Epilepsy

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Introduction

- Definition: Epilepsy is a group of CNS disorders characterized by sudden excessive cerebral discharge(EEG discharge) (abnormal), resulting in brief episodes of loss or disturbance of consciousness with or without characteristic body movements.
- Seizures that are prolonged or repetitive can be life-threatening.
- The effect epilepsy has on patient's lives can be extremely frustrating (patients with epilepsy are concerned about driving, their future, forming relationships, safety, social isolation, social stigma, and so on).

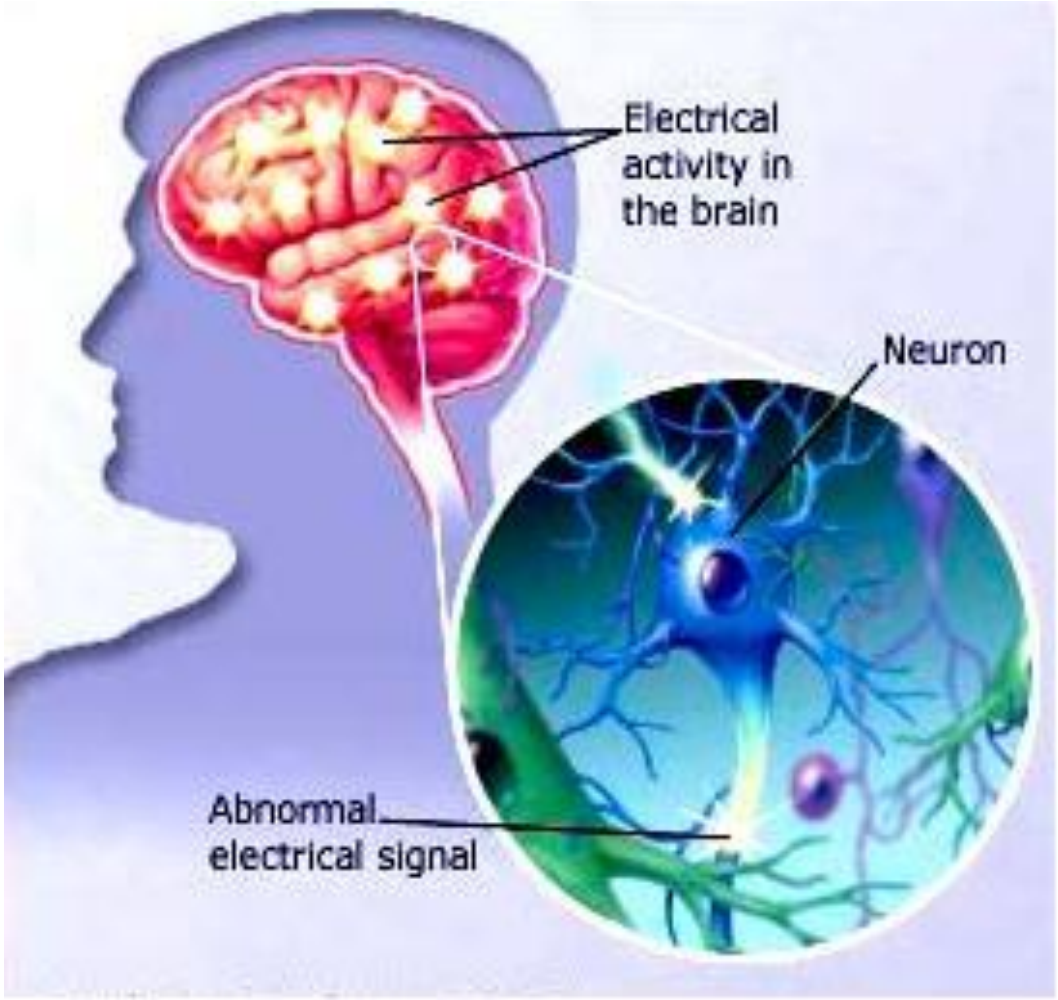


Fig: Abnormal electrical activity in brain neurons

Epidemiology

- Each year, 120 per 100,000 people in the United States come to medical attention because of a newly recognized seizure.
- At least 8% of the general population will have at least one seizure in a lifetime.
- Some seizures may occur as single events resulting from withdrawal of central nervous system (CNS) depressants (e.g., alcohol, barbiturates, and other drugs) or during acute illnesses (such as meningitis or encephalitis) or toxic conditions (e.g., uremia or eclampsia).

Etiology

1. Primary/Idiopathic epilepsy
   - No known cause.
   - A genetic predisposition has been suggested.
   - Patients with mental retardation and cerebral palsy are at increased risk for seizures.
2. Secondary/Symptomatic epilepsy
   a. Brain hemorrhage, head injury, brain tumors, hypoxia, fever, increased intracranial pressure, sleep deprivation, sensory stimuli, and emotional stress.

b. Drugs & chemicals:

- Theophylline, caffeine, phenothiazines (high-dose), antidepressants (especially maprotiline or buproprion), lignocaine, cocaine, nikethamide, ethanol, Penicillin G, isoniazid (INH), camphor, picrotoxin, pentylenetetrazol (PTZ).

Pathophysiology

- An abnormality of potassium conductance, a defect in the voltage-sensitive ion channels, or a deficiency in the membrane ATPases linked to ion transport may result in neuronal membrane instability and a seizure.
- Selected neurotransmitters (e.g., glutamate, aspartate, acetylcholine, norepinephrine, histamine, corticotropin releasing factor, purines, peptides, cytokines, and steroid hormones) enhance the excitability and propagation of neuronal activity.
- Where as GABA and dopamine inhibit neuronal activity and propagation.
- A relative deficiency of inhibitory neurotransmitters such as GABA or an increase in excitatory neurotransmitters such as glutamate would promote abnormal neuronal activity.

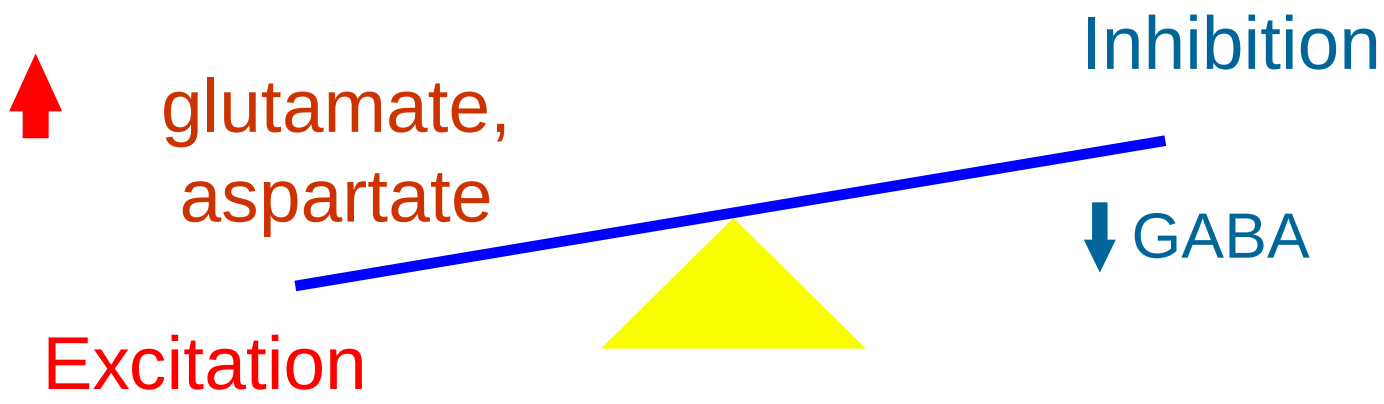


Fig: Imbalance between inhibitory & excitatory transmission

Modified from White, 2001

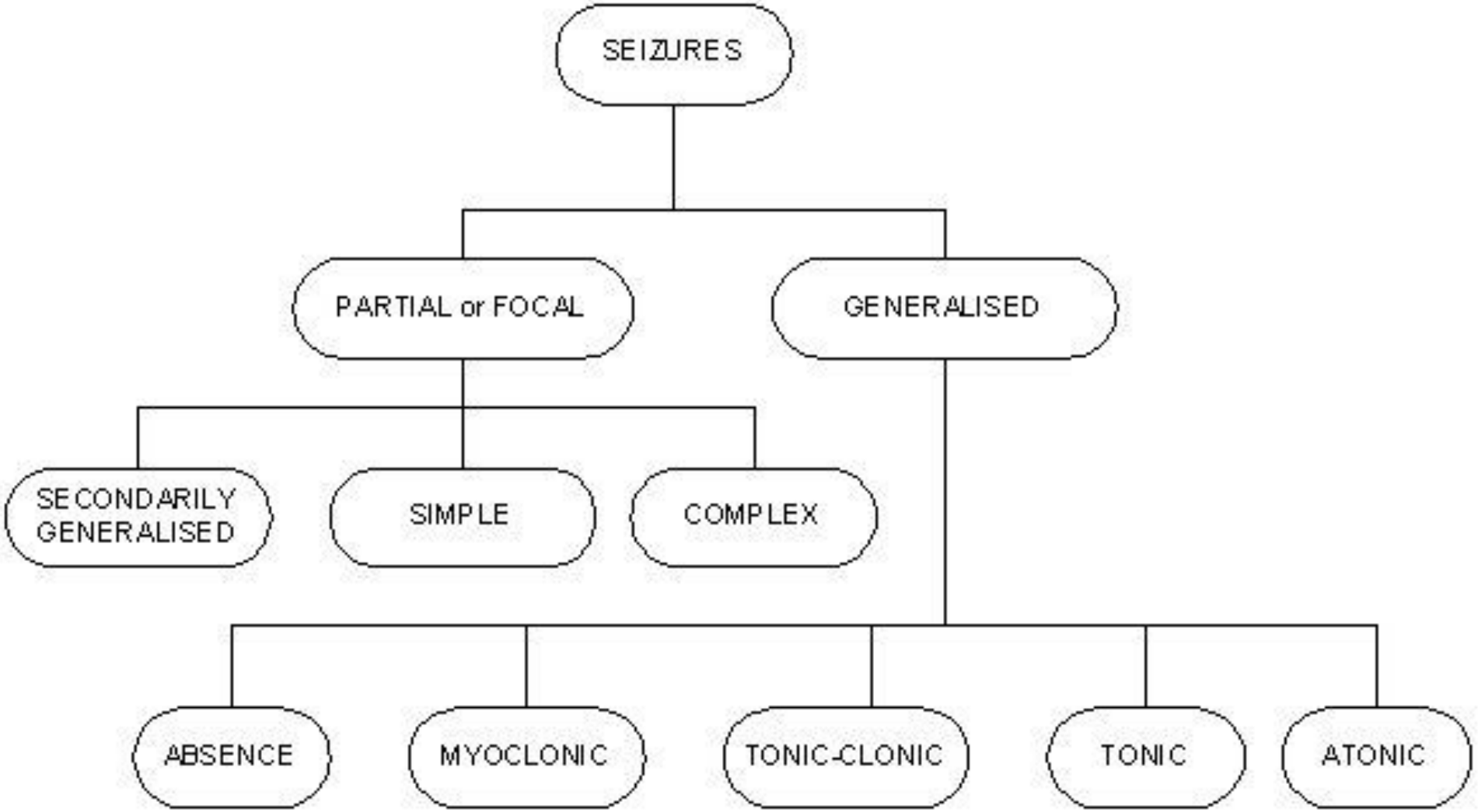
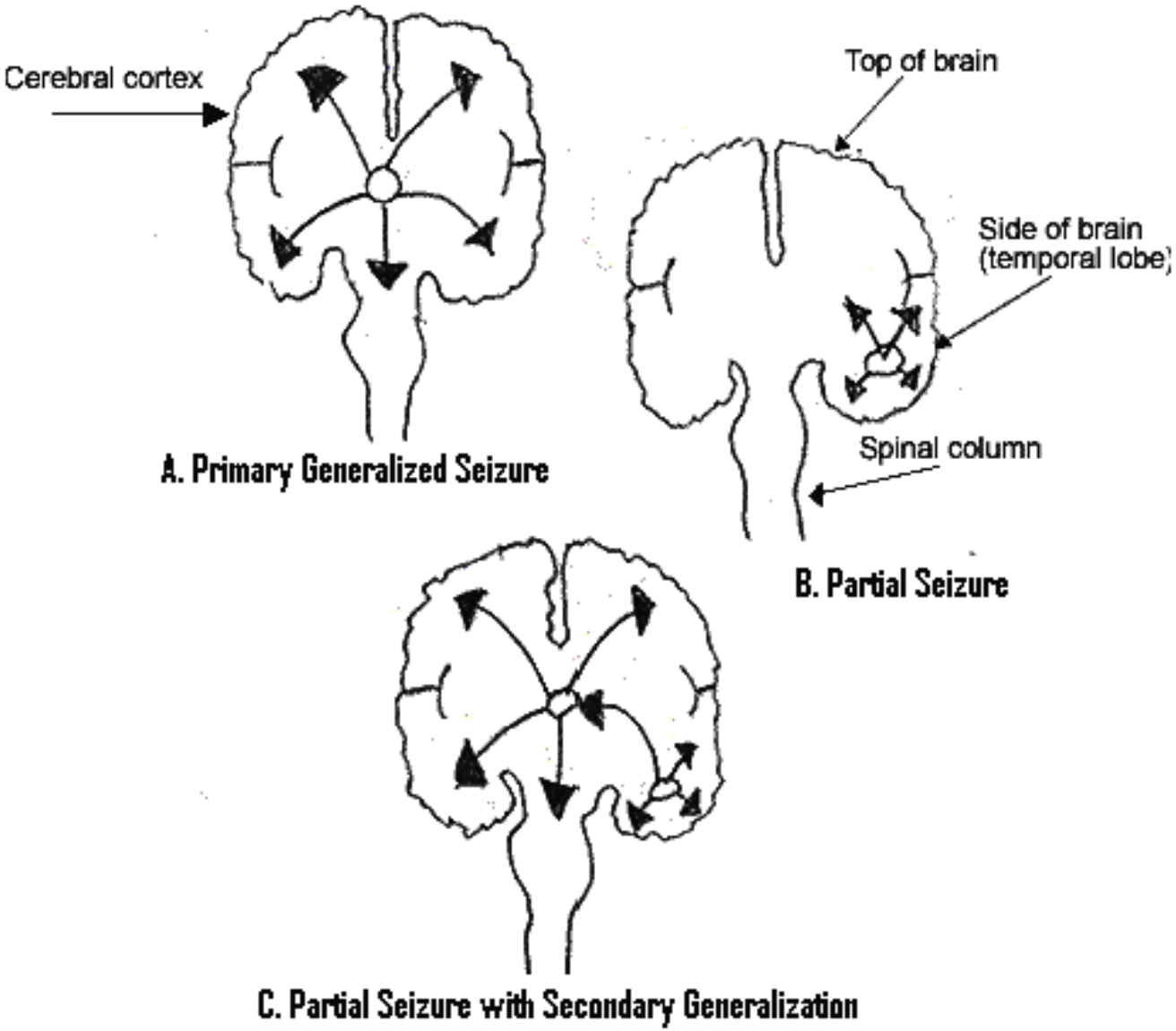


Fig: Types of seizures

Classification of Epilepsy

I. Partial seizures (seizures begin locally)
   1. Simple (without impairment of consciousness)
      a. With motor symptoms
      b. With special sensory or somatosensory symptoms
      c. With psychic symptoms
   2. Complex (with impairment of consciousness)
      a. Simple partial onset followed by impairment of consciousness—with or without automatisms.
      b. Impaired consciousness at onset—with or without automatisms
   3. Secondarily generalized (partial onset evolving to generalized tonic-clonic seizures).

II. Generalized seizures (bilaterally symmetrical and without local onset)
    1. Absence
    2. Myoclonic
    3. Clonic
    4. Tonic
    5. Tonic-clonic
    6. Atonic
    7. Infantile spasms
III. Unclassified seizures
IV. Status epilepticus


Cerebral cortex
A. Primary Generalized Seizure
Top of brain
Side of brain
(temporal lobe)
Spinal column
B. Partial Seizure
C. Partial Seizure with Secondary Generalization

Signs & symptoms

Symptoms

- Symptoms of a specific seizure will depend on seizure type.

1. Simple partial seizure:
   - Localized jerking of a limb or the face, stiffness or twitching of one part of the body, numbness or abnormal sensations (aura).
   - Consciousness is not impaired.
2. Complex partial seizure:
   - Automatic behaviors such as plucking his/her clothes, fiddling with various objects and acting in a confused manner.
   - Lipsmacking or chewing movements, grimacing, undressing, performing aimless activities and wandering around in a drunken fashion.
   - Consciousness is impaired for about 30 seconds.
3. Secondarily generalized seizures:
   - Convulsive attack with the same characteristics as a generalized tonic-clonic convulsions.

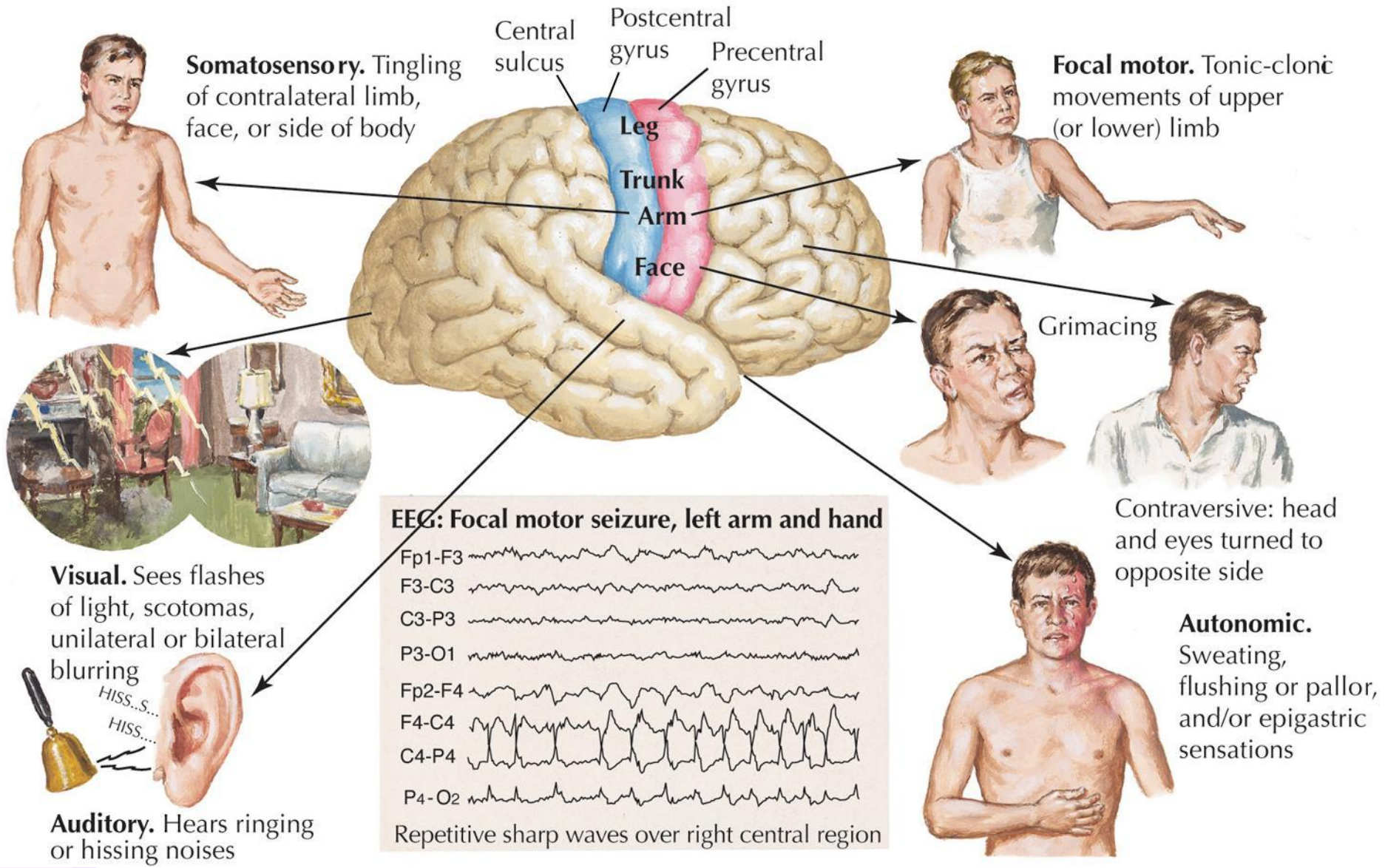


Fig: Symptoms of simple partial seizure

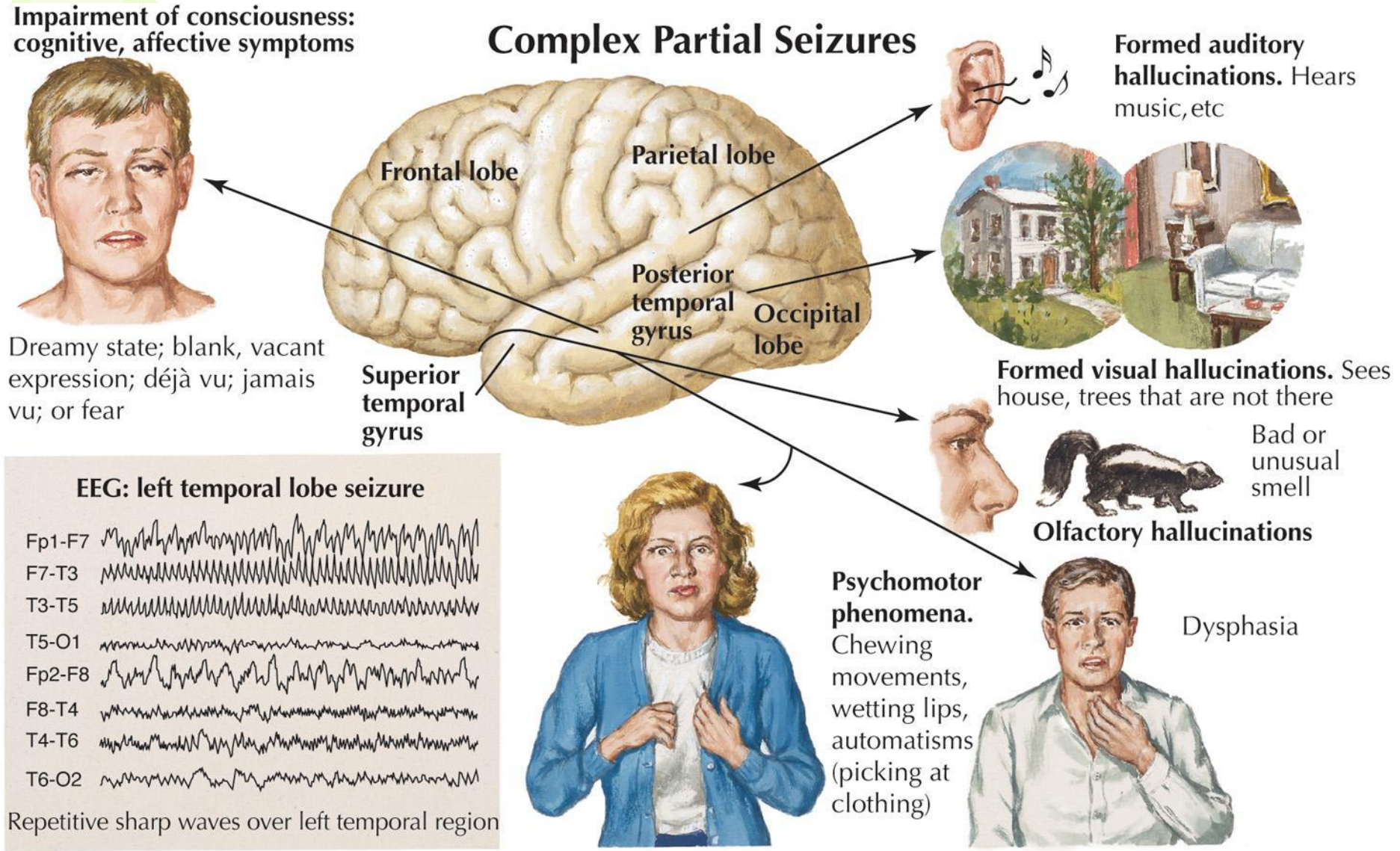


Fig: Symptoms of complex partial seizure

4. Tonic-clonic convulsions(Grand-mal):
   - The patient suddenly goes stiff, falls and convulses, laboured breathing and salivation.
   - Cyanosis, urination, defecation and tongue biting may occur.
   - Patient remains unconscious for about 2-4 minutes.
   - Convulsion is followed by a period of drowsiness, confusion, headache and sleep.
5. Petit mal epilepsy (absence seizure)
   - The child goes blank and stares vacantly for a moment.
   - Fluttering of eyelids and flopping of the head may occur.
   - Consciousness is impaired & seizure lasts for about 30 seconds.

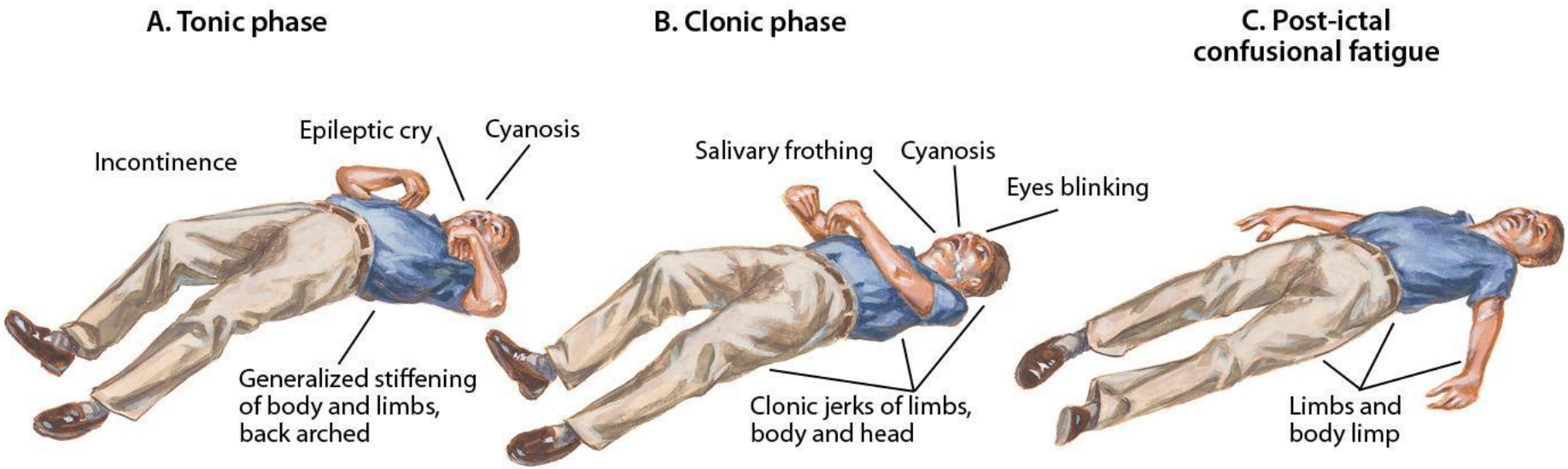
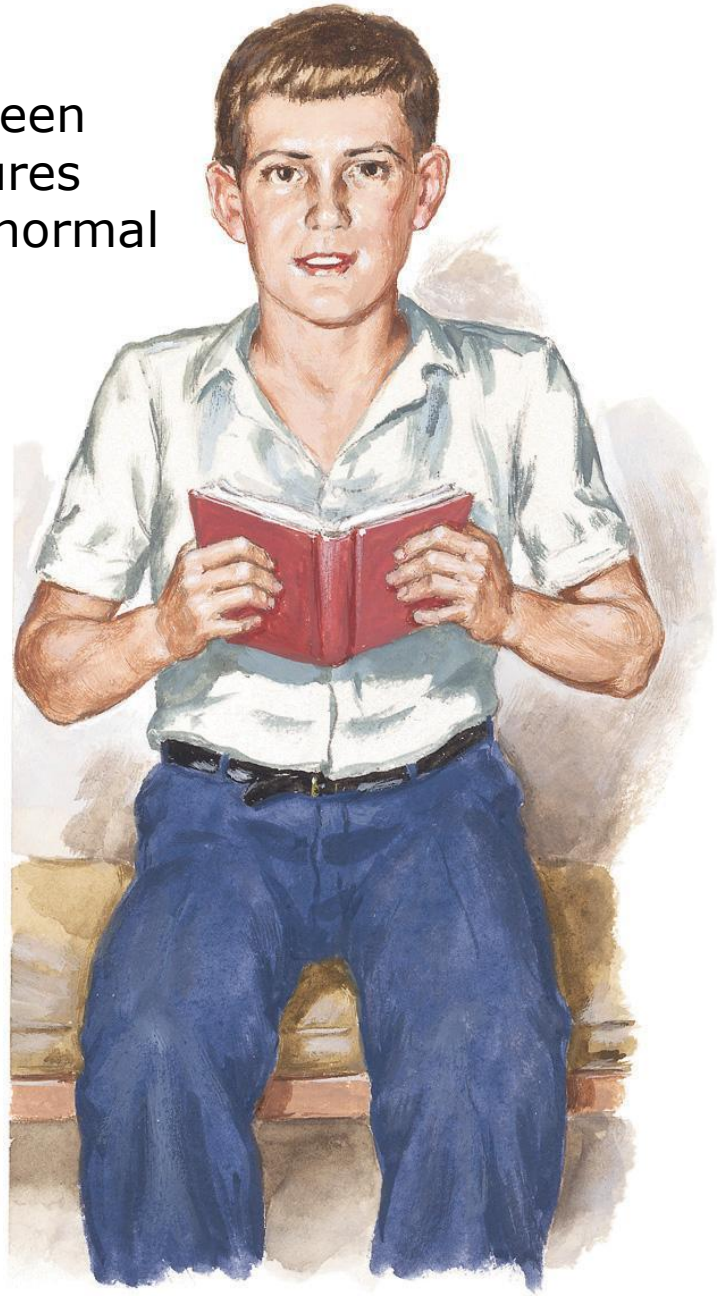
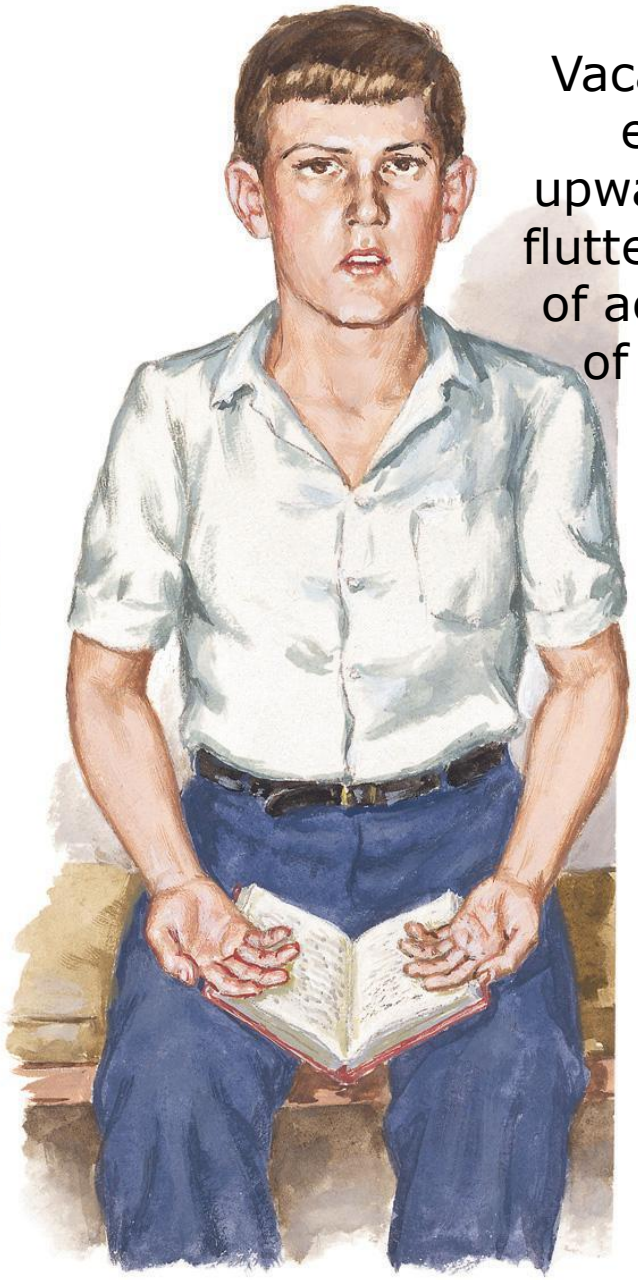


Fig: Symptoms of tonic-clonic seizure

Between seizures patient normal





Vacant stares, eyes roll upward, eyelids flutter, cessation of activity, lack of response

Fig: Symptoms of Petitmal epilepsy

6. Myoclonic seizure:
   - Abrupt, very brief involuntary shock-like jerks, which may involve the whole body, or the arms or the head.
   - Usually happens in the morning, shortly after waking.
7. Atonic seizures
   - Sudden loss of muscle tone causing the patient to collapse to the ground.
8. Status epilepticus:
   - Continuous tonic-clonic seizure activity lasting longer than 30 minutes.

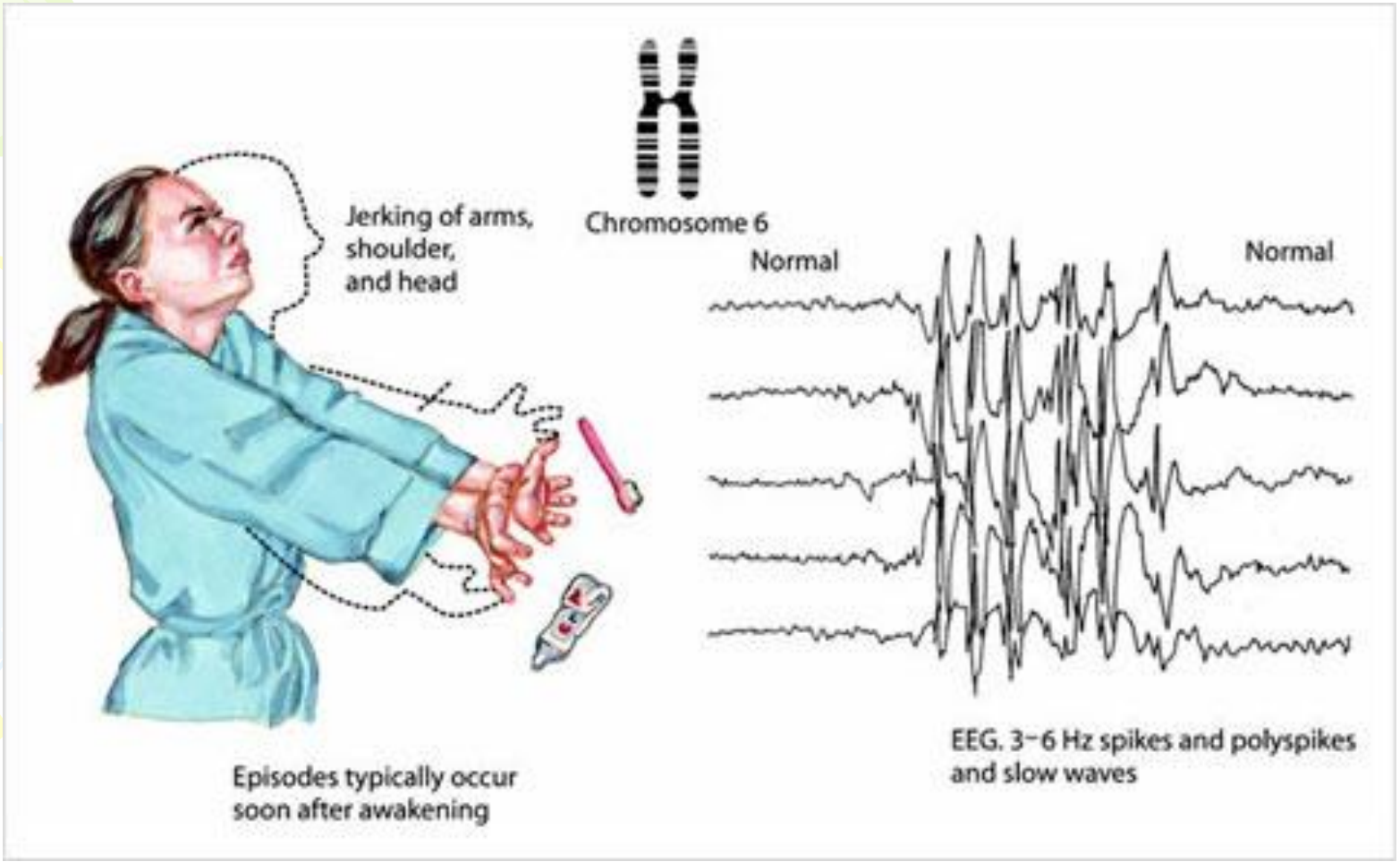
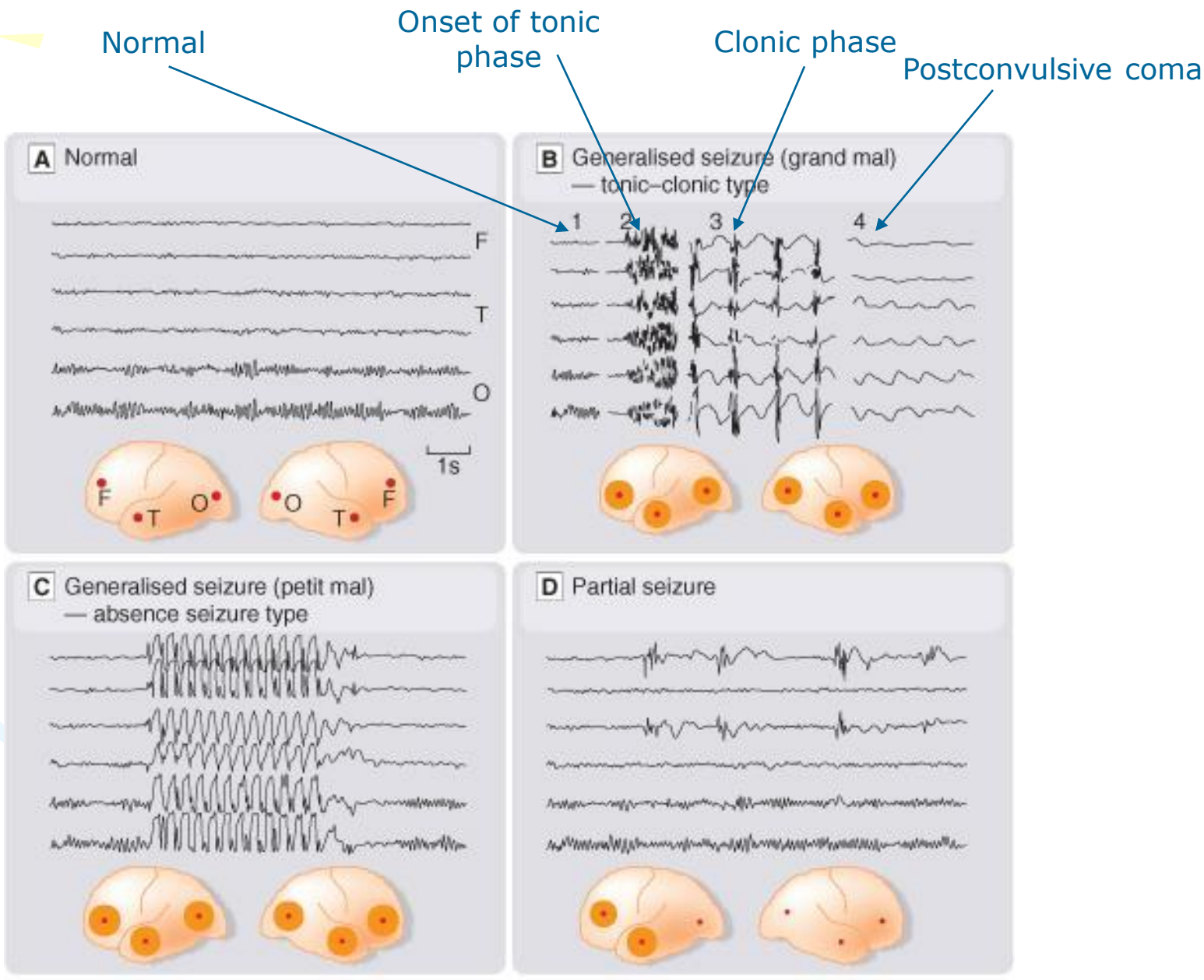


Fig: Symptoms of Myoclonic seizure

Signs & diagnosis

- Interictally (between seizure episodes), there are typically no objective, pathognomonic signs of epilepsy.
- EEG is very useful in the diagnosis of various seizure disorders.
- The EEG may be normal in some patients who still have the clinical diagnosis of epilepsy.
- While MRI is very useful (especially imaging of the temporal lobes)



F=frontal

T=temporal

O=occipital

Fig: Electroencephalography (EEG) records in epilepsy

Pharmacotherapy

Goals of therapy

1. No seizures and no side effects with an optimal quality of life.
2. To drive out misconceptions about epilepsy, such as possession by demons or punishment by God.
3. Patient may encouraged to contact or join the Epilepsy Foundation of America or other support groups that encourage patients with epilepsy to lead normal lives.

Classification of AED

1. Partial seizures:
   a. Simple partial seizure:
      i. First line drugs: Carbamazepine, Phenytoin, Lamotrigine, Sodium valproate, Oxcarbazepine
      ii. Second line (alternative) drugs: Gabapentin, Topiramate, Levetiracetam, Zonisamide, Tiagabine, Primidone, Phenobarbital, Felbamate, Vigabatrin
   b. Complex partial seizure:
      i. First line drugs: Phenytoin
      ii. Second line drugs: Clobazam
   c. Secondarily generalized
      a. First line drugs: Sodium valproate, Lamotrigine
      b. Second line drugs: Phenobarbital, Acetazolamide, Gabapentin, Topiramate

2. Generalized seizures:

a. Petitmal epilepsy (absence seizure):

i. First line drugs: Sodium valproate, Ethosuximide

ii. Second line (alternative) drugs: Lamotrigine, Levetiracetam, Clonazepam, Acetazolamide

b. Myoclonic

i. First line drugs: Sodium valproate, Clonazepam

ii. Second line (alternative) drugs: Lamotrigine, Topiramate, Felbamate, Zonisamide, Levetiracetam, Phenobarbital, Acetazolamide

c. Tonic-clonic

i. First line drugs: Phenytoin, Carbamazepine, Sodium valproate

ii. Second line (alternative) drugs: Lamotrigine, Topiramate, Phenobarbital, Primidone, Oxcarbazepine, Levetiracetam, Vigabatrin, Clobazam

d. Atonic

i. First line drugs: Clonazepam, Clobazam

ii. Second line drugs: Lamotrigine, Carbamazepine, Phenytoin

e. Status epilepticus

a. First line drugs: Diazepam, Lorazepam, Midazolam

b. Second line drugs: Phenytoin, Fosphenytoin, Sodium valproate, Phenobarbital, Propofol

Carbamazepine

- Carbamazepine should be considered a first line therapy for patients with newly diagnosed partial seizures and for patients with primary generalized convulsive seizures.
- Its pharmacological actions resemble phenytoin.
- It modifies max. Electroshock seizures as well as raises threshold to PTZ & electroshock convulsion.
- Its action on Na^+ channels similar to phenytoin.
- ADR: sedation, dizziness, vertigo, ataxia, vomitting, diarrhoea, rashes, photosensitivity, apastic anaemia,leucppenia.
- Water retention and hyponatremia occur in elderly patient because it enhances ADH action.

- **Water retention and hyponatremia occur in elderly patient because it enhances ADH action.**
- **Interaction:**

It is an enzyme inducer, can reduce efficacy of haloperidol, Oral contraceptive, lamotrigine and topiramate.

Metabolism of carbamazepine is induced by phenobarbitone, phenytoin, valproate and vice versa.

Erythromycin, fluoxetine, INH inhibit metabolism of carbamazepine.

Oxcarbazepine

- **Oxcarbazepine is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and as monotherapy and adjunctive therapy in the treatment of partial seizures in patients as young as 4 years of age with epilepsy.**
- **It acts by blocking of Na+ channel & increasing K+ conduction.**
- **Disadvantages:**
  - **There are more reports of hyponatremia with oxcarbazepine.**
  - **This drug is not likely to be effective in seizure types where carbamazepine is ineffective, such as absence or myoclonic seizures.**
  - **Dizziness,ataxia, drowsiness. Headache are more common.**

Phenytoin

- Phenytoin has long been a first-line AED for primary generalized convulsive and partial seizures
- It is available in oral solid, oral liquid, extended-release oral solid, and parenteral (phenytoin & fosphenytoin) dosage forms, allowing flexibility in dosing and use in emergent conditions.
- It produce anti-epileptic action without causing CNS depressant or sedation.
- It prevent the spread of PTP and cause membrane stabilization. The Na^+ transport as activated and Na^+ permeability is decrease.
- PK: when given with barbiturates its metabolism is slightly increase.
- Therapeutically it is used in all types of epilepsy except petil mal. It is also used in arrhythmias.
- ADR:Hypertrophy of gums, hirsutism, acne, skin rashes, megaloblastic anaemia, vit D deficiency(Therapeutic dose).Higher dose: Nystagmus, ataxia, diplopia,sedation

Phenobarbital

- Phenobarbital is the drug of choice for neonatal seizures but in other situations is reserved for patients who have failed other AEDs.
- Multiple dosage forms (e.g., oral solid, oral liquid, intramuscular, and intravenous) are available.
- It is also used to treat recurrent tonic-clonic seizures especially in patient who do not respond to diazepam plus phenytoin.
- Limits the spread of seizures discharge in the brain & elevate the seizure threshold. It acts by potentiating the inhibitory effects of GABA – mediated neurons.
- ADR: sedation, ataxia, nystagmus, nausea, vomitting, vertogo, headache, skin rashes.

Sodium valproate

- Sodium valproate is first-line therapy for primary generalized seizures such as grandmal ,myoclonic, atonic, and absence seizures(petitmal).
- It can be used as both monotherapy and adjunctive therapy for partial seizures.
- It induced the elevation in the functional levels of GABA in the CNS. This results from the inhibition of enzyme gamma-transaminase, which block the conversion of GABA to succinic semialdehyde & more of GABA is available in the CNS.
- It is available in multiple dosage formulations & has a wide therapeutic index.
- ADR:Weight gain-which may limit compliance, Hepatitis, gastric irritation, alopecia, tremor, pancreatitis, polycystic ovary disease, and thrombocytopenia.

Ethosuximide & Phensuccimides:

- Ethosuximide is still a first-line treatment for absence seizures.
- They give protection specially against chemical induced seizures.
- Succinamides act by reducing threshold T-type ca^{++} currents in thalamic neurons.
- It is generally well tolerated and has few pharmacokinetic interactions.
- ADR: Tiredness, mood change, agitation, headache, drowsiness, lethargy, skin rashes, urticaria.

Lamotrigine

- Lamotrigine is useful as both adjunctive treatment in patients with partial seizures and as monotherapy.
- Lamotrigine is potentially a broad-spectrum AED, having efficacy in partial seizures as well as several types of generalized seizures.
- It does not induce or inhibit the metabolism of other AEDs.
- It act by inhibits voltage sensitive sodium channel leading to diminished neuronal excitability. It also affect excitatory amino acid transmission.
- It does not antagonize PTZ seizures or block NMDA type of Glutamate receptors.
- Lamotrigine appears to be generally well tolerated in both children and elderly adult patients and does not cause weight gain.
- ADR:Ataxia,dizziness, diplopia, nausea, vomits, headache, sedation, skin rashes

Gabapentin

- Gabapentin is a second-line agent for patients with partial seizures who have failed initial treatment.
- It has a broad therapeutic index with minimal CNS adverse effects and no drug interactions.
- This lipophilic GABA derivatives crosses to the brain and enhance GABA release, but does not act as agonist at GABAA receptor.
- It modifies max electroshock as well as inhibit PTZ induce Clonic seizures.
- Disadvantage:
  - Gabapentin is absorbed by an active process that saturates at higher doses, which requires more frequent daily dosing.
  - There is no parenteral formulation.

ADR:Diziness, nausea, vomitting, tremors, diplopia,ataxia, Fatigue, Somnolence.

Clonazepam & Diazepam

- Is a drug of choice for myoclonic seizure and a second line drug for tonic clonic seizure, absence seizure and as adjunctive therapy for partial seizure
- They do not abolish focal discharge.
- It act by stimulation of GABA receptors. It mimics the action of GABA which is an inhibitory neurotransmitter in brain.
- Parenteral clonazepam is useful in status epilepticus.
- ADR:Sedation,dullness, salivation and increase respiratory secretion

VIGABATRIN

- It is γ-vinyl GABA.
- It produce irreversible inhibition of GABA transminase enzyme and hence increase GABA levels in the brain.
- It is as effective as carbamazepine in partial seizures.

ADR: sedation, dizziness, memory impairment, psychotic reaction, weight gain, visual disturbance.

TIGABIN

It inhibits GABA transminase enzyme as well as GABA reuptake into pre-synaptic neurons.
It inhibits both electrically as well as chemical induce seizures.
It has shorter half life & avoided in hepatic dysfunction.

ADR:Dizziness, somnolence, headache, ataxia, tremors, fatigue.

ZONISAMIDE

It is a sulfonamide derivatives that inhibits T-types Ca^{++} currents.

In addition, t also inhibit the sustained repeated firing of spinal cord neurons by prolonging inactivation state of Na^{+} channels like phenytoin.

It specially inhibits electrically induced seizures.

ADR: Somnolence, ataxia, anorexia, fatigue.

TRIMETHADIONE

It specially blocks chemically induced seizures and is selective for petitmal epilepsy.
It has mild analgesic activity. It does not affect post-tetanic potentials or pre-synaptic potential.
It increase threshold of excitability in thalamus & depressed post synaptic transmission. It also increase K efflux in the neurons.

ADR: Drowsiness, blurred vision, skin rashes, hepatitis.

PRIMIDONE

It has action similar to barbiturates, but it is more selective in modifying electroshock seizures.
It is used in all types of epilepsy except petitmal.

It is metabolised to phenobarbitone and phenyl ethyl malonamide and both are active metabolotes.

ADR: sedation, vomiting, vertigo, ataxia, osteomalacia, skin rashes, thrombocytopenia.

TOPIRAMATE

This weak carbonic anhydrase inhibitors has broad spectrum anticconvulsant activity in max electroshock, PTZ induced clonic seizures and in kindling model.

It act by multiple mechanism like prolonging of Na^+ channel inactivation, GABA potentiation by post synaptic effect and antagonism of certain glutamate receptors.

ADR: memory disturbances, somnolence, dizziness, diplopia, anorexia,weight loss.

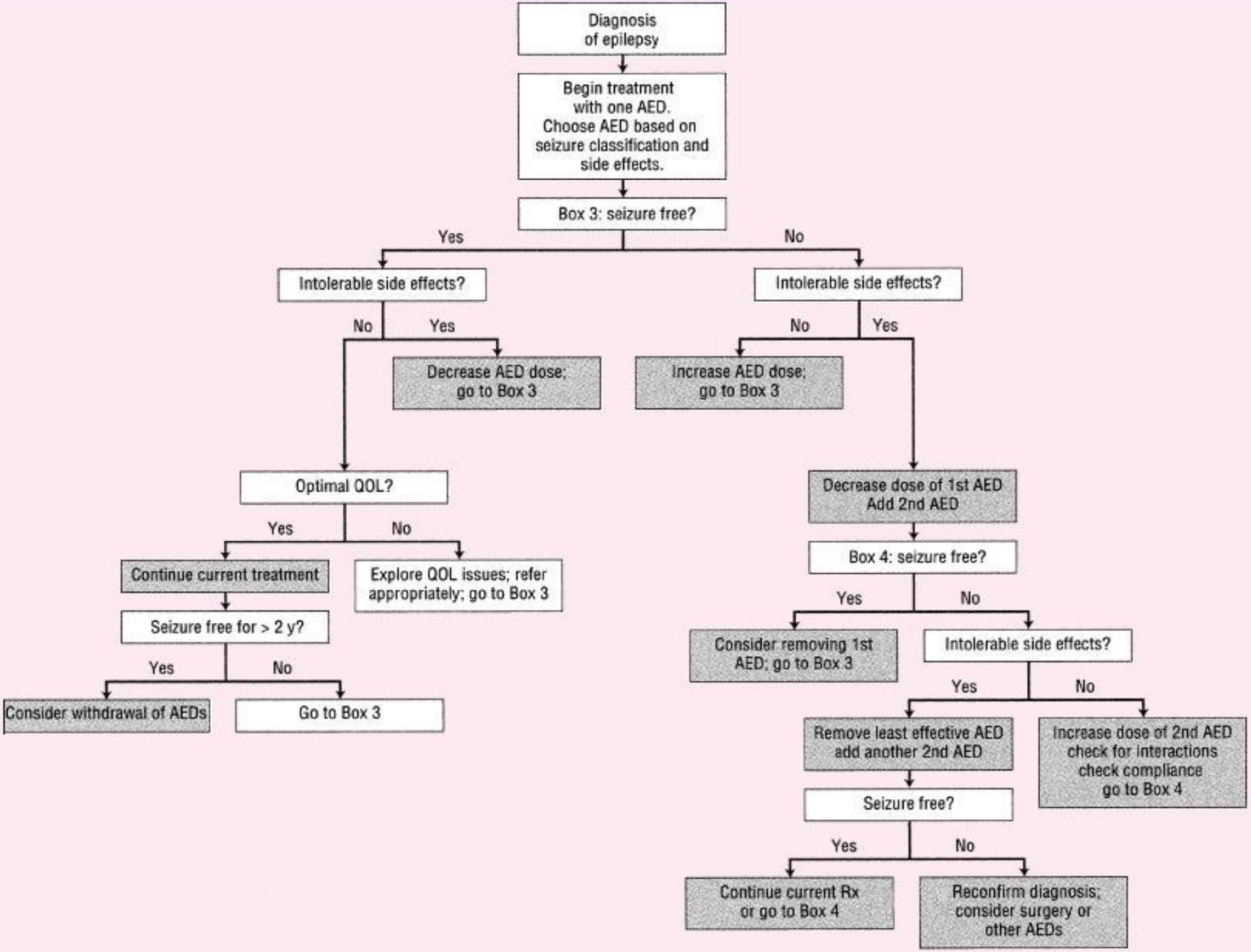
LEVITIRACETAM

A unique anticonvulsant which suppresses kindled seizures but is ineffective against max electroshock or PTZ.

None of the usual anticonvulsant mechanism of action appear to be applicable to levitiracetam.

	Usual Initial Dose	Usual Maximum Daily Dose
Barbiturates		
Mephobarbital	50–100 mg/day	400–600 mg
Phenobarbital	1–3 mg/kg/day (10–20 mg/kg LD)	180–300 mg
Primidone	100–125 mg/day	750–2000 mg
Benzodiazepines		
Clonazepam	1.5 mg/day	20 mg
Clorazepate	7.5–22.5 mg/day	90 mg
Diazepam	PO: 4–40 mg IV: 5–10 mg	PO: 4–40 mg IV: 5–30 mg
Lorazepam	PO: 2–6 mg IV: 0.05 mg/kg IM: 0.05 mg/kg	PO: 10 mg IV: 0.044 mg/kg
Hydantoins		
Ethotoin	<1000 mg/day	2000–4000 mg with food
Mephenytoin	50–100 mg/day	200–800 mg
Phenytoin	PO: 3–5 mg/kg (200–400 mg) (15–20 mg/kg LD)	PO: 500–600 mg
Succinimides		
Ethosuximide	500 mg/day	500–2000 mg
Methsuximide	300 mg/day	300–1200 mg
Other		
Carbamazepine	400 mg/day	400–2400 mg
Felbamate	1200 mg/day	3600 mg
Gabapentin	900 mg/day	4800 mg
Lamotrigine	25 mg qod if on VPA; 25–50 mg/day if not on VPA	100–150 mg if on VPA; 300–500 mg if not on VPA
Levetiracetam	500–1000 mg/day	3000–4000 mg
Oxcarbazepine	300–600 mg/day	2400–3000 mg
Tiagabine	4–8 mg/day	80 mg
Topiramate	25–50 mg/day	200–1000 mg
Valproic acid	15 mg/kg (500–1000 mg)	60 mg/kg (3000–5000 mg)
Zonisamide	100–200 mg/day	600 mg

Treatment algorithm


Diagnosis of epilepsy
Begin treatment with one AED. Choose AED based on seizure classification and side effects.
Box 3: seizure free?
Yes
No
Intolerable side effects?
Intolerable side effects?
No
Yes
No
Yes
Decrease AED dose; go to Box 3
Increase AED dose; go to Box 3
Optimal QOL?
Yes
No
Continue current treatment
Explore QOL issues; refer appropriately; go to Box 3
Seizure free for > 2 y?
Yes
No
Consider withdrawal of AEDs
Go to Box 3
Decrease dose of 1st AED Add 2nd AED
Box 4: seizure free?
Yes
No
Consider removing 1st AED; go to Box 3
Intolerable side effects?
Yes
No
Remove least effective AED add another 2nd AED
Increase dose of 2nd AED check for interactions check compliance go to Box 4
Seizure free?
Yes
No
Continue current Rx or go to Box 4
Reconfirm diagnosis; consider surgery or other AEDs

Parameters to be monitored

1. A therapeutic range (dose range with minimal side effects and optimal seizure control) should be established for each patient.
2. Patients should be monitored chronically for seizure control, comorbid conditions, social adjustment drug interactions, compliance, and adverse effects.
3. Periodic screening for comorbid neuropsychiatric disorders such as depression and anxiety is also important.
4. Patients should be given a seizure diary, and the severity as well as the frequency of seizures should be monitored.


End