HARRISON

EDITION 22nd

NEUROLOGY

Neurology

Seizures And Epilepsy	Completed
Cerebrovascular Diseases - Stroke	Completed
Parkinsons Disease	Completed
Hyperkinetic Movement Disorders	Completed
Dementia	Completed
Intracranial Hemorrhage	Completed
Demyelinating Disorders	Completed
Amyotrophic Lateral Sclerosis And Other Motor Neuron Diseases	Completed
Ataxia	Completed
Myasthenia Gravis	Completed
Peripheral Neuropathy And Myopathy	Completed
Paraneoplastic Neurologic Syndromes And Autoimmune Encephalitis	Completed
Headache	Completed

Harrison 22nd Edition Based Neurology Classes

Dr. Joban Preet Singh Deol

Seizures and Epilepsy

GTCS

- MC seizure type resulting from metabolic derangements
- Usually no aura

1. Tonic phase	• Loud moan or ictal cry • Cyanosis • Biting of tongue • Increase in HR, BP & pupillary size • EEG : polyspike discharges
2. Clonic phase	• EEG : spike & slow wave pattern
3. Postictal phase	• Unresponsiveness • Muscular flaccidity • Stridorous breathing : excessive salivation • Bladder or bowel incontinence • Post-ictal confusion • EEG : Diffuse slowing

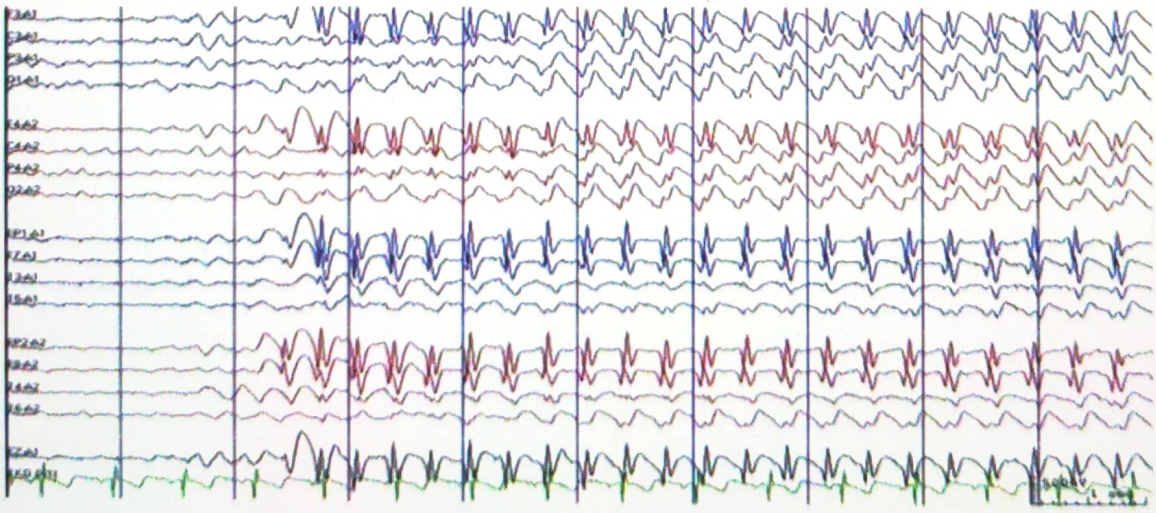
Focal seizures

Focal seizures with intact awareness	Focal seizures with impaired awareness
• Jacksonian march (Hughlings Jackson) • Todd's paralysis • Epilepsia partialis continua : often refractory to medical therapy • Auras	• Unable to respond appropriately during seizure • Impaired recollection • Begin with stereotypic aura • Start of ictal phase with motionless stare • Usually associated with automatisms • Post-ictal confusion • Post-ictal anterograde amnesia or transient neurological deficit

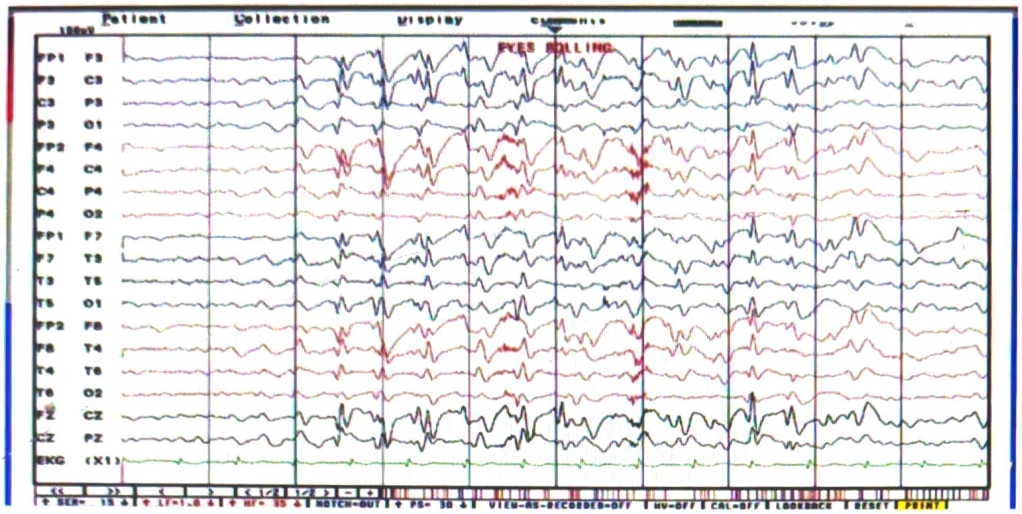
Absence seizures

Typical absence seizures	Atypical absence seizures
• Sudden, brief loss of consciousness without loss of postural control • Last only for seconds • No postictal confusion • Usually associated with subtle, bilateral motor signs • EEG : 3 Hz spike & slow wave discharge • Hyperventilation provoke • Unexplained daydreaming & decline in school performance	• Less abrupt in onset & cessation • Lapse of consciousness of longer duration • A/w more obvious motor signs; may include focal or lateralizing features • EEG : generalized slow spike & slow-wave pattern with a frequency of ≤2.5 per second • Usually a/w diffuse or multifocal structural abnormalities • Mental retardation ± • Less responsive to anticonvulsants

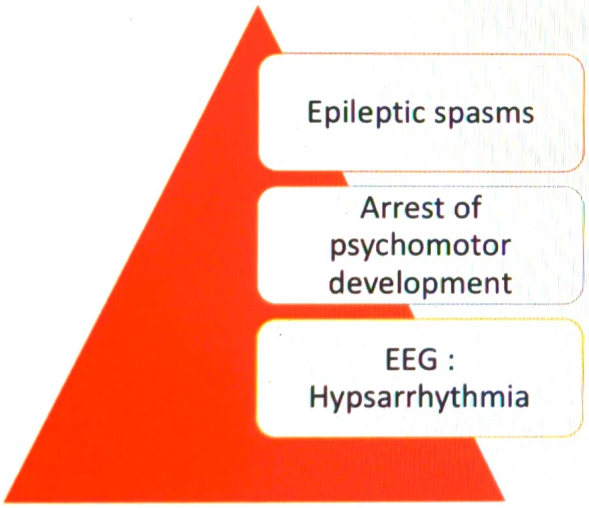
Typical Absence Seizures



Atypical absence seizures

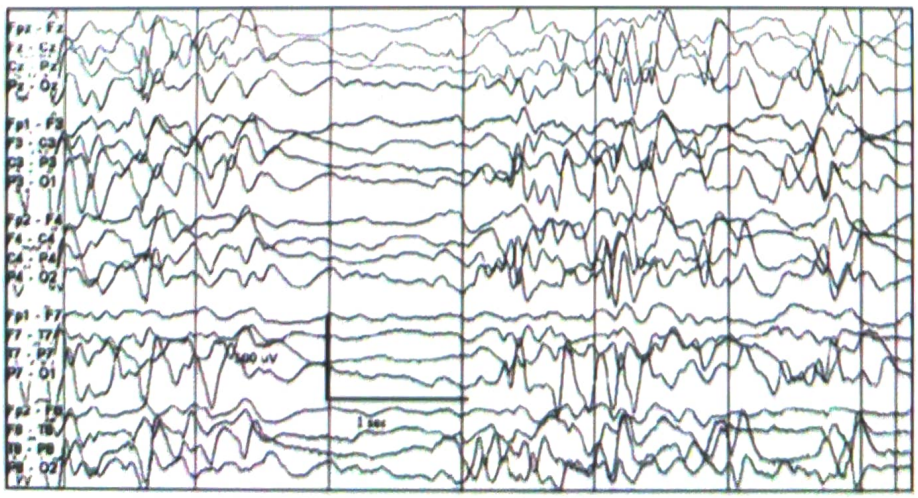


West syndrome/infantile spasms

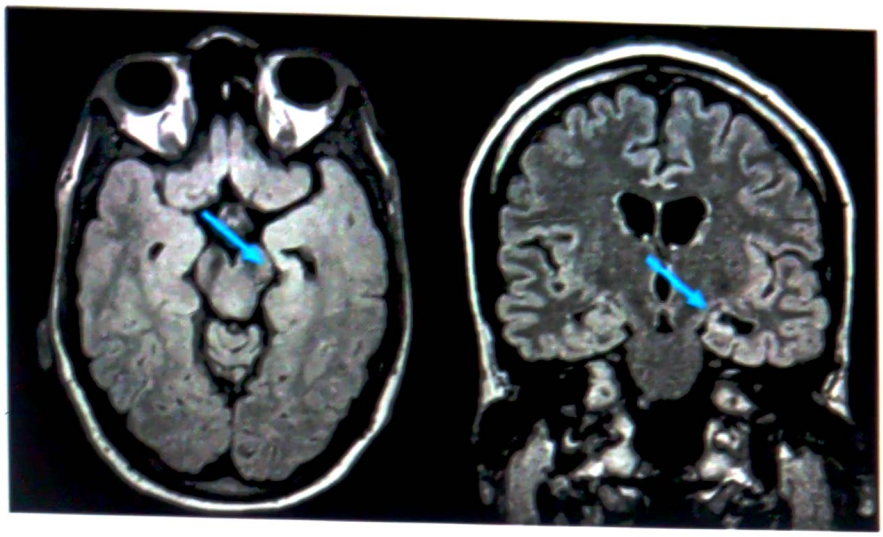


- Peak onset : 3 to 7 months of age
- 2/3rd have brain lesions
- Association with tuberous sclerosis
- T/T : ACTH, prednisone
- Vigabatrin : if associated tuberous sclerosis

West syndrome/Infantile spasms

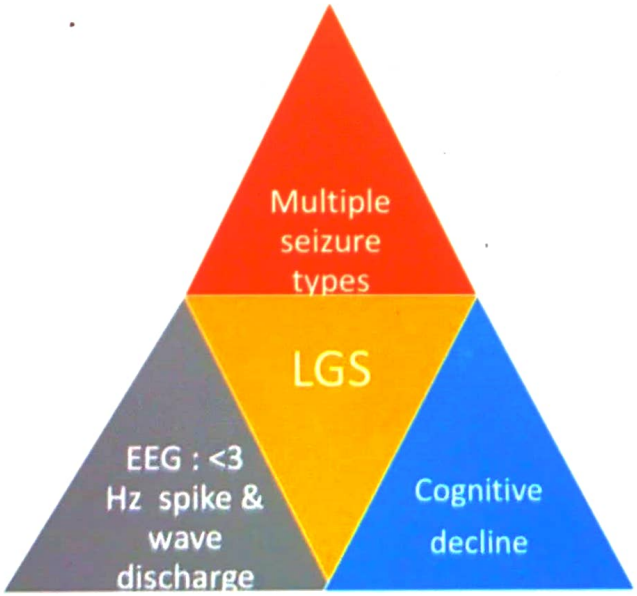


Mesial Temporal Lobe Epilepsy



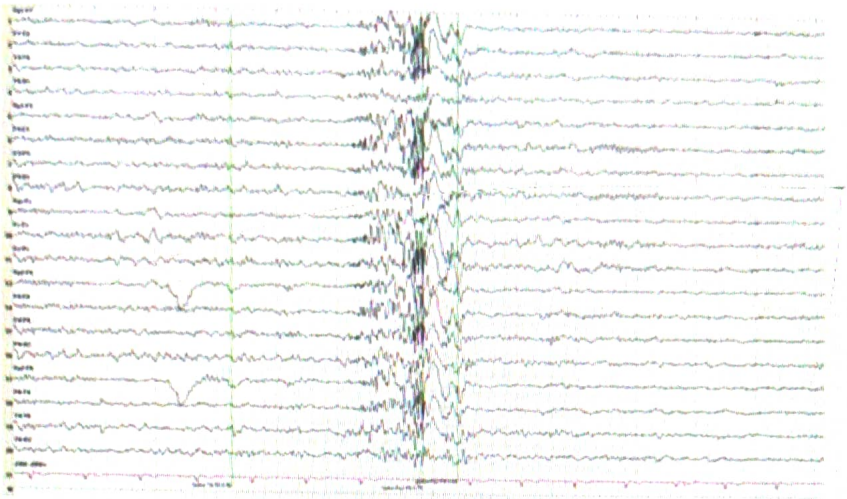
Mesial Temporal Lobe Epilepsy syndrome

- Most common syndrome associated with FIAS
- History of antecedent febrile seizures is frequent
- Decreased volume & increased signal in affected hippocampus, blurring of internal laminar architecture
- EEG : anterior temporal spikes
- Wada test : Material-specific memory deficits on intracranial amobarbital test
- Refractory to treatment with anticonvulsants but responds well to surgical intervention



Poor prognosis : in many due to severe, poorly controlled epilepsy & underlying CNS disease

Myoclonic epilepsy



Juvenile Myoclonic Epilepsy (JME)

- Onset : 12-18 yrs of age
- Often family history (+)
- Bilateral myoclonic jerks (100%) : most frequent in morning after awakening, provoked by sleep deprivation; consciousness is preserved & mild
- GTCS (in many)
- Absence seizures (upto 1/3rd)
- Usually respond well to anticonvulsant
- Complete remission uncommon
- EEG : generalized irregular 4 to 6 Hz spike & wave activity occurring in bursts

Progressive Myoclonic Epilepsies

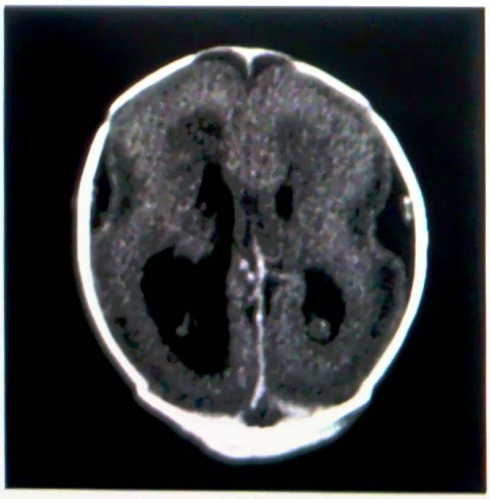
Myoclonus, GTC seizures, progressive neurological dysfunction, predominantly cerebellar ataxia & dementia	
Unverricht-Lundborg disease/ Baltic myoclonus	• AR • Mutation in cystatin B gene (chromosome 21)
Lafora disease	• AR • Loss of function mutation in EPM2A or NHLRC1 (chromosome 6) • Diagnosis : skin biopsy → Lafora bodies
Treatment : Seizures often drug-resistant; Valproate- DOC, Perampanel	

Genes associated with Epilepsy syndromes

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)	CHRNA 4 gene
Benign Familial Neonatal Seizures (BFNS)	KCNQ2 gene
Generalized Epilepsy with Febrile Seizures Plus (GEFS+)	SCN1A
Autosomal Dominant Partial Epilepsy with Auditory Features (ADPEAF)	LGI1 gene
Autosomal dominant Familial Focal Epilepsy with Variable Foci (FFEVF)	DEPDC5 gene

ADNFLE	• Childhood onset • Prominent motor movements, brief
BFNS	• AD • Onset in 1st week of life, otherwise normal infant • Remission within weeks to months • Long-term epilepsy in 10-15%
GEFS+	• AD • Presents with febrile seizures (~ 1 year) → may persist >6 years, variable seizure types not associated with fever
ADPEAF	• Lateral temporal lobe epilepsy with auditory symptoms or aphasia
FFEVF	• Family members have seizures originating from different cortical regions • Neuroimaging : usually normal • Associated with benign epilepsy with centrotemporal spikes

Doublecortin gene mutation



- X-linked dominant
- Males
- Classic lissencephaly + severe MR + seizures

GRIN2A (NMDAR subunit GluN2A)	• Spectrum: benign childhood epilepsy with centrotemporal spikes **(BECTS)** to epilepsy-aphasia syndrome such as Landau-Kleffner syndrome **(LKS)** and other epileptic encephalopathies.	Complex inheritance
CDKL-5 (Cyclin-dependent kinase-like 5)	• Mutation in CDKL5 gene leads to CDKL-deficiency disorder (CDD). • **CDD is a severe developmental epileptic encephalopathy characterized by very-early-onset seizures.** • **X-linked.** • **Affects females more** than males.	**Ganaxolone** is a recently approved antiseizure drug that ahs been shown to significantly reduce CDD-associated seizures

Febrile seizures

- Affects 2-5% of children
- 3 months to 6 years of age
- Occur during rising phase of temperature curve
- Most GTC in morphology
- Recurrence : 30-40%
- Risk of later epilepsy : 7% by 25 years
- Febrile status epilepticus may injure hippocampus, leading to hippocampal sclerosis
- Can evolve into Dravet syndrome or GEFS+
- T/T : Oral or rectal diazepam in patient with frequent recurrences or for prolonged seizures

	Simple febrile seizures	Complex febrile seizures
Morphology	GTC, symmetrical	Focal
Duration	<15 minutes	>15minutes
Frequency	Once in a febrile illness	>1 seizure in 24 hours or with same febrile illness

Predictors of Recurrence	Predictors of later epilepsy
• Early age at onset (<1 year) • Presence of epilepsy or febrile seizures in 1st-degree relatives • Attendance at daycare : increases the risk of febrile infectious illnesses	• Pre-existing neurodevelopmental abnormalities • Complex features (prolonged duration, focal features & multiple occurrences per day) • Family history of epilepsy • Recurrent febrile seizures

Dravet syndrome

- Severe myoclonic epilepsy of infancy/ Vaccine encephalopathy
- Mutation in SCN1A gene
- Febrile status epilepticus at 6 months of age → Recurrent generalized or shifting hemiclonic seizures, often triggered by fever
- After 1 year : myoclonic seizures, absence seizures, FIAS, atonic seizures
- Drug-resistant seizures
- Exacerbated by carbamazepine, lamotrigine
- Prognosis : Poor
- Majority develop intellectual disability, ataxia, spasticity

Causes according to age

Neonates (<1 month)	• Perinatal hypoxia & ischemia • ICH & trauma • CNS infection • Metabolic disturbances • Drug withdrawal • Developmental disorders • Genetic disorders • Inborn errors of metabolism
Infants & Children (>1 month & <12 years)	• Febrile seizures • Genetic disorders : Metabolic, degenerative, primary epilepsy syndromes) • CNS infection : especially viral encephalitis • Developmental disorders • Trauma

Adolescents (12-18 years)	• Trauma • Genetic disorders • Infection (including cysticercosis) • Illicit drug use • Brain tumors • Autoimmune encephalitis
Young adults (18-35 years)	• Trauma • Alcohol withdrawal • Illicit drug use • Brain tumor • Autoantibodies
Older adults (>35 years)	• Cerebrovascular disease • Brain tumor • Trauma (including SDH) • Metabolic disorders : uremia, hepatic failure, electrolyte abnormalities, hypo- or hyperglycemia • Alzheimer's disease & other degenerative CNS disease

Drugs that cause seizures

Alkylating agents	• Busulfan • Chlorambucil
Antimalarials	• Chloroquine • Mefloquine
Antimicrobials/ Antivirals	• Beta-lactams • Quinolones • Isoniazid • Acyclovir • Ganciclovir
Anaesthetics & Analgesics	• Meperidine • Fentanyl • Tramadol • Local anesthetics
Drug withdrawal	• Alcohol • Baclofen • Short-acting Barbiturates & BDZs • Zolpidem
Immunomodulatory agents	• Cyclosporine • Tacrolimus • Interferons • OKT3 (monoclonal antibodies to T cells)
Psychotropics	• Antidepressants (e.g., Bupropion) • Antipsychotics (e.g., Clozapine) • Lithium
Dietary supplements	• Gingko • Ephedra (ma huang)
Others	• Radiographic contrast agents • Flumazenil (in BDZ-dependent patients)

Psychogenic Non-epileptic Seizures (PNES)

- Turning to a prone position during ictus
- Sustaining burn injuries
- Postictal sterotorous respiration
- Eye closure during unresponsiveness
- D.D. : Frontal lobe FIAS
- Gold-standard : Video-EEG

True

PNES



AURA	LOCALIZATION
Auditory aura Vertigo Complex visual hallucinations	Lateral temporal lobe
Epigastric sensation Olfactory aura Gustatory aura	Medial temporal lobe
Somatosensory manifestations (tingling, numbness, pins, needles, burning or pain)	Parietal
Elementary visual hallucinations (flashing coloured lights or geometric figures)	Occipital

Evaluation of seizures

- **High-density EEG** provides **higher resolution localization by utilizing up to 257 scalp electrodes, as opposed to the 21 electrodes** used in a standard EEG recording
- This makes use of scalp voltage filed data to determine dipole location, orientation, and propagation
- EEG source imaging (ESI) permits visualization of these dipoles by mapping them onto a three-dimensional model that is co-registered on brain MRI

Stereo-EEG (depth electrodes) vs. Subdural electrodes

- **Robot-assisted stereotactic EEG (stereo-EEG)** has surged in use as a less invasive surgical option
- It involves **placing depth electrodes through burr holes in the skull and into the brain parenchyma to record from regions suspected of generating seizures**
- Although **subdural electrodes** provide extensive cortical sampling. They are **unable to record from deep structures**
- Depth electrodes permit sampling of both cortical and subcortical tissue, albeit with more restricted spatial resolution
- **Stereo-EEG** studies are typically associated with **shorter hospital stays and lower complication** rates than subdural electrode studies

Selection of ASM

- Mutations in SCN1A/Dravet syndrome : Avoid phenytoin or lamotrigine

- Can be treated with valproic acid, stiripentol

- Mutations in SCN2A or SCN8A : Respond favorably to high-dose phenytoin
- Asians with HLA-B*1502 allele : Avoid carbamazepine, oxcarbazepine, phenytoin & lamotrigine
- GLUT-1 deficiency (SLC2A1 gene) : Ketogenic diet
- ALDH7A1 gene mutation (Antiquitin) : Pyridoxine

First-line ASMs

GTCS	• Lamotrigine • Valproic acid • Levetiracetam
Focal	• Lamotrigine • Carbamazepine • Oxcarbazepine • Phenytoin • Levetiracetam
Typical Absence	• Ethosuximide (1st choice in pure forms) • Valproic acid (1st choice in mixed seizure types) • Lamotrigine
Atypical absence, myoclonic, atonic	• Valproic acid • Lamotrigine • Topiramate

Mechanism of ASMs

Inhibition of sodium dependant action potentials in a frequency-dependant manner	• Phenytoin • Carbamazepine • Lamotrigine • Topiramate • Zonisamide, Lacosamide, Rufinamide • Cenobamate
Inhibition of voltage-gated calcium channels	• Phenytoin • Gabapentin, Pregabalin
Facilitating opening of potassium channels	• Ezogabine
Modulation of release of synaptic vesicles	• Levetiracetam • Brivaracetam
Attenuation of glutamate activity	• Lamotrigine • Topiramate (AMPA) • Felbamate (NMDA)
Facilitation of GABA receptor function	• Benzodiazepines • Barbiturates
Increase in availability of GABA	• Valproic acid • Gabapentin • Tiagabine
Inhibition of T-type calcium channels in thalamic neurons	• Ethosuximide • Valproic acid

Choice of ASMs in presence of comorbidities

a. Panic attacks	Clonazepam
b. Bipolar disorder	Carbamazepine, Valproate, Lamotrigine
c. Migraine prophylaxis	Valproate, Topiramate
d. Postherpetic neuralgia	Gabapentin, Pregabalin
e. Diabetic peripheral neuropathy	Pregabalin
f. Obesity	Topiramate, Zonisamide, Felbamate

Side effects of ASMs

Phenytoin - Enzyme inducer - Nonlinear kinetics → acute toxicity	• Hirsutism, Gum hypertrophy, Coarsening of facial features • Ataxia, Diplopia, Sedation • Osteomalacia, Vitamin K deficiency • Megaloblastic anemia • Lymphadenopathy/Pseudolymphoma • Teratogenic • Inhibit insulin release • Fulminant hepatitis • Purple glove syndrome • SJS/TEN
Fosphenytoin	• Hyperphosphatemia in renal failure • Arrrthymias

Carbamazepine - Enzyme inducer - Linear kinetics	• Leukopenia, Aplastic anemia • Hepatotoxicity • SIADH • Diplopia • Dose-related neurotoxicity, blurred vision • SJS/TEN
Oxcarbazepine	• More hyponatremia than CBZ (avoids an intermediate metabolite "toxic epoxide" a/w some of the side effects of carbamazepine)
Ethosuximide	• Bone marrow suppression
Lamotrigine - Enzyme inducer	• Skin rash • SJS • Ataxia, Diplopia
Levetiracetam	• Irritability, anxiety, psychiatric symptoms, increased suicide risk • Anemia, leukopenia • Increase BP in <4 yrs

Valproic acid - Enzyme inhibitor	• Thrombocytopenia • Tremor, Alopecia • Weight gain • Reversible BM suppression & hepatotoxicity : rare • Idiosyncratic, irreversible hepatic necrosis : <2 yrs • Teratogenic (NTDs), Autism • Hyperandrogenism (↓fertility), polycystic ovaries • Hyperammonemia • Pancreatitis
Topiramate - Enzyme inducer	• Weight loss • Renal stones • Glaucoma • Psychomotor slowing, Psychosis • Cognitive impairment : speech/language problem • Paresthesia • Hypohidrosis

Zonisamide	• Weight loss • Renal stones • Hypohidrosis • Psychosis
Felbamate	• Aplastic anemia • Weight loss • Hepatic failure
Lacosamide	• PR prolongation
Rufinamide	• QT shortening
Tiagabine	• Speech or language problem • Paresthesias • Psychosis
Vigabatrin	• Permanent vision loss • Weight gain : highest • Psychosis

Brivaracetam	• Weakness
Perampanel - Enzyme inducer	• Psychiatric side effects X Not to be given with OCPs, Warfarin
Barbiturates & BDZs	• Sedation • Frozen shoulder & Dupuytren's contracture (chronic use of barbiturates)
Pregabalin, Gabapentin	• Weight gain

Fenfluramine (oral)	**Dravet and Lennox-Gastaut syndromes**	• Ataxia • **Behavioral disturbance** • Headache,somnolence • Anorexia, constipation • **Hypertension** • **Serotonin syndrome** • **Weight loss**
Ganaxolone (oral)	**CDKL-5 deficiency disorder-associated seizures**	• Gait disturbance • Somnolence • **Bronchitis** • **Fever** • **Nasal congestion**
Cenobamate (oral)	**Focal onset** (Significantly improve seizure control in patients with focal epilepsy, not adequately treated with up to three medications)	• **Cognitive dysfunction** • Dizziness • **Disequilibrium** • Gait disturbance • Headache • Anorexia, constipation, diarrhea, dyspepsia, nausea

Phenytoin	t1/2 : 24 hr	10-20 ug/ml
Carbamazepine	t1/2 : 10-17 hr	6-12 ug/ml
Valproic acid	t1/2 : 15 hr	50-125 ug/ml

Treatment of poorly localized, spatially extensive, or multifocal seizure foci

- **Stimulation of thalamic nuclei**, which project broadly to different cortical regions, **with RNS or DBS** is an appealing approach to treating poorly localized, spatially extensive, or multifocal seizure foci.

Epilepsy in pregnancy & lactation

- Seizure frequency is unchanged in 50% of patients
- Valproic acid : strongly a/w increased risk of adverse fetal outcomes (7-20%)
- Other than topiramate, newer AEDs are far safer than valproic acid
- Pregnant mother on enzyme-inducing drugs should be treated with vitamin K
- Levetiracetam has highest concentration in breast milk while valproate has least

- **Estrogen-containing OCPs induce glucuronidation of lamotrigine and can decrease lamotrigine serum levels by >50%**

- **Catamenial epilepsy: Vulnerability to seizures is typically highest just before and during menses and during ovulation due to relatively high estrogen and low progesterone levels**

Sudden Unexpected Death in Epilepsy (SUDEP)

- Sudden, unexpected, witnessed or unwitnessed, nontraumatic & nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure, & excluding documented status epilepticus
- SUDEP is most common cause of epilepsy-related death
- Incidence of death in SUDEP : 1 per 1000 population
- Most important risk factor : high frequency of bilateral tonic-clonic seizures (>3/year, uncontrolled)
- Most commonly sleep-related
- Central apnea plays an important role

Definition of Status Epilepticus - *ILAE*

- A condition resulting from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1), & can have long-term consequences (after time point t2)
- Time point t1 for status epilepticus :

a. Bilateral tonic-clonic seizures – 5 minutes
b. Focal seizures – 10 minutes
c. Absence seizures – 10-15 minutes

- Most dangerous type of SE : GCSE

- Refractory SE (RSE) : SE persisting despite sufficient dose of benzodiazepines and at least one antiepileptic drug (AED), irrespective of time

- Super refractory SE (SRSE) : SE that continues for 24 hours or more after the use of anesthetic therapy, including cases that recur on weaning of the anesthestic agent

- Early refractory SE : 30 min to 48 hours

- Late refractory SE : >48 hours

Prehospital treatment of SE

Caregiver	• Rectal diazepam • Buccal midazolam • Nasal midazolam • Nasal lorazepam
Paramedics	• 2 mg of IV lorazepam • Intramuscular autoinjector midazolam

Benzodiazepine : 1st line treatment

Intravenous lorazepam	**0.1 mg/kg/dose, max. 4 mg**
Intravenous diazepam	0.1-0.3 mg/kg/dose, max 10 mg
Intramuscular midazolam	0.2 mg/kg/dose, max. 6 mg
Rectal diazepam	**0.2-0.5 mg/kg/dose, max. 20 mg**

1st line	IV BDZ
2nd line	• IV Phenytoin (20 mg/kg) /Fosphenytoin • IV Valproic acid (20-30 mg/kg) • IV Levetiracetam (20-30 mg/kg)
3rd line	• GCSE or subtle SE : IV Midazolam (0.2 mg/kg f/b 0.2-0.6 mg/kg/hr) &/or IV Propofol (2 mg/kg f/b 2-10 mg/kg/hr) • Focal-complex, myoclonic or absence SE : IV/PO VPA, LEV, Lacosamide, TPM, PGB
Late refractory SE	• PTB (THP) • Lidocaine, Verapamil, Magnesium, Ketogenic diet, Immunomodulation • Isoflurane, Desflurane, Ketamine • Surgery, VNS, rTMS, ECT, Hypothermia

New FDA approved drug for Rett syndrome ≥2 years

Trofinetide

MCQ's

Q. Which of the following is not included in category of progressive myoclonic epilepsy?

a. Juvenile myoclonic epilepsy of Janz
b. Unverricht-Lundborg disease
c. Lafora body disease
d. MERRF
e. Ceroid lipofuscinosis

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