurrent episodes of such seizures.
- a patient should not be described as having epilepsy until a few episodes of "non-febrile" seizures have appeared.
- The site of the origin of discharge is called "epileptic focus".
- From here the discharge spreads to the surrounding areas of the brain.

Epilepsy

- The word fit is often used to describe an epileptic seizure.
- Convulsions are involuntary, violent and spasmodic or prolonged contractions of skeletal muscle.
- That means, a patient may have epilepsy without convulsions and vice versa.

CLASSIFICATION OF SEIZURES

- At present there are two systems of classification of seizure disorders.
- The first system is based on seizure types and their characteristic features.
- This system is more useful in selecting the appropriate drug for a treating a particular type of seizure.
- The second system is based on epilepsy syndrome which includes aetiological factors, frequency of attacks, age at the onset and clinical manifestation of epilepsy

CLASSIFICATION OF SEIZURES

- Syndrome Classification" is more useful in assessing the long-term prognosis after deciding the therapeutic strategy.
- Since syndrome classification is more complex, because of too many variables, a simplified approach based on classification of "seizure types“ is more suited to our discussion on antiepileptic drugs.
- Broadly speaking, the seizure activity is either generalised or partial.

Generalised Seizures

- These seizures arise from both cerebral hemispheres and diencephalon simultaneously, involving the entire body, and have characteristic bilateral pattern in EEG recording.
- These are of following types.
- **Grand Mal or Tonic-Clonic Seizures**
  These are usually associated with an aura prior to seizures.
- The patient falls to the ground in stiff tonic phase (legs extended) with an epileptic cry, caused by tonic contraction of laryngeal muscles.
- This is followed by clonic convulsions (repetitive bilateral muscle jerking) and then to coma which may last for about 15-30 min.

Generalised Seizures

- Recovery is associated with amnesia, mental confusion, postictal (post seizure) depression, incontinence and exhaustion.
- EEG shows a bilateral diffused pattern of high-voltage polyspikes of 10-30 Hz/sec in tonic-clonic phase.
- Almost 10% of total epileptic cases suffer from grand mal epilepsy but fortunately respond well to pharmacotherapy.
- In some cases, grand mal seizures occur repeatedly with no recovery of consciousness in between the attacks.
- These type of seizures are called as status epilepticus, which represent a state of clinical emergency.

Petit Mal or Absence Seizures

- There is no aura associated with this disorder and attack appears without warning.
- no loss of consciousness.
- seizure typically lasts for few seconds, so if there is a lapse of consciousness, it is hardly for 5 sec with no loss of postural control.
- no postictal confusion or amnesia.
- characterised by bilateral motor symptoms such as rapid blinking of eyelids, chewing movements or small amplitude clonic jerks of the hands for a few seconds.
- EEG hallmark of typical absence seizures is a generalised symmetric 3 Hz spikes and wave pattern of discharge per second that begins and ends suddenly

Petit Mal or Absence Seizures

- These are the main seizure types in 15-20% of epileptic children.
- These children may experience absence seizures hundred times per day.
- About 60-70% of such patients will have spontaneous remission during adolescence.
- These seizures too, are responsive to pharmacotherapy.
- **Atypical absence seizures** are of slower onset and of longer duration.
- These are less responsive to pharmacotherapy as these are associated with other neurologic complications like mental retardation.

Myoclonic Seizures

- These are bilateral epileptic myoclonus characterised by sudden and brief skeletal muscle contraction that may involve the entire body or one part of the body.
- Most commonly the patient complains of sudden jerking movements appearing during sleep.
- EEG shows 2 Hz spikes and wave pattern per second.

Akinetic (Atonic) Seizures

- These are characterised by sudden loss of postural tone.
- The head may sag to one side or the patient may fall all of a sudden.
- The consciousness may be impaired for a brief period but there is no postictal confusion.
- The EEG shows brief generalised spike and wave discharge followed by diffused slow waves that correlate with loss of muscle tone.

Generalised Seizures

- **Clonic Seizures**
  These are characterised by repetitive muscle jerks.
  EEG shows fast activity (10 Hz or more) slow waves.
- **Tonic Seizures**
  These are characterised by rigid violent muscular contraction with stiff and fixed extended limbs.
- EEG shows low-voltage fast-activity waves.
- **Partial Seizures (Localised/Focal)**
  These are the most common seizure types occurring in approximately 80% of epileptic patients.
- The seizure activity is restricted to a discreet area belonging to one cerebral hemisphere only.
- These are of three types:

Partial Seizures

- **Simple Partial Seizures (Jacksonian Seizures)**

- These are characterised by unilateral clonic movements that begin in one group of muscles and spread gradually to adjacent group reflecting the march of epileptic activity (e.g., mouth, thumb, great toe).
- Such type of Jacksonian seizures are called Jacksonian motor seizures.
- Alternatively, the patient may have somatosensory symptoms such as auditory, visual or olfactory hallucinations or at times "pins and needle" sensations with no reason (Jacksonian sensory seizures).
- There is no loss of consciousness in simple partial seizures.

Partial Seizures

- **Complex Partial Seizures (Psychomotor Epilepsy)**
  These usually originate in the temporal or the frontal lobe and are accompanied by partial loss of consciousness.
- It is a dreamy state of psychic seizures where the patient behaves as partially conscious with automatism.
- He may get up, put on his clothes, start walking or even drive his car but does not follow your commands and does not even recollect the events after the attack is over.
- The attack is usually associated with auditory, visual or olfactory aura.
- Sometimes patient shows other types of automatisms like lip smacking, fumbling and scratching of which the patient has no memory.

Partial Seizures

- **Partial Seizures Evolving to Secondary Generalised Seizures**
  These are the type when partial seizures progress to generalised/tonic/clonic/tonic-clonic seizures.
- Patients usually report aura beforehand.
- **Unclassified Seizures**
  It covers undetermined epilepsies and epileptic syndromes such as:
- (a) **Febrile seizures** wherein young children frequently develop seizures with illness accompanied by hyperpyrexia,
- (b) **Infantile spasm** with progressive mental retardation.
- These are generalised tonic-clonic convulsions of short duration which may appear frightening but are usually benign.

CLASSIFICATION BASED ON EPILEPSY SYNDROMES

- type of seizure,
- aetiology,
- anatomy,
- precipitating factors,
- age of onset,
- severity and chronicity of attacks as well as
- prognosis.

syndrome classification

- One major advantage of the "syndrome classification" is to recognise that a simple partial seizure can later progress to complex partial seizure and then to a secondary generalised seizure.
- There are at present more than 40 distinct epilepsy syndromes and more may follow.
- All of them fall into three categories:

syndrome classification

- **1. IDIOPATHIC**
- in which no cause could be identified except for genetic linkage.
- Examples include: Juvenile myoclonic epilepsy syndrome, mesial
  temporal lobe epilepsy syndrome and juvenile absence epilepsy syndrome.

- **2. SYMPTOMATIC**
- in which the seizures are associated with some identifiable underlying disorders.
- Examples include Lennox-Gastaut epilepsy syndrome (impaired cognitive functions)

syndrome classification

- 3. **CRYPTOGENIC**
- In which the epilepsy appears to be symptomatic but the exact cause is not known.
- Examples include: West's syndrome (infantile spasm), neonatal seizures and febrile convulsions.

AETIOLOGY OF SEIZURES AND EPILEPSY

- **Genetic or heredity**:
- It is apparent that hereditary factors do play a role in the etiology of human epilepsies and that epilepsy genes do exist and the aetiology of at least may be quite important in some forms of epilepsies such as
- juvenile myoclonic epilepsy syndrome,
- childhood absence epilepsy syndrome,
- juvenile absence epilepsy syndrome
- progressive myoclonic epilepsy syndrome.

AETIOLOGY OF SEIZURES AND EPILEPSY

- Brain lesions, mainly due to birth trauma.
- Infections like cerebral meningitis and brain abscess.
- Metabolic disorders like lack of oxygen, alkalosis, hypoglycemia, hypocalcaemia, hyperpyrexia and vitamin B_6 deficiency.
- Sudden withdrawal of many drugs of abuse such as barbiturates and alcohol.
- Viewing television, disco flashes and listening full blast Pop music (Musicogenic temporal lobe seizures).

ENDOGENOUS ANTISEIZURE SUBSTANCES (EAS)

- It seems, some sort of regulatory mechanism must be existing within the body, otherwise why, without outside drug intervention, there should be a spontaneous arrest of seizure activity after an attack and why the brain could remain seizure free for sometime between the two intervening attacks (postictal refractory period).
- The available reports are strongly in favour of an involvement of the purine nucleoside-adenosine-asan endogenous antiseizure substance (EAS) in epilepsy.
- Adenosine has been shown to inhibit spontaneous firing of cells in virtually all areas of brain including cerebral cortex.
- It has been identified endogenously, causes hyperpolarisation and exhibits A_1 receptor mediated anticonvulsant effects in animal models when administered exogenously.

ENDOGENOUS ANTISEIZURE SUBSTANCES (EAS)

- Since it is released postictally and itself is not tonically active, A_1 receptor antagonists per se do not exhibit any convulsant activity.
- Elevated adenosine levels have been reported immediately after the seizure activity both in animal models as well as in patients.
- Adenosine, therefore, seems to fulfil all the criteria for an EAS for development of newer antiepileptic drugs.

MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS IN GENERAL

- Anticonvulsant drugs act by different mechanisms to suppress repetitive firing action potentials by an epileptic focus in the brain.
- However, some drugs act by multiple mechanisms

A)MECHANISMS OF DRUGS USED IN GRAND MAL AND PARTIAL SEIZURES

- **1. Inhibition of Use-Dependent Na Channels**
- Many drugs (e.g. phenytoin, carbamazepine,valproate, lacosamide and lamotrigine)
- preferentially block the voltage-gated (VG) Na channels that remain open due to repetitive neuronal firing.
- higher the frequency of the firing the greater is the block.
- These drugs, prolong the duration of 'inactivated phase' of VG-Na channel and delay its reversion to the 'resting phase'.
- reduces their chances of becoming available again for activation
- Inhibition of VG-Na channels ultimately diminish glutamate release from the glutamatergic neurons.

2. Enhancement of GABAergic Action

- Some of the antiepileptic drugs (e.g. phenobarbital and benzodiazepines) activate GABA, receptors to facilitate GABA-mediated opening of CI channels.
- Benzodiazepines increase the frequency while phenobarbital increases the duration of the opening of Cl channel
- Some drugs (e.g., vigabatrin) inhibit the enzyme GABA-transaminase, which is responsible to metabolise GABA, and thus increase the neuronal concentration of GABA.
- Tiagabine and valproate rather inhibit GABA uptake by inhibiting the GABA uptake transporter (GAT) in neurons as well as in glia.
- It enhances the availability as well as the inhibitory actions of GABA at postsynaptic GABA, receptors.
- Valproic acid, also activates glutamic acid decarboxylase (GAD) and thus increases the synthesis of GABA .

3. Blockade of NMDA or AMPA Receptors

- Activation of NDA and AMPA receptors by glutamate produces depolarising responses and initiates seizure activity.
- The anticonvulsant action of felbamate involves blockade of NMDA receptors.
- Phenobarbital, topiramate and lamotrigine block AMPA receptors.
- Valproate possibly inhibits glutamate synthesis.

A)MECHANISMS OF DRUGS USED IN GRAND MAL AND PARTIAL SEIZURES

- **4. Blockade of Voltage-gated N- Type Ca Channels**

- Some drugs (lamotrigine and gabapentin) act by inhibiting VG-Ca channels (N-type) which ultimately decrease the synaptic release of glutamate.

- **5. Selective Binding to Synaptic Vesicular Protein (SV_2A**

- Levetiracetam selectively binds to SV_2A protein of synaptic vesicles in glutamatergic and GABAergic neurons
- decrease the synaptic release of glutamate while increase the release of GABA (modulates the release).

6. By Blocking the Effects of Neurotrophic Factors

- Lacosamide inhibits Collapsin-Response Mediator Protein (CRMP-2).
- This protein is involved in the production and release of Brain-Derived Neurotrophic Factor (BDNF) and other neurotrophins (NT-3).
- BDNF and NT-3 play on important role in epileptogenesis by provoking membrane excitability and by promoting synaptic plasticity.

B) Mechanisms of Drugs Used in Petit Mal (Absence Seizures)

- **Inhibition of T-type Ca^{2+} Channels**
- Ethosuximide is a major drug used for the treatment of absence seizures.
- It inhibits the low threshold Ca currents carried by T-type Ca channels .
- T-type Ca currents are responsible for generating the thalamic cortical pacemaker currents, in the form of 3 Hz spikes and waves, seen in petit mal attack.
- Inhibition or reduction of the low-threshold T-type Ca channels also account for the anti-seizure activity of valproic acid against absence seizures.

ANTICONVULSANT DRUG THERAPY: GENERAL CONSIDERATIONS

- Antiepileptic drugs can control but do not cure epilepsy.
- The primary objective of anticonvulsant therapy is to suppress seizures and provide neuroprotection by minimising deleterious effects from seizure attacks.
- Many patients with epilepsy have to take medication throughout their life to ensure control of seizures.
- Over the past 15 years there has been an introduction of at least 30 new antiepileptic drugs

GENERAL CONSIDERATIONS

- (vigabatrin, topiramate, gabapentin , levetiracetam, lamotrigine, felbamate, oxcarbazepine , lacosamide and many more)
- But none has been found to be superior to major standard anticonvulsant drugs such as phenytoin,
  carbamazepine and sodium valproate.
- Newer additions are merely serving as "add-on" drugs.

GENERAL CONSIDERATIONS

- Broadly speaking, the drugs effective in generalised tonic-clonic seizures (grand mal) are usually effective in partial seizures (more specifically complex partial seizures).
- Sudden withdrawal of these drugs carries a greater risk of precipitating withdrawal seizures.
- These drugs are not effective in, rather can aggravate, absence (petit mal) and myoclonic seizures.

GENERAL CONSIDERATIONS

- On the contrary, the drugs effective in petit mal (absence) seizures can be used for treating myoclonic seizures but not grand mal or partial seizures.
- A sudden withdrawal of drugs belonging to this category, carries a lower risk of precipitating withdrawal seizures.
- Nevertheless, it is generally recommended that the antiepileptic drug should always be withdrawn slowly over a period of six months.

GENERAL CONSIDERATIONS

- Among the currently available antiepileptic drugs, phenytoin, phenobarbital, primidone, carbamazepine and oxcarbazepine are enzyme inducers.
- Oxcarbazepine appears to induce hepatic enzymes to a lesser extent than carbamazepine which minimises its drug interactions.

GENERAL CONSIDERATIONS

- On the other hand, valproic acid is a potent enzyme inhibitor.
- Many clinicians no longer undertake routine monitoring of plasma concentration for most anticonvulsant drugs because plasma concentrations hardly serve as a useful guideline to change the dose.
- It is not a substitute for clinical assessment.
- The exception is phenytoin which follows mixed- order elimination kinetics. As a result, a monitoring of its plasma concentration becomes essential because its therapeutic window is also smaller

GENERAL CONSIDERATIONS

- With other drugs, usually the dose is increased to the maximum tolerated level and, if seizures do not stop, it is replaced by another.
- Newer drugs may also be added, if desired. Most antiseizure drugs are not highly boundto plasma proteins except for phenytoin (90-92%) and sodium valproate (93-95%) which may lead to drug displacement reactions.
- As a rule, the antiepileptic drugs should not be stopped during pregnancy.
- One can use the lowest dose of the least teratogenic drug but maternal seizures should not be allowed to go unchecked as they are harmful to the foetus because of the possibility of anoxia and metabolic disorders.

GENERAL CONSIDERATIONS

- Minor seizures can be ignored.
- Folic acid supplements may be added, as many antiepileptic drugs cause folic acid deficiency which is reponsible for neural tube defects (spina bifida and anencephaly).
- Antiepileptic drugs which are enzyme inducers lower the maternal plasma levels of vitamin K, leading to postpartum haemorrhage.
- Hence oral vitamin K, may also be supplemented during the last two weeks of the pregnancy.

GENERAL CONSIDERATIONS

- Some antiepileptic drugs (phenytoin, phenobarbital, primidone, carbamazepine and oxcarbazepine) induce steroid metabolising enzymes to cause failure of normal contraception.
- Even topiramate for some unknown reasons makes birth control pills less effective. Hence if the pills are to be continued, higher doses of estrogen (50 mg/day) are needed.
- Such dose adjustments are not needed with sodium valproate or lamotrigine as theseare enzyme inhibitors not inducers.
- Though antiepilepsy drugs are secreted through breast milk to some extent, the risk: benefit ratio favours breast feeding to continue whilst taking antiepileptic drugs.

GENERAL CONSIDERATIONS

- In spite of controversies, it is at least clear that children born to mothers taking anticonvulsant drugs have an increased risk of teratogenicity leading to congenital malformations.
- Available literature shows teratogenic rank order of various antiseizure drugs as follows:
- Trimethadione > valproic acid > phenytoin > phenobarbital = primidone > carbamazepine >oxcarbazepine > topiramate > lamotrigine = ethosuximide.
- With current information, among the standard drugs, carbamazepine, oxcarbazepine, lamotrigine and ethosuximide seem to be the safest drugs during pregnancy.

Phenytoin

- Phenytoin is an oldest non-sedative antiepilepsy drug.
- Chemically it is diphenylhydantoin.
- Fosphenytoin is a prodrug which is rapidly converted to phenytoin in the plasma.
- It is better tolerated than phenytoin on parenteral administration.
- Phenytoin provides a good example of the application of pharmacokinetics

Mechanism of Action

- Phenytoin, at therapeutic plasma levels (10-20 ug/ ml), blocks the use-dependent Na channels and thus inhibits the generation of repetitive action potentials
- At higher doses it also reduces the influx of Ca (during depolarisation) and suppresses repetitive firing of neurons
- Both these actions decrease glutamate release.

Therapeutic Uses and Plasma Levels

- 1. ANTIEPILEPTIC USE: To treat partial seizures (specially psychomotor), generalised tonic-clonic and status epileptics (fosphenytoin slow I.V.)
- For psychomotor seizures, it is the drug of firstchoice.
- For generalised tonic-clonic and status epilepticus it serves as a second choice.
- Phenytoin is contraindicated in petit mal (absence) and in myoclonic seizures

2. NON-ANTIEPILEPTIC USE

- a) To treat trigeminal neuralgia where it is second choice (carbamazepine serves as first choice),
- (b) to treat toxicity ventricular arrhythmias due to digitalis
- (c) to enhance wound healing as recent reports suggest that phenytoin holds promise in healing of wounds

3. THERAPEUTIC PLASMA PEUTIC PLASMA LEVEL

- for most of the epileptic patients is between 10-20 ug/ml.
- In usual practice, oral therapy is started with a dosage of free 300 mg/day which keeps the patient seizure with minimal side effects.
- If seizures are not controlled, doses may be increased in smaller increments of 25-30 mg giving ample time for attainment of steady state levels before further increasing the dose.
- Plasma levels above 20 ug/ml lead to toxicity.

Pharmacokinetics

- Oral absorption is slow but is complete (80-90%). Changing from one dosage form of a particular brand to another can lead to suboptimal or toxic plasma levels, due to differences in bioavailability.
- Phenytoin is not given by I.M. or I.V. route (except for fosphenytoin). I.M. injection of phenytoin gets precipitated in muscle and causes pain, while I.V. injection can produce thrombophlebitis and hypotension.
- Even fast I.V. injection of fosphenytoin can lead to cardiovascular collapse and hence should be administered slowly

Phenytoin

- Phenytoin is 90-92% protein bound
- It is a potent enzyme inducer both for CYP3A4 and glucurony] transferase enzymes.
- Metabolites are eliminated through urine.
- Phenytoin, as free drug , is also excreted through saliva.
- Its elimination is dose dependent and follows saturation (mixed order) kinetics.
- Up to plasma levels of 10-20 ug/ml, its elimination obeys I order kinetics.
- Hence its half-life remains constant and plasma levels do not fluctuate.
- Beyond 20 Mg/ml, the elimination follows zero-order kinetics and hence a slight increase in its dose results into larger increase in to toxicity.

Phenytoin

- Periodic assessment of plasma concentration and subsequent dose adjustments are therefore needed particularly in neonates and in patients suffering from uraemia, liver disease and hypoproteinaemia.
- Its plasma half-life is about 24 hrs; hence five days are needed to attain steady state plasma levels.
- This time lag can be shortened by giving a loading dose (if required) followed by a maintenance dose.

Adverse Effects

- OVERDOSE TOXICITY (Plasma levels beyond 30 ug/ml):
- It is manifested by nystagmus, ataxia, CNS depression, lethargy, and blurred vision.
- If the dose is very high or if I. V. injection is administered faster, it can lead to cardiovascular collapse and coma.

CHRONIC TOXICITY
(after prolonged use)

- **Gingival hyperplasia and coarsening of facial features**:
- Phenytoin after being secreted through saliva, inhibits the enzyme collagenase which is responsible for the breakdown of collagen of connective tissues.
- It has recently been reported that phenytoin increases platelet-derived growth factors-B (PDGF-B) and its mRNA from macrophages that are thought to enhance wound healing, induce gingival fibroblast and promote local angiogenesis.

CHRONIC TOXICITY

- **Megaloblastic anemia**:
- Phenytoin induces hydroxylating enzyme activity for the which folates are cofactors.
- As serum folic acid levels go down, the body's demand for folic acid increases.
- This leads to megaloblastic anemia, which is responsive to folic acid supplements.

CHRONIC TOXICITY

- **Vitamin K deficiency**: caused by phenytoin, leads to hypoprothrombinaemia and haemorrhage in the newborn consequently if the mother had received phenytoin during pregnancy.
- Vitamin K supplements can therefore be used either for treatment or as prophylaxis.

CHRONIC TOXICITY

- Phenytoin increases the metabolism of calciferol and produces vitamin-D deficiency.
- Phenytoin also increases the metabolism of vitamin K and reduces the concentration of vitamin K-dependent proteins which are necessary for normal Ca metabolism in bone.
- This leads to rickets in malnourished children and osteomalacia in adults.
- These conditions can be prevented by administering both vitamin D and vitamin K.

CHRONIC TOXICITY

- Hirsutism (in females) and acne may appear due to increased secretion of androgens.
- Phenytoin inhibits insulin secretion and may cause hyperglycaemia.
- It also decreases ADH release.
- Use of phenytoin during pregnancy increases the risk of congenital malformation (cleft lip, cleft palate and congenital heart disease).
- These are associated with the formation of a toxic epoxide metabolite and also with the impaired DNA synthesis due to folate deficiency.
- Other adverse effects include hypersensitivity reactions like skin rashes, fever, hepatitis and some CNS effects such as vertigo, nausea, tremors and confusion.

Drug Interactions

- Phenytoin should not be discontinued suddenly as it may precipitate withdrawal seizures
- Drug Interactions
- 1. Phenytoin, being enzyme inducer, increases the metabolism of corticosteroids, oral contraceptives doxycycline, rifampicin, theophylline, levodopa, vit. D and vit. K.
- The therapeutic efficacy of these drugs is, therefore, impaired by phenytoin.

Drug Interactions

- 2. Enzyme inhibitors like disulfiram, cimetidine, isoniazid, chloramphenicol decrease the metabolism of phenytoin (increase its plasma concentration)
- 3. Carbamazepine and phenytoin or phenobarbital and phenytoin increase each other's metabolism.
- 4. Sodium valproate displaces protein bound phenytoin and inhibits its metabolism also.
- Hence plasma level of free phenytoin increases.

Phenobarbital and Primidone

- Barbiturates having an aromatic (phenyl) ring at position-5, exhibit anticonvulsant action
- Primidone is a deoxyphenobarbital (one oxygen less).
- It is metabolised to phenobarbital and phenylethyl malonamide and all these three anticonvulsants.
- Since both agents are phenobarbital and primidone are similar chemically and pharmacologically

Mechanism of Action

- Phenobarbital binds to the channel modulatory site the GABA on the GABA receptor and enhances mediated inhibitory effects by increasing the duration of Cl channel opening
- It also inhibits glutamate mediated excitatory effects by blocking AMPA receptor
- Both the increase in GABA-mediated inhibition and the decrease in glutamate-mediated excitation are seen with therapeutic doses of phenobarbital and primidone
- At higher doses, however, they block L type Ca channels and the use-dependent Na" channels.

Therapeutic Uses and Plasma Levels

- Both are effective against partial seizures and generalised tonic-clonic seizures but are less effective than phenytoin and carbamazepine.
- Phenobarbital has been indicated for prophylaxis after febrile seizures in children but its use has declined

Phenobarbital and Primidone

- Combination of phenobarbital and phenytoin works better than either drug alone.
- Though both are enzyme inducers, they competitively inhibit each other's metabolism.
- Tolerance develops to its sedative action but not to its anticonvulsant action.
- Phenobarbital should not be discontinued suddenly as it precipitates withdrawal seizures.
- These are contraindicated in petit mal (absence) seizures and in porphyria

Phenobarbital and Primidone

- Therapeutic levels for phenobarbital in most patients range from 10-40 ug/ml; but many patients appear to tolerate chronic levels above 40 ug/ml,
- While in febrile seizures levels below 15 ug/ml are ineffective.
- Hence only the clinical response serves as a guildeline for dose adjustments.
- Usual doses for phenobarbital are 60-180 mg daily orally at night; of primidone are initially 125 mg daily at night, slowly increased to 250 mg BD orally.

Pharmacokinetics

- Oral absorption is slow but almost complete (85-90%).
- It is metabolised by 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.
- Plasma half-life of phenobarbital is around 100 hrs; hence once steady state is reached there are very small fluctuations in plasma levels for 24 hrs.

Adverse Effects

- Adverse effects due to enzymatic induction are same as for phenytoin.
- However, phenobarbital does not cause gingival hyperplasia, coarsening of facial features and hirsutism.
- Paradoxically, it can cause irritability and hyper-excitability in children. Being longer acting, the chances of developing dependence are much less
- Compared to phenytoin it is relatively free of teratogenic effects; but when both are given together (a commonly used combination) teratogenicity increases for some unknown reasons.

Carbamazepine and Oxcarbazepine

- Carbamazepine is structurally related to tricyclic antidepressants while oxcarbazepine is a keto analogue of carbamazepine.
- The therapeutic profile of oxcarbazepine is similar to, while its toxicity profile is better than, carbamazepine.
- Oxcarbazepine is a mild enzyme inducer and hence chances of drug interaction are less compared to carbamazepine.

Mechanism of Action

- Like phenytoin, carbamazepine blocks the use-dependent Na channels
- inhibits high-frequency repetitive firing of the neurons in brain, at therapeutic doses.
- Therapeutic Uses and Plasma Levels
- ANTIEPILEPTIC USE: It is the drug of first choice for partial as well as generalised tonic-clonic seizures.
- Its use is contraindicated in absence seizures.

1 NON-ANTICONVULSANT USE

- It is a drug of first choice for
- (a) trigeminal neuralgia and in other neuropathic pain such as glossopharyngeal neuralgia and post-herpetic neuralgia.
- However, it is not an analgesic as it is ineffective in other types of pain such as headache or backache.
- It seems to interrupt temporal summation of high-frequency afferent nerve impulses;
- (b) carbamazepine is also effective in treating manic depressive psychosis

THE THERAPEUTIC PLASMA LEVELS

- 4-8 ug/ml, but these barely correlate with the clinical response as some patients report diplopia even at plasma levels of 6-7 ug/ml while others can tolerate levels above 10 ug/ml.
- The usual adult dose, given orally, is 100-200 mg twice or thrice daily increasing slowly to a maximum of 200-400 mg twice or thrice daily.
- For oxcarbazepine the usual oral dose is 300 mg BD daily which can be slowly increased to 450 mg BD daily.

Pharmacokinetics

- Oral absorption of carbamazepine is slow.
- Giving the drug after meals helps the patients to tolerate. It is distributed mainly in brain, liver and kidneys.
- Carbamazepine is metabolised by CYP3A4, a cytochrome P-450 isoform which it induces along with glucuronyl transferase leading to various drug interactions.
- Its metabolites are excreted through urine.
- Oxcarbazepine is, however, a poor enzyme inducer.
- It is rapidly converted to 10-hydroxy metabolite which itself has anticonvulsant effects.

Adverse Effects

- (a) The dose-related adverse effects of carbamazepine start with drowsiness followed by dizziness, headache, slurred speech , vertigo, ataxia and diplopia.
- For drowsiness and headache, the tolerance develops over a period of few weeks;
- (b) The drug can cause allergic reaction such as rashes and fever.

Adverse Effects

- Other idiosyncratic reactions include blood dyscrasias, aplastic anaemia, leukopenia, hepatitis and systemic lupus erythematosus but these are seen in patients being treated for trigeminal neuralgia;
- (c) Since carbamazepine stimulates ADH secretion it can cause water retention and hyponatraemia,

Adverse Effects

- (d) Risk of teratogenicity with carbamazepine is low but can craniofacial defects and induce finger nail hypoplasia, delayed development of foetus.
- However, its combination with valproic acid increases the risk of teratogenicity.
- Nonetheless, the overall incidence of toxicity of carbamazepine seems to be fairly low at usual therapeutic doses.

Drug Interactions

- Oxcarbazepine shows reactions and lesser hypersensitivity has milder side effect profile compared to carbamazepine.
- Drug Interactions
- Erythromycin, fluoxetine and isoniazid inhibit the metabolism of carbamazepine and precipitate toxicity.

Drug Interactions

- Carbamazepine and phenytoin increase each other's metabolism.
- Being enzyme inducer, it reduces the plasma concentration of haloperidol and oral contraceptives.
- No clinically significant drug displacement reactions occur with carbamazepine.

Ethosuximide

- Ethosuximide belongs to the succinimide group of anticonvulsants.
- Being the drug of first choice for absence (petit mal) seizures it is also called "pure petitmal drug".
- Earlier, another drug trimethadione was used to treat absence seizures, but it is now no longer employed because of its toxicity and teratogenicity.

Mechanism of Action

- It inhibits the low-threshold T-type Ca channels
- Therapeutic Uses and Plasma Levels
- It is used as a pure petit mal drug.
- The therapeutic plasma levels are 60-100 ug/ml.
- These can be achieved by an oral dose of 20-30 mg/kg/day
- Some patients can tolerate plasma concentrations up to 120 ug/ml without any complaints of side effects.
- Salivary titres also reflect plasma concentrations accurately, and may be useful to monitor blood levels.

Pharmacokinetics

- Absorption is almost complete after oral administration.
- It is metabolised in liver and its metabolites are excreted through urine.
- The drug obeys first-order elimination kinetics.
- **Adverse Effects**
- It commonly causes GIT distress, headache, dizziness, hiccups, lethargy and euphoria.
- Serious reactions with ethosuximide are rare; yet non-dose related idiosyncratic adverse effects may include skin rashes, fever, eosinophilia and bonemarrow depression.
- Ethosuximide is lesser teratogenic compared to other drugs and hence is preferred in pregnancy.
- Drug Interactions
  Valproic acid inhibits ethosuximide metabolism and clearance and increases its plasma levels.

Trimethadione

- Though no longer used these days, it can still be used in patients not responding to any other drug.
- Its mechanism of action and therapeutic uses are similar to ethosuximide.
- Oral doses for adults are 30 mg/kg/day.
- The drug is much more toxic than ethosuximide.
- **Adverse effects** include sedation and reversible hemeralopia
- (glare effect and photophobia due to drug effects on neural layers of retina).
- If it occurs, there is no need to withdraw the drug but the patient should be advised to wear coloured glasses.
- The drug has serious teratogenic effects and if it is to be used during pregnancy, a medical termination of pregnancy should be advised

Valproic Acid (Sodium Valproate)

- Whether it is used as valproic acid or as sodium valproate or as valproate semisodium (divalproex),
- It is the valproate ion which is the active form and is absorbed from GIT.
- The latter is also available as enteric-coated tablet and in extended release form.

Mechanism of Action

- The drug probably owes its broad spectrum of activity to more than one molecular activity.
- It has been shown to
- (1) block use-dependent Na channels
- (2) increase GABA activity by activating glutamic acid decarboxylase (GAD) and by inhibiting GABA transaminase
- (3) decrease the release of excitatory neurotransmitter glutamate in the brain and
- (4) blocks T-type Ca channels

Therapeutic Use and Plasma Levels

- **ANTIEPILEPTIC USE:**
- Valproate has a broader spectrum of antiepileptic activity.
- It is very effective against absence seizures
- It is usually preferred if the patient has concomitant generalised tonic-clonic attacks and myoclonic seizures.
- In combination with clonazepam it can be used to treat cortical myoclonus.
- A few patients of atonic attacks and many cases of partial seizures also respond with valproic acid.
- It is also a drug of choice for Lennox-Gastaut syndrome and for infantile spasm because of its wider therapeutic spectrum.
- As discussed above the withdrawal of valproate should be gradual to avoid precipitation of withdrawal seizures.

THERAPEUTIC PLASMA LEVELS

- valproate range from 50-100 ug/ml which may be attained by giving an oral dose of sod. valproate as 300 mg BD orally, slowly increased to 500 mg - 1 g BD.
- For valproate semisodium (Divalproex sod.) the dose is 500 mg BD, slowly increased to 1 g BD.
- Some patients can tolerate levels in excess of 100 ug/ml or a dose of 60 mg/kg/day, so the clinical assessment is a better index than plasma levels.

NON-ANTIEPILEPTIC USE

- (1) enteric-coated tablet of valproate semisodium (divalproex sodium) is used to treat manic depressive bipolar disorder;
- (2) Divalporex is also used for the tension prophylaxis of migraine and type cluster headache in a dose equivalent to 250 mg of valproic acid twice daily;

NON-ANTIEPILEPTIC USE

- (3) Valproate has beenused with metyrapone to reduce cortisol secretion in the management Cushing's syndrome;
- (4) Valproate due of to its GABAergic action has been tried with encouraging results in the management of tardive dyskinesia and
- (5) It can also be used as an alternative drug to carbamazepine to treat trigeminal neuralgia.

Pharmacokinetics

- Valproate is well absorbed dose.
- Food delays (80%) following an oral absorption, but the toxicity is reduced if the drug is given after meals.
- It is 90-95% bound to plasma proteins.
- It is potent enzyme intibitor and can inhibit its own metabolism and that of other drugs like phenobarbital.
- The protein binding property OE and its enzyme inhibiting action can contribute to many drug interactions.
- An enteric-coated tablet as well as slow release preparation of divalproex sodium is also available.

Adverse Effects

- Dose related side effects include weight gain, increase in appetite, GIT distress, tremors and reversible alopecia.
- Idiosyncratic toxicity is limited to hepatotoxicity which may be fatal.
- The risk is greater in children below 3 years and in those taking a combination of valproate with phenobarbital.
- Other idiosyncratic toxicities include pancreatitis and thrombocytopenia .
- Valproic acid is associated with neural tube defects and its use during pregnancy results in a higher risk of spina bifida.

Drug Interactions

- It is not a CNS depressant but potentiates the CNS depressant effects of phenobarbitone and benzodiazepines.
- increases the plasma concentration of phenobarbital.
- It decreases the metabolism as well as displaces phenytoin from protein binding sites which results in increased phenytoin toxicity.

Benzodiazepines

- The remarkable antiseizure potency of benzodiazepines has two prominent drawbacks which limit their usefulness as antiepileptic drugs.
- The first is their pronounced sedative effects and second is the development of tolerance to their anticonvulsant effects.
- Several benzodiazepines are used in the management of epileptic seizures.

Benzodiazepines

- **<u>Mechanism of Action</u>**
- They enhance the frequency of GABA mediated Cl channel opening
- At higher doses they also block use-dependent Na channels which contributes to their effectiveness in treating generalised status epilepticus.

Benzodiazepines

- **Diazepam**
- 20-30 mg (slow I.V.) is highly effective for stopping generalised tonic-clonic status epilepticus.
- I.V. for treating local anaesthetic induced seizures.
- For children at high risk of developing recurrent febrile seizures, rectally administered diazepam, at the time of fever, may prevent recurrent seizures.
- Clonazepam is more potent and longer acting than diazepam.
- greater efficacy against absence seizures and is also useful as an adjuvant in myoclonic and akinetic epilepsy.

Benzodiazepines

- **Clorazepate**
- is used as an adjunct drug for the treatment of complex partial seizures, in childhood myoclonic epilepsy and in complex partial seizures.
- **Clobazam**
- is less sedative and longer acting than diazepam.
- It is active against partial and generalised seizures in the patients of all ages but is usually indicated for adjunctive therapy.

NEWER ANTIEPILEPTIC DRUGS

- Newer agents are mostly "add-on" drugs that are expected to have more favourable safety profile in terms of toxicity, teratogenicity and drug interactions.
- **Vigabatrin**
  It is an irreversible inhibitor of GABA transaminase elevates GABA levels in the brain
- The primary indication for vigabatrin is in the treatment of simple and complex partial seizures but it can also be used for generalised seizures.

Vigabatrin

- It can also be used as an adjunct drug for treating drug-refractory epilepsy and infantile spasm.
- It should not be used in cases of absence epilepsy or myoclonic seizures.
- The usual dose is 2 g/day orally, to be taken in equally divided doses.
- Side effects include behavioural changes (caution for psychic or elderly patients), sedation, amnesia and weight gain.
- Vigabatrin in 1 % of cases causes irreversible visual field defects due to peripheral retinal atrophy.
- Hence, it should not be used in patients with pre-existing visual field defects and in children suffering from infantile spasm, in whom visual field monitoring is not possible.

Tiagabine

- It inhibits GABA uptake by neurons and glia and thus increases the GABA content of brain
- It is primarily used for the treatment of partial complex seizures, and as an adjunctive drug for refractory complex epilepsy.
- Side effects include dizziness, fatigue, sedation, tremors and confusion.
- Usual doses for adults are 20-60 mg/day in three to four equally divided doses.

Gabapentin and Pregabalin

- Both are GABA analogues which readily cross BBB and increase the synthesis and release of GABA to increase the GABA concentration in the brain.
- They also inhibit N-type Ca channels and decrease the synaptic release of glutamate in therapeutic doses.
- Recent evidence suggests that they also function as GABA, receptor agonists.

Gabapentin and Pregabalin

- The absorption of gabapentin from intestine depends on the carrier system and shows the property does not of saturation.
- Therefore increasing the dose proportionately increase the amount of drug absorbed which makes it relatively safe drug even after over dosing.
- It is neither metabolised, nor bound to plasma proteins and is excreted unchanged by kidneys.
- Drug interactions are also minimal.

Gabapentin and Pregabalin

- As an adjunct, it is effective in treating drug resistant partial seizures and generalised tonic-clonic seizures.
- Usual adult dose is 200-300 mg orally TDS.
- During chronic nerve injury, the α2δ subunits of L-type Ca channels, in peripheral nerves, get upregulated resulting in various types of neuropathies.
- Gabapentin binds tightly to α2δ type subunits and therefore has been found useful in treating diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia and pain associated with multiple selerosis, (1800 mg/day orally in divided doses).
- Side effects include drowsiness, fatigue, dizziness, weight gain and ataxia.
- Dose of pregabalin is 200-600 mg orally TDS.
- Uses and effects are similar to gabapentin.

Topiramate

- It is a broad-spectrum anticonvulsant drug acting by multiple mechanisms such as
- (1) blockade of use- dependent Na channels
- (2) activation of GABA, receptor and
- (3) inhibition of AMPA receptors for glutamate .
- It is most useful for generalised tonic-clonic, partial and absence seizures as well as for Lennox-Gastaut syndrome.
- Usual adult dose ranges from 300-600 mg/day orally in divided doses.
- Side effects include sedation, somnolence, amnesia, urolithiasis (as it also inhibits carbonic anhydrase enzyme) and teratogenic risk (hypospadias in male infants).

Zonisamide

- This is also a broad-spectrum anticonvulsant drug having multiple modes of action which include
- (1) blockade of use-dependent Na channels and inhibition of T-type Ca channels
- It has a good bioavilability, linear elimination kinetics, negligible protein binding and renal excretion.
- The drug is effective against partial, generalised tonic-clonic and myoclonic seizures,
- It is also useful against infantile spasm and Lennox-Gastaut syndrome.
- Usual dose for adults ranges from 100-600 mg/day orally in two or three equally divided doses.
- Side effects include drowsiness, amnesia, skin rash and kidney stones (due to carbonic anhydrase inhibition).

Lamotrigine

- It also has a broad spectrum of antiepileptic action.
- It directly blocks voltage-gated Na channels as well as N-type Ca channels and ultimately inhibits the release of excitatory neurotransmitter glutamate.
- It is quite effective in treating partial, generalised tonic-clonic, secondary generalised, absence and atonic seizures.
- It also appears to be effective in myoclonic seizures in children.
- Usual adult oral dose ranges from 100-300 mg/day in divided doses.
- The drug in a dose of 100- 200 mg/day orally is also effective in treating bipolar disorder as an "add-on" drug
- Side effects include dizziness, ataxia, diplopia and skin rash (more common and severe in children below 16 yrs).
- Enzyme inducers like phenytoin and carbamazepine decrease while enzyme inhibitors like valproic acid increase the half-life of lamotrigine.

Felbamate

- It also has a wider spectrum of antiepileptic activity, yet not popular because of its unpredictable toxicity.
- Although it blocks voltage-gated Na channels,
- blockade of NMDA receptors by antagonism at glycine sites of this receptor
- It is useful in drug refractory epilepsies such as Lennox-Gastaut syndrome.

Felbamate

- Other indications include atonic seizures, atypical absence seizures, partial seizures and generalised tonic-clonic seizures.
- Oral adult dose ranges from 2000-4000 mg/day in three or four equally divided doses.
- Usual side effects are insomnia, nausea, dizziness and ataxia.
- Unfortunately, felbamate is associated with unpredictable aplastic anaemia and hepatotoxicity, hence its use is not popular.
- It has been **withdrawn** from market in some countries.

Levetiracetam

- It is a piracetam derivative whose mechanism of action is uncertain.
- However, it binds selectively to SV_2A protein of synaptic vesicles in glutamatergic and GABAergic neurons
- The drug is used specifically for treating partial seizures.
- Its elimination kinetics is linear and hence drug interactions are minimal.
- Usual oral adult dose is 500 mg twice daily.
- Side effects include somnolence, asthenia and dizziness.

Lacosamide

- This drug has recently been approved by FDA (2008) for the treatment of partial seizures.
- It acts by inhibiting
- (1) VG-Na+ channels
- (2) Collapsin-Response Mediator Protein-2 (CRMP-2)
- Usual doses start with 50 mg BD orally and increasing by 100 mg every week till 300 mg BD.
- Side effects are mild, e.g., headache, nausea and dizziness.
- Oral bioavailability is 100%.
- No clinically important drug interactions have been reported.
- It is neither an enzyme inducer nor inhibitor.

NON-PHARMACOLOGICAL APPROACH

- Vagus nerve stimulation (VNS) has recently been for treatment of partial approved by FDA as an option complex seizures with or without secondary generalisations.
- It is believed that visceral afferents from the left vagus stimulate the solitary nucleus which induces neuronal or neurotransmitter changes protect against seizures.
- This unique therapy is to safe with tolerable side effects such as transient hoarseness of voice with coughing and pain during stimulation.