Epilepsy
& its Management

Presentation Flow

- **Basic definitions**
- Epidemiology of epilepsy
- Classification of epilepsy and seizures
- Diagnosis of epilepsy
- Pathophysiology of epilepsy
- Management of epilepsy

EPILEPSY

- Most common disorder of the brain
- One of the oldest recorded medical conditions
- No age, racial, social class, national nor geographic boundaries
- There are over 50 million sufferers in the world today, 85% of whom live in developing countries
- An estimated 2.4 million new cases occur each year globally
- 70% to 80% of people with epilepsy could lead normal lives if properly treated
- In developing countries, 60% to 90% of people with epilepsy receive no treatment due to inadequacies in health care resources and delivery, and due to social stigma.

http://www.who.int/mental_health/neurology/epilepsy/en/index.html

Basic Definitions

The terms ‘seizure’ and ‘epilepsy’ are not synonymous

Term	Definition
Seizure *	Seizure is an event caused by abnormal, excessive and hypersynchronous discharge from a group of neurons in the brain (‘epileptic focus’)
Epilepsy	Epilepsy is a disorder of the brain characterised by a predisposition to generate multiple and recurrent episodes of seizures (≥ 2 seizure attacks)
Epilepsy syndrome	Epileptic disorder characterized by a cluster of signs and symptoms occurring together, including seizure type, precipitating factors, age of onset and severity.
Epileptogenesis	Sequence of events that converts a normal neuronal network into a hyperexcitable network

(*from the Latin sacire, **"to take possession of")**

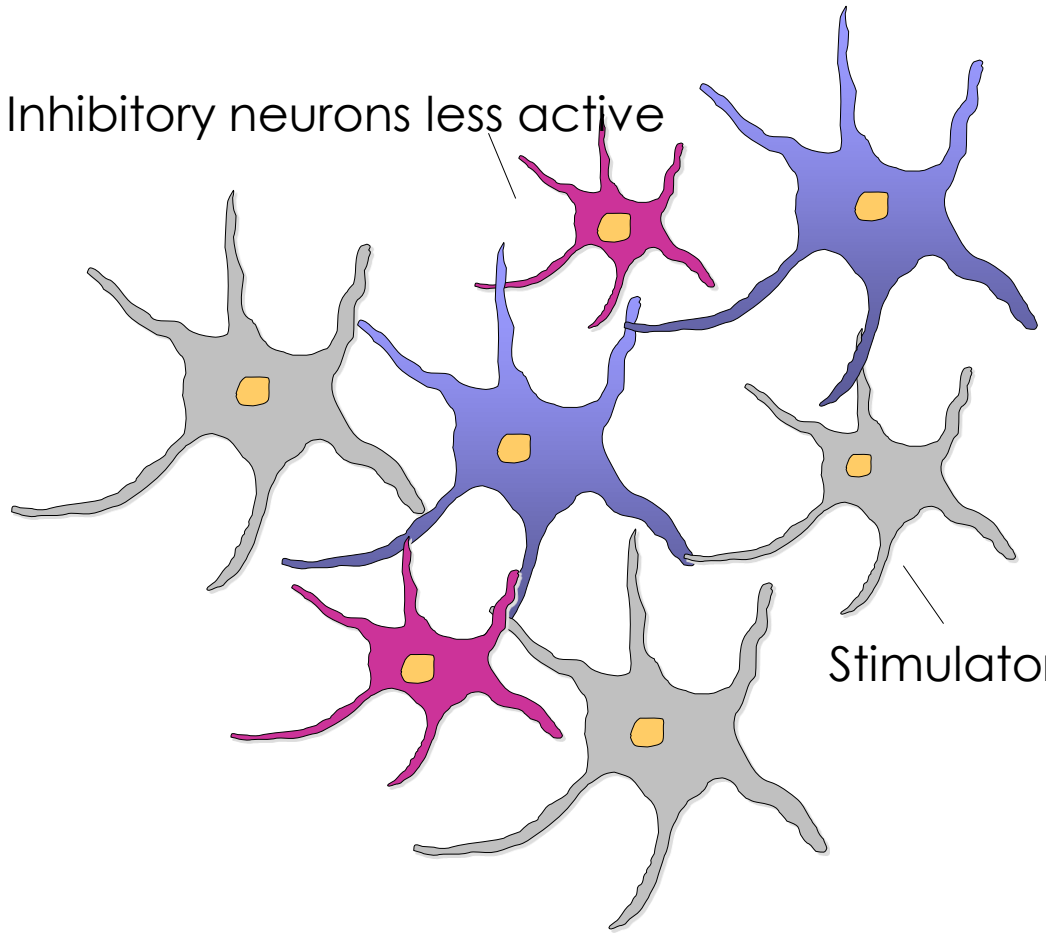
Ref: Lowenstein. Harrison's Principles of Internal Medicine; 2008; Duncan, et al. Adult epilepsy. Lancet. 2006; Seizure List. ILAE website. Accessed Dec 13, 2019.

ILAE definition of epilepsy

Epilepsy is a disease of the brain defined by any of the following conditions:

- At least two unprovoked (or reflex) seizures occurring >24 h apart;
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) occurring over the next 10 years;
- Diagnosis of an epilepsy syndrome.

Abnormal excessive synchronous firing



Normal rate of neuronal firing: 80 times per second

During epileptic attack: 500 times per second

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Epilepsy: Facts & Figures

Epidemiology

- India alone has approximately 10 million persons with epilepsy are there in India
- Its prevalence is about 1% in our population

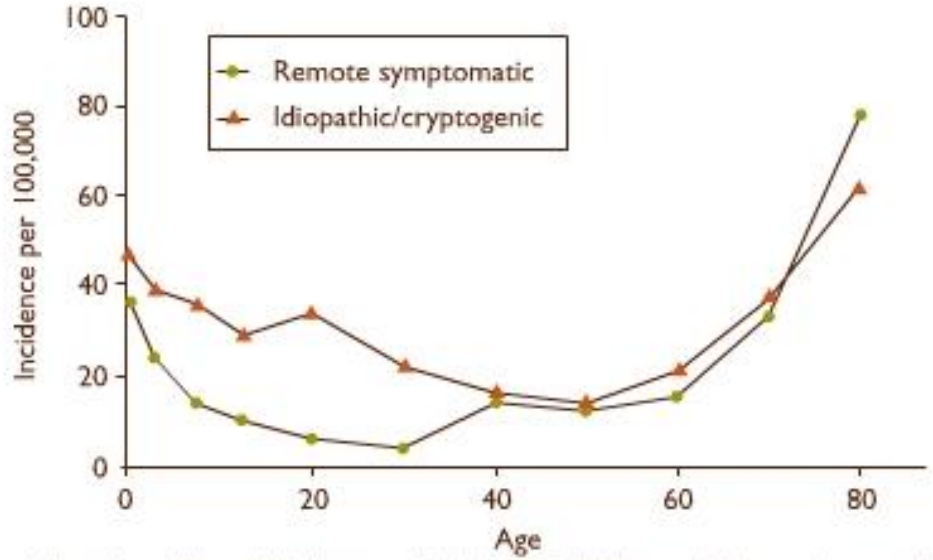
The prevalence is higher in the rural (1.9%) compared to urban population (0.6%)

- Females were more affected than males
- The estimated burden of epilepsy using the DALYs accounts for 1% of the total burden of disease in the world

Santosh NS et al. Ann Indian Acad Neurol. 2014 Mar; 17(Suppl 1): S3–S11.

Epilepsy: Age groups

- Epilepsy shows a bimodal age distribution
- High incidence is seen in childhood and old age



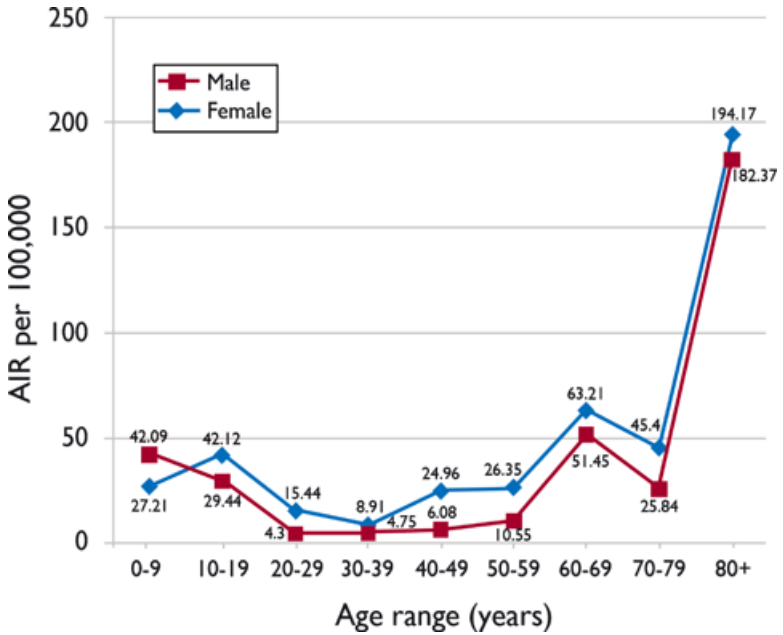
Source: Adapted from Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia*. 1993;34:453-468.

Trescher. *Neurology in Clinical Practice; 2008.*

A longitudinal study of epilepsy in Kolkata

N= 52,377

- Prevalence rate = 572.8 (509.79–641.54) per 100,000
- AAIR = 27.27 (21.03–34.80) per 100,000 per year
- The incidence was high during childhood,
  - declined by 20 years of age,
  - remained low throughout the adult years
  - again rose steeply after the fifth decade of life.
- The AAIR of epilepsy is comparable to that observed in developed countries, but AAMR is higher. (7.63/100,000 per year)



AAIR = Average annual incidence rate; AAMR = average annual mortality rate ; Epilepsia. 2010 Dec;51(12):2384-91.

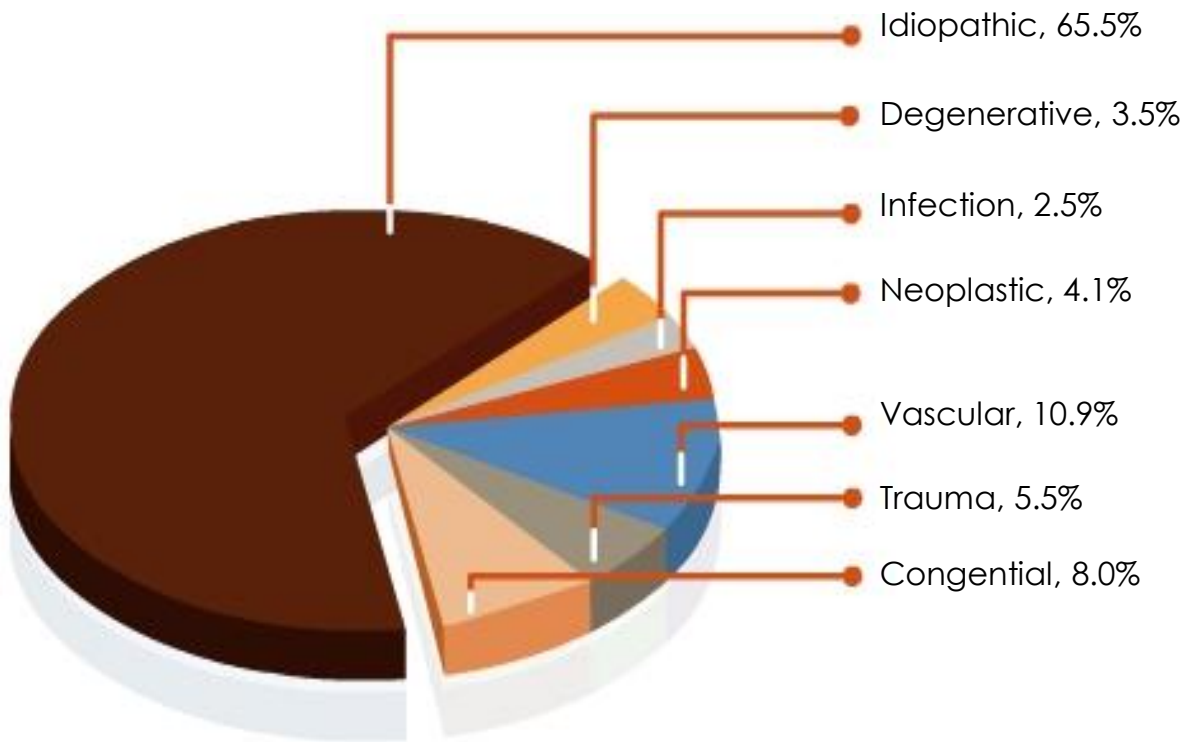
Etiology of Epilepsy

Causes of epilepsy can be grouped into 3 main categories

- Symptomatic – known structural abnormality
- Idiopathic – no previous history of brain insult, no underlying structural brain lesion or other neurological signs or symptoms
- Cryptogenic – believed to be symptomatic, but no etiology identified

Kwan. *N Engl J Med*. 2000 ; Hauser. *Epilepsia*.1993.

Proportion of Incidence Cases by Etiology of Epilepsy (All Ages)



Adapted from: Hauser. *Epilepsia*.1993

Hauser. *Epilepsia*.1993; Trescher. *Neurology in Clinical Practice*; 2008; Kwan. *N Engl J Med*. 2000.

Precipitating Factors for Seizures

- Infection/fever
- Non-compliance with antiepileptic drugs
- Medication withdrawal (barbiturate or benzodiazepine withdrawal)

- Sleep deprivation
- Alcohol
- Flashing lights
- Stress
- Menstruation
- Recreational drugs

Further…DEFINITIONS

Type	Meaning
Active epilepsy	at least 1 seizure in preceding 2 years
Remission	no seizure in previous 2 years
Provoked epilepsy	seizures with obvious preceding cause (metabolic problems, stroke, cerebral injury & infection)
Status epilepticus	epileptic seizures continue, or repeated without gaining consciousness, for a period of 30 minutes (10 - 60 minutes)

Lowenstein. Harrison's Principles of Internal Medicine; 2008; Duncan, et al. Adult epilepsy. Lancet. 2006; Seizure List. ILAE website. Accessed Dec 13, 2019.

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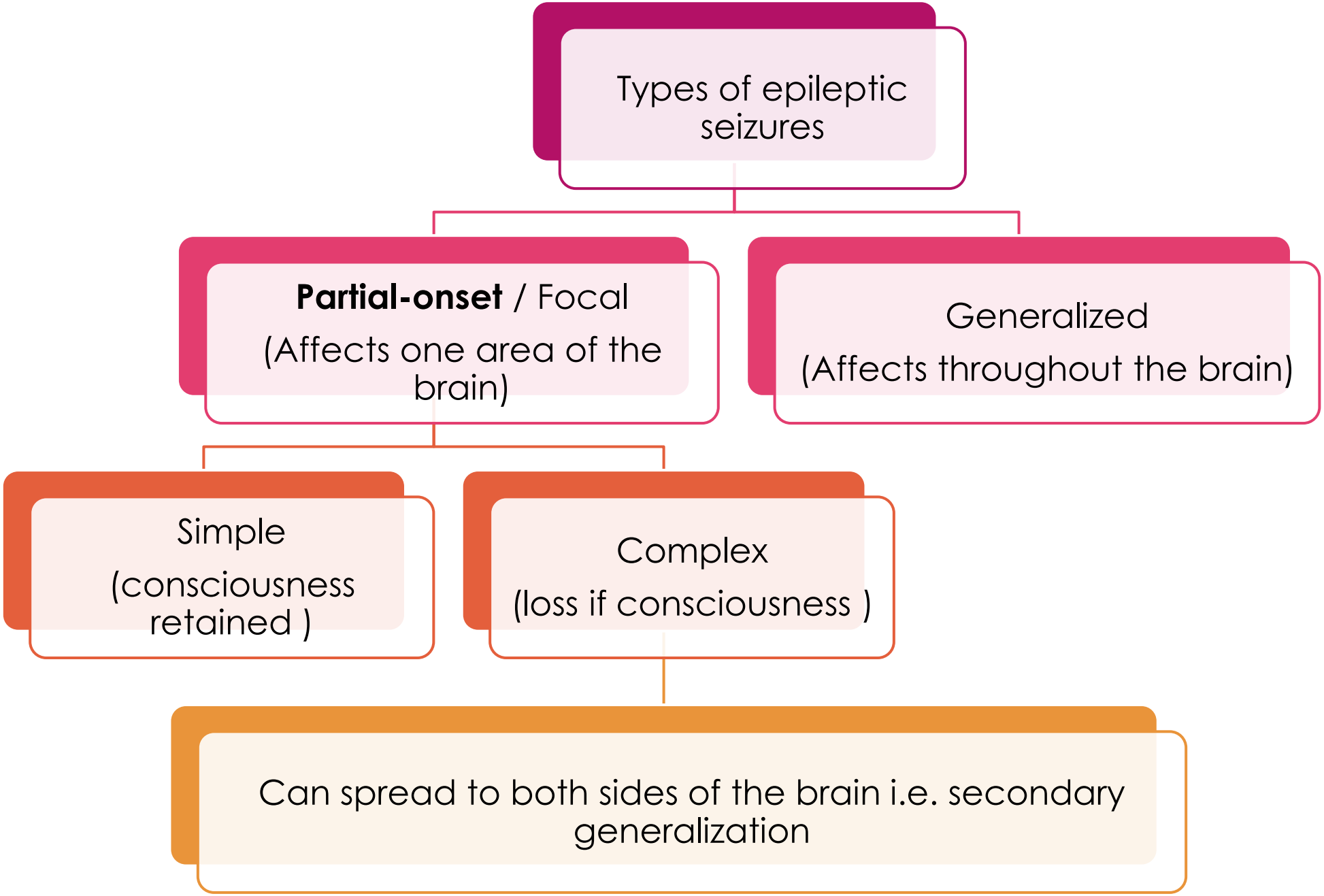
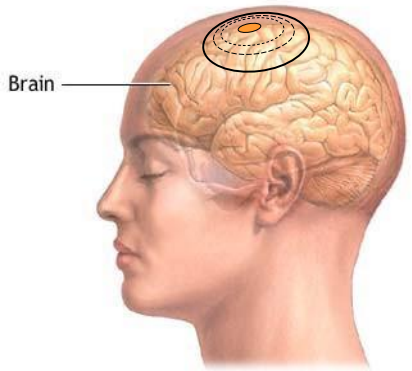
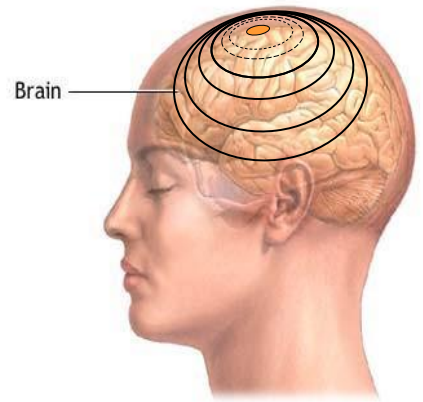


Seizure List. ILAE website. Accessed Dec 13, 2019.

ILAE CLASSIFICATION

Partial (Focal) Epilepsy	Generalized Epilepsy
simple partial seizures	absence seizures
complex partial seizures	generalized tonic-clonic seizures
partial progressing to generalized seizures	tonic seizures
	clonic seizures
	atonic seizures
	myoclonic seizures

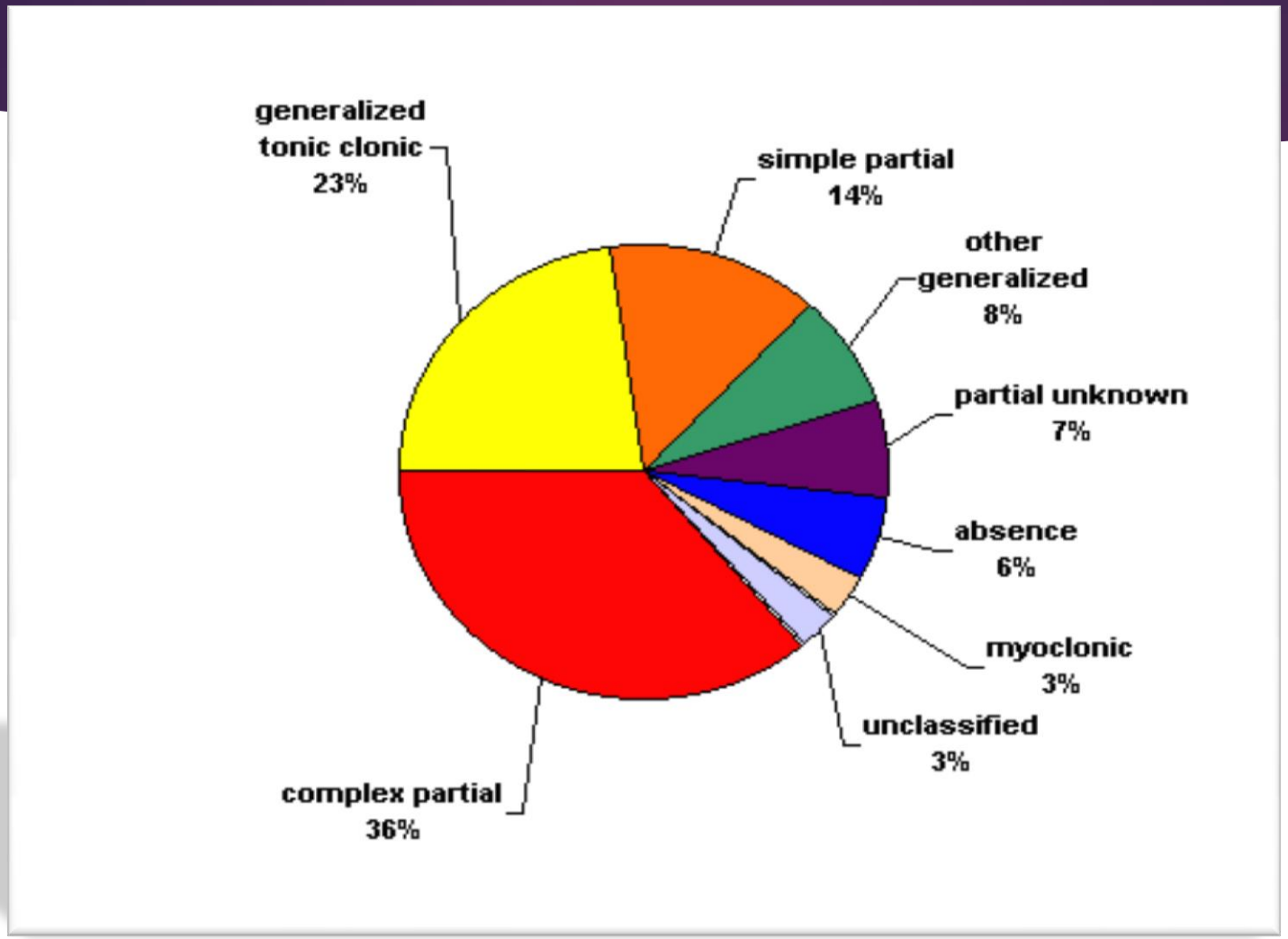




* Partial seizures usually present as single seizure type but may also occur in pts with mixed seizures

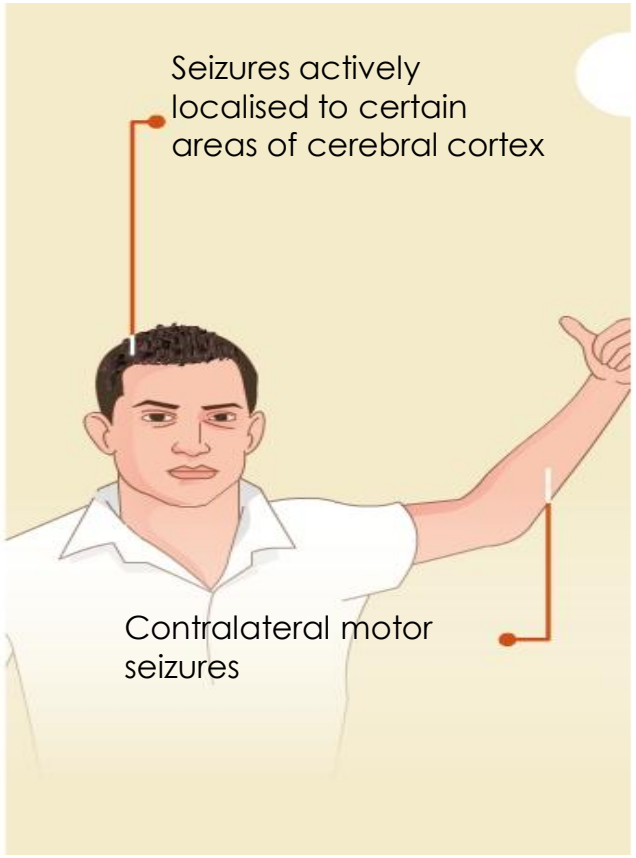
Seizure List. ILAE website. Accessed Dec 13, 2019.

SEIZURE TYPES



Seizure List. ILAE website. Accessed Dec 13, 2019.

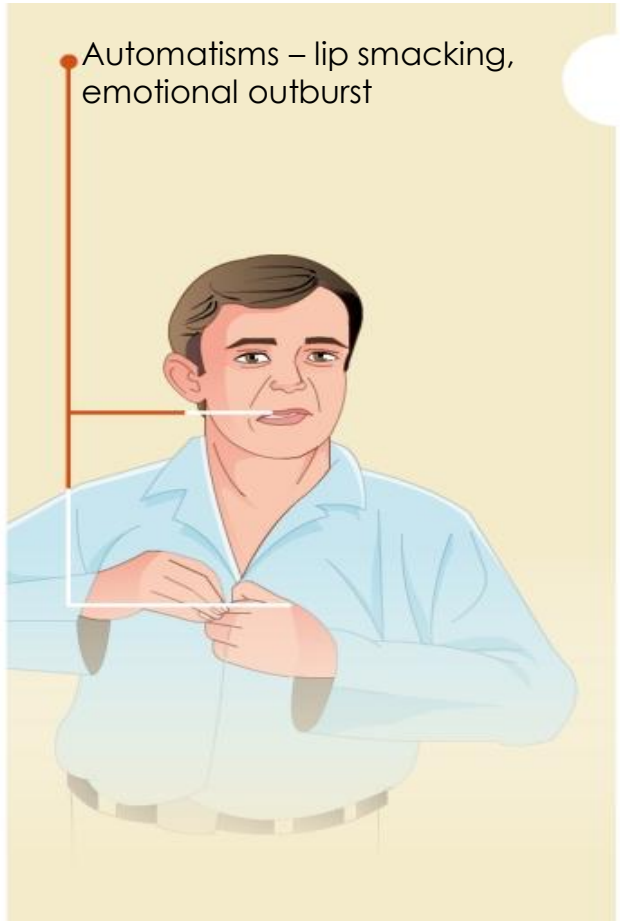
SIMPLE PARTIAL SEIZURES



- Piloerection : involuntary erection or bristling of hairs due to a sympathetic reflex
- Dysphasic : inability to speak.
- Dysmnesic : memory impairment

MAIN FEATURES
C - no loss of consciousness
A - changes in skin color, BP, HR, pupil size, piloerection , AURA +
M - muscle spasms (‘march’) or jerking
P - dysphasic, amnesia, cognitive, mood- affective changes, illusions, hallucinations
S - tingling, numbness, electric shock-like feeling, burning, pain, heat, altered smell, taste
last for few seconds

COMPLEX PARTIAL SEIZURES

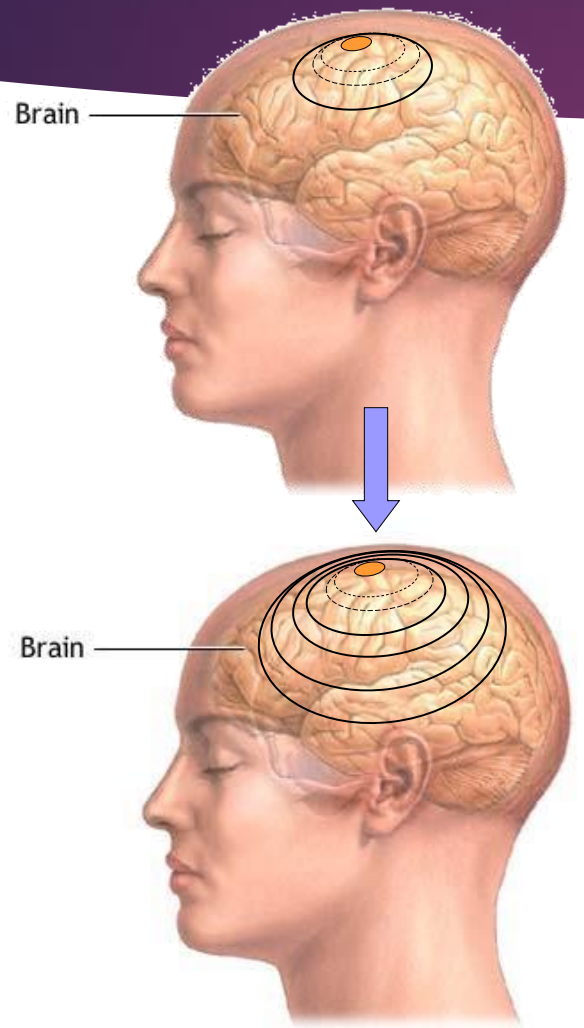


MAIN FEATURES
A = aura similar to simple partial seizures
A = altered consciousness (motion arrest) – unresponsive to commands (confusion , loss of awareness, staring)
A = automatisms (hand rubbing, lip smacking, arm positioning, uncontrolled shouting or swallowing)

Complex Partial Seizures (CPS)

- Distinguishing feature of CPS
  - Impaired or lost consciousness at some point during the seizure.
- Duration
  - Untreated CPS usually last more than 60 seconds
- The timing of impaired consciousness varies
  - Consciousness can be impaired from the outset.
  - Seizure may begin with elementary sensory or psychic experience (aura) followed by impaired consciousness.

SECONDARY GENERALIZED SEIZURES



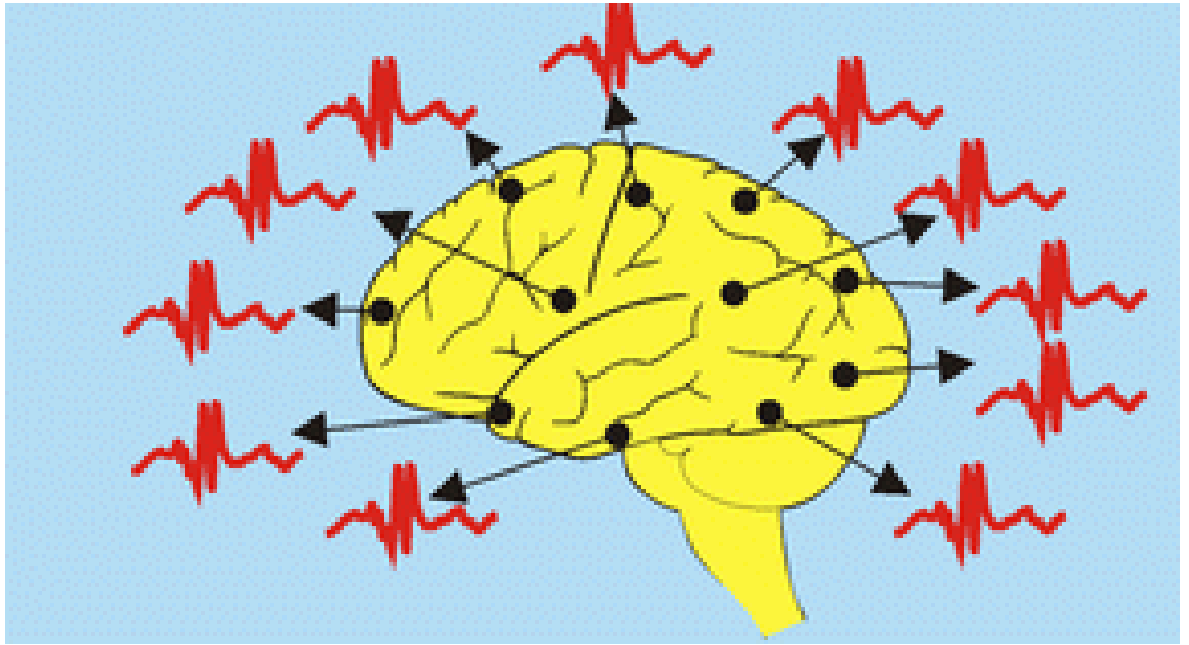
MAIN FEATURES
Begins like partial seizures
Further progression to generalized seizures .

Partial, Secondary Generalized Seizures

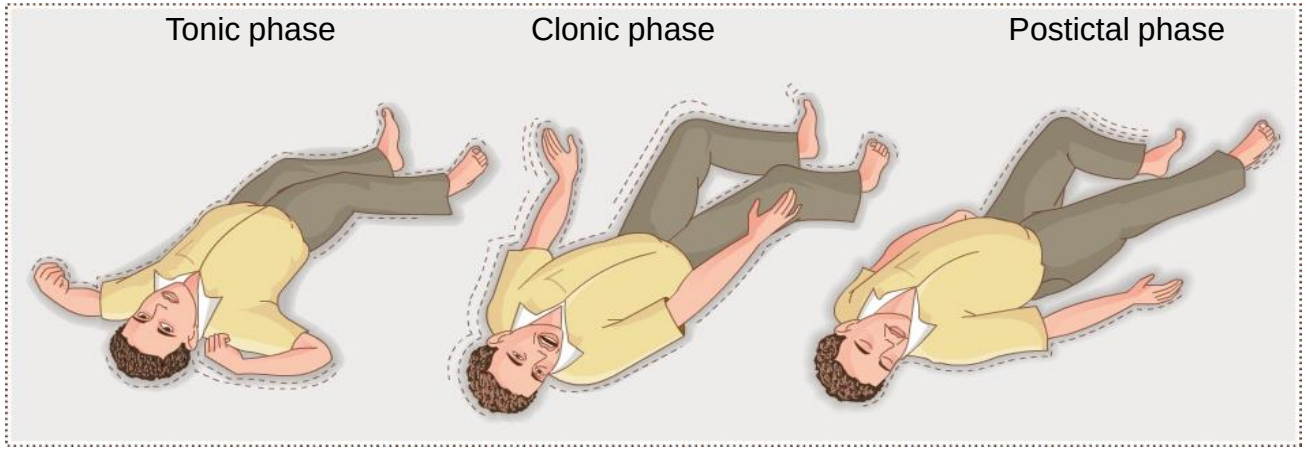
- Secondary generalized seizures occur when the localized seizure discharge spreads to involve both hemispheres causing the following sequence of events.
  - Generalized stiffening (the tonic phase).
  - Clonic jerking.
  - Exhaustion with hypotonia (abnormally low pressure of the intraocular-eyeball fluid) and sleep.

GENERALIZED SEIZURES

- The discharge affects the entire cortex simultaneously & causes unconsciousness at the outset



GENERALIZED TONIC CLONIC SEIZURES (Grand Mal)



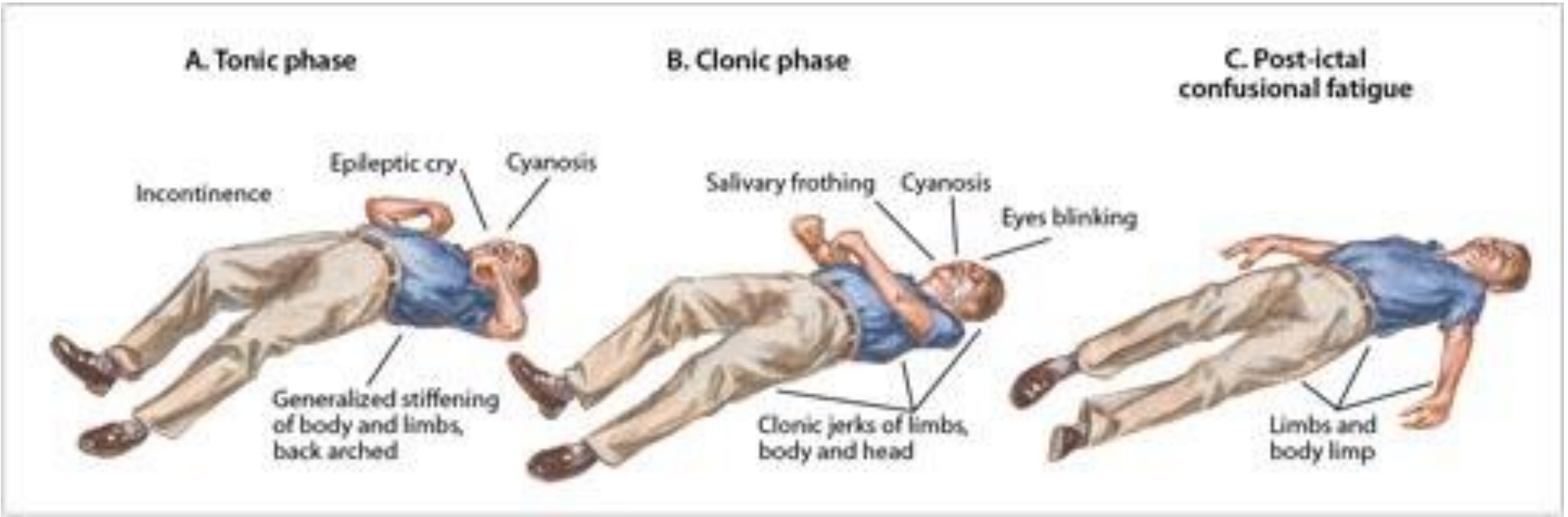
MAIN FEATURES

Aura phase – similar to simple partial seizures

Ictal phase – cry out & fall, loss of consciousness, brief phase of sustained muscle contraction (tonic phase), followed by rapid contraction and relaxation of muscles (clonic phase), frothing from mouth, tongue bite

Post-ictal phase – sleepy or drowsy, disoriented for some time, muscle aches, headaches, amnesia for seizure events

GENERALIZED SEIZURES



Cyanosis : Bluish-purple discoloration of skin and mucous membranes usually resulting from a deficiency of oxygen in the blood

ABSENCE SEIZURES

MAIN FEATURES
C - loss of consciousness, vacant stare, unresponsive to commands (day-dreaming)
A - none
M – all motor activity stops for few seconds
P - none
S - none
Blinking, slight clonic movements, alterations in tone and automatisms can occur
Lasts for < 10 seconds in 80% of cases, hundreds of episodes may occur/day
Common in children and in girls

ATONIC SEIZURES

MAIN FEATURES
No loss of consciousness
Last for few seconds
Muscle tone completely lost and patient suddenly falls to ground; patients regain quickly and start walking again
P – none
S - none

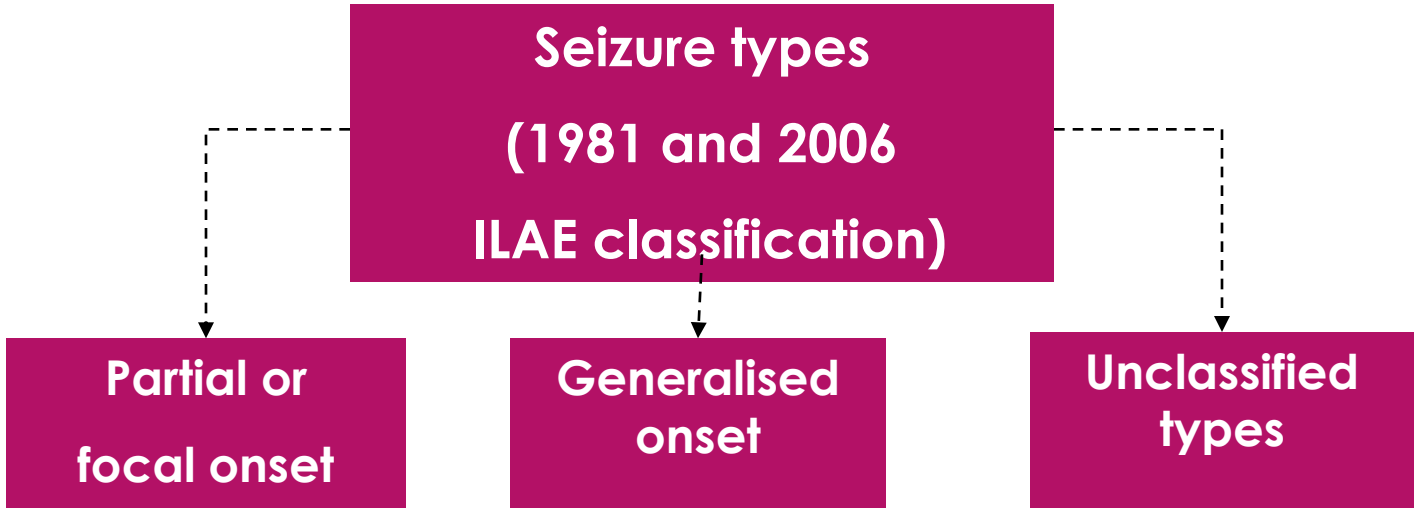
ATONIC SEIZURES

- Atonic seizures are characterized by sudden loss of postural muscle tone lasting 1 to 2 s.
- Consciousness is briefly impaired, but there is usually no post ictal confusion.
- A very brief seizure may cause only a quick head drop or nodding movement, while a longer seizure will cause the patient to collapse.

MYOCLONIC SEIZURES

MAIN FEATURES
C – very, brief loss of consciousness
A – none
M – muscles suddenly contract, usually of arms or head, more in mornings
P - none
S - none

Classification of Seizures



Ref: Seizure List. ILAE website. Accessed Dec 13, 2019.

EPILEPSY SYNDROME

Epilepsy + Common underlying mechanisms

Important syndromes

- JME
- LGS
- MTLE

JUVENILE MYOCLONIC EPILEPSY (JME)

- Inherited condition
- Myoclonic jerks, tonic-clonic seizures +/- absence seizures.
- Seizures usually occur after awakening in the morning.
- Usually responds well to treatment but lifelong treatment needed.
- EEG pattern 4-6 Hz spike with wave pattern & multiple spike and wave complexes that may be precipitated by photic stimulation and sleep deprivation.

JUVENILE MYOCLONIC EPILEPSY (JME)

- 15% of children with childhood absence epilepsy later develop JME

Appears in early adolescence

Provoked by sleep deprivation

Most frequent in the morning after awakening

Characterized by bilateral myoclonic jerks

Consciousness preserved

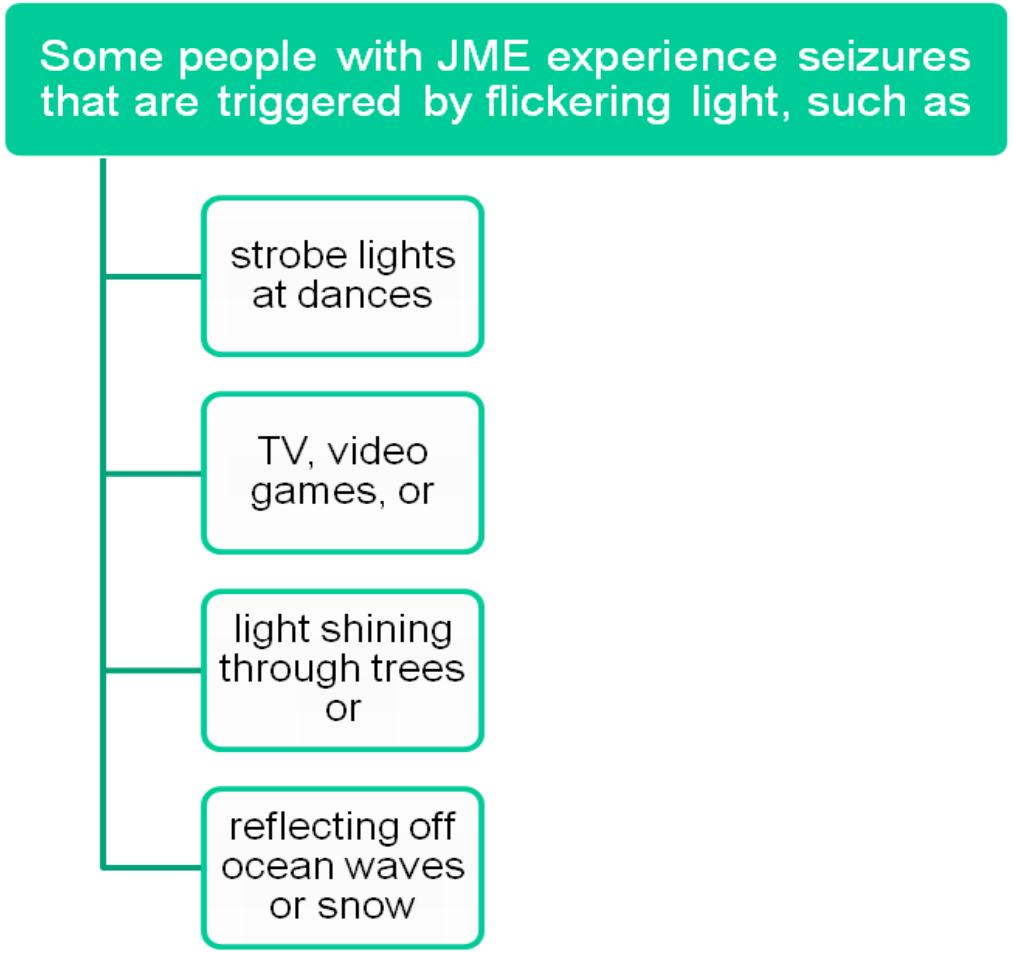
JME --> Tonic clonic or absence

Family history positive

Respond well to treatment

Complete remission - uncommon

PHOTOSENSITIVE SEIZURES



LENNOX–GASTAUT SYNDROME (LGS)

- Most difficult to treat childhood form of Epilepsy.
- Daily multiple seizures are typical in LGS.
- The most frequently occurring seizure types are
  - Tonic which are often nocturnal (90%);
  - The second most frequent are myoclonic seizures, which often occur when the patient is over-tired.
  - Atonic, atypical absence, complex-partial, focalized and tonic-clonic seizures are also common.
- Accompanied by mental retardation), psychological and behavioral problems.

LENNOX–GASTAUT SYNDROME (LGS)

- Children.
- Diffuse Neuronal injury.
  - Developmental abnormalities.
  - Perinatal hypoxia.
  - Trauma
  - Infection
- Poor prognosis
- Multiple seizure types.
- EEG < 3 HZ spike-and –wave
- Impaired cognition

Medial Temporal Lobe Epilepsy Syndrome (MTLE)

- Most common syndrome associated with CPS.
- Arises in Hippocampus, para hippocampal gyrus & amygdala (located in inner aspect of temporal lobe).
- High Resolution MRI – hippocampal sclerosis.
- Refractory to treatment with anticonvulsants.
- Responds extremely to surgical resection.

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Epilepsy: Diagnosis

History

- Description of the attack
- Family history
- Past history of brain infection, head injury, stroke, tumor, febrile seizures
- Medication history
- Careful psychiatric history

Physical Examination

- Detailed CNS examination
- Examination of the skin for neurocutaneous disorders

Lab Tests to Rule out Metabolic Causes

- Blood glucose
- Electrolytes
- Renal and liver function tests

Trescher. *Neurology in Clinical Practice.* 2008; Lowenstein. *Harrison's Principles of Internal Medicine*. 2008.

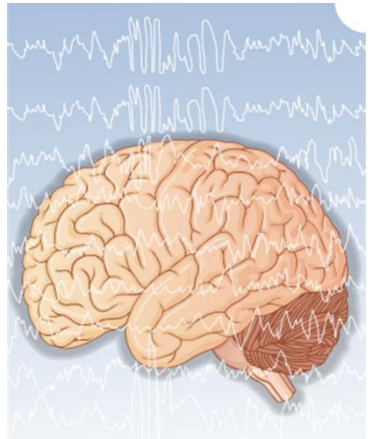
Seizures: Differential Diagnosis

- Syncope
- Psychological disorders such as hyperventilation, panic attack
- Metabolic disturbances such as hypoglycemia, hypoxia,
- Migraine
- Transient ischemic attack
- Sleep disorders such as narcolepsy
- Movement disorders such as tics, nonepileptic myoclonus
- Special considerations in children such as breath-holding spells, apnea, sleepwalking

Lowenstein. *Harrison's Principles of Internal Medicine*. 2008.

Electroencephalogram

- All patients with a seizure should be evaluated with an EEG as soon as possible
- Evidence of typical epileptic electrographic activity during the clinical event indicates that the event is epilepsy
- Capturing EEG changes during seizures may require continuous long-term monitoring by ambulatory EEG or in-hospital video EEG
- EEG may be normal in the seizure-free interval in patients with established epilepsy
- Benign variant patterns may be misdiagnosed as epilepsy
- Absence of an EEG abnormality does not rule out epilepsy



Lowenstein. *Harrison's Principles of Internal Medicine*. 2008; Trescher. *Neurology in Clinical Practice.* 2008.

Brain Imaging

CT Scan

- Screening tool to rule out tumors or vascular lesions

MRI

- Most important investigation to identify structural lesions and epileptogenic foci amenable to surgical resection

Functional MRI

- Allows the identification of brain areas that are critical to memory and language function, which should not be resected during surgery

SPECT Scan

- Useful when MRI and EEG cannot accurately localise epileptic focus

Magnetoencephalography (MEG)

- A noninvasive technique used to record cortical activity.

Trescher. *Neurology in Clinical Practice.* 2008.

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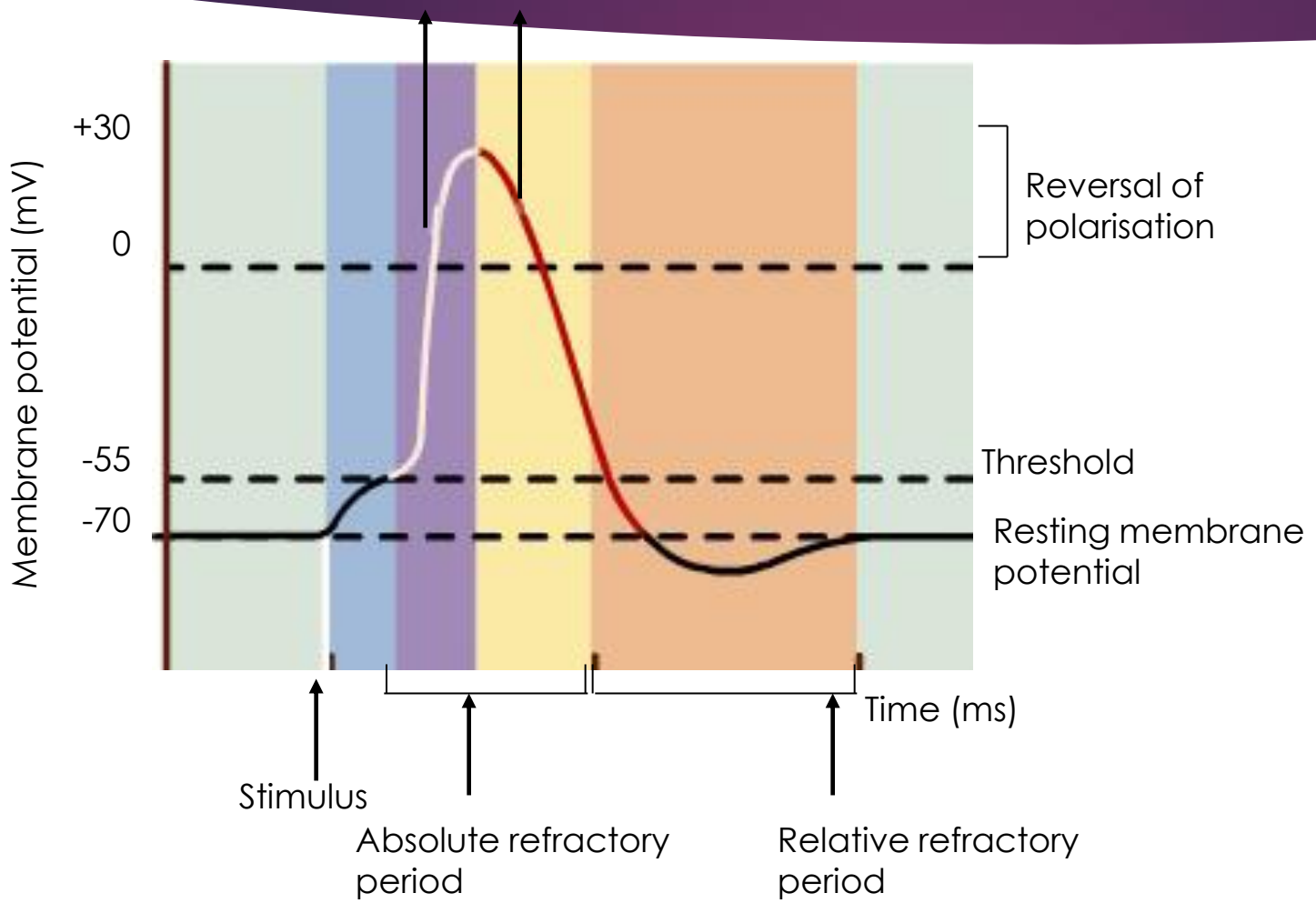
Normal Generation of Nerve Impulse



Adapted from: Tortora. *Principles of Anatomy and Physiology.* 2003.

Neurotransmitters

- Neurotransmitter is a specific chemical agent released by a presynaptic cell on excitation that crosses the synaptic cleft to stimulate or inhibit the postsynaptic cell

- The major neurotransmitters in the brain are
  - GABA
  - Glutamate
  - Acetylcholine
  - Dopamine
  - Serotonin
  - Histamine

Tortora. *Principles of Anatomy and Physiology*. 2003.

Inhibitory Neurotransmitter

- **Major inhibitory neurotransmitter: GABA**
  - Stimulation of GABA receptors produces hyperpolarisation and inhibits neuronal activity
  - GABA enhancement and facilitation and direct stimulation of GABA receptors are established principles in the drug treatment of seizures

Trescher. *Neurology in Clinical Practice.* 2008; Schachter. *Epilepsia*. 1999.

Excitatory Neurotransmitter

- **Major excitatory neurotransmitter: Glutamate**
  - Stimulation of glutamate receptors causes depolarisation and transmission of nerve impulses
  - Some antiepileptic drugs act by blocking the glutamate receptors

Trescher. *Neurology in Clinical Practice.* 2008.

Neurotransmitter Systems

Nerve impulse arrives at the synapse

↓

Voltage-gated calcium channels open

↓

Calcium enters the neuron

↓

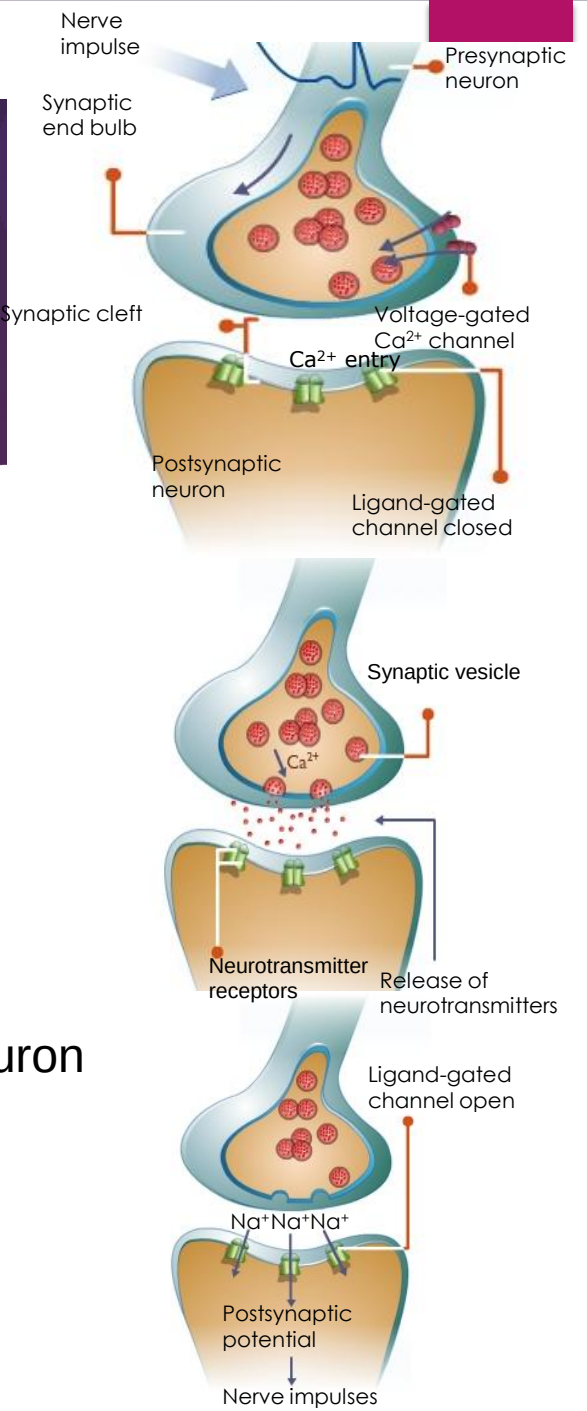
Neurotransmitter molecules are released into synapse

↓

Neurotransmitter binds to the receptor in the postsynaptic neuron

↓

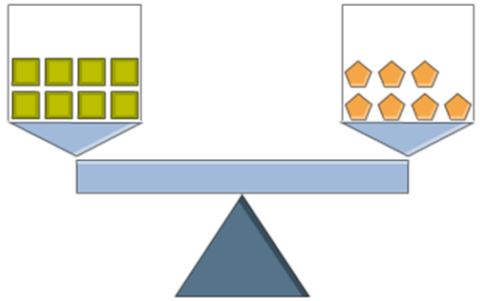
This causes propagation or termination of action potential (depending on the type of neurotransmitter)

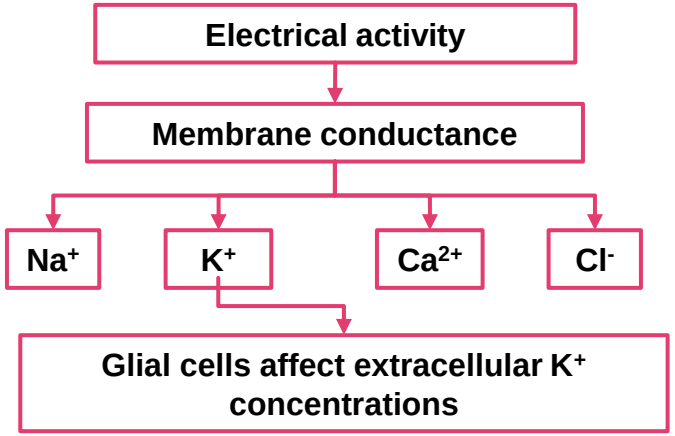


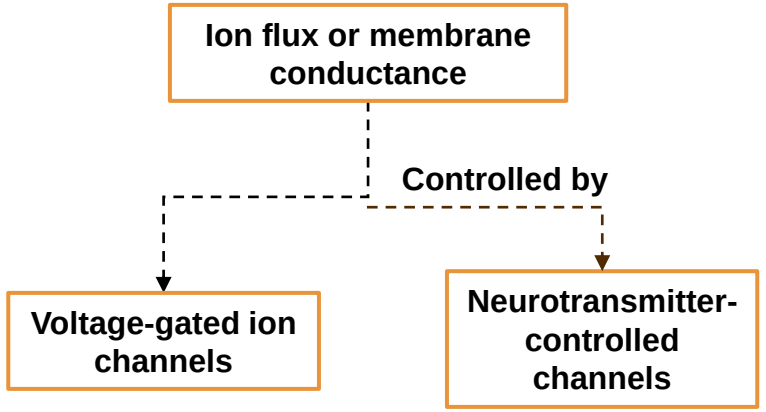
Tortora. *Principles of Anatomy and Physiology.* 2003.

Pathophysiology: Neuronal Excitation-Inhibition Balance

- Seizures occur when the balance between neuronal excitation and inhibition is disturbed
- Central to epileptogenesis is the alteration in electrical activity of neurons



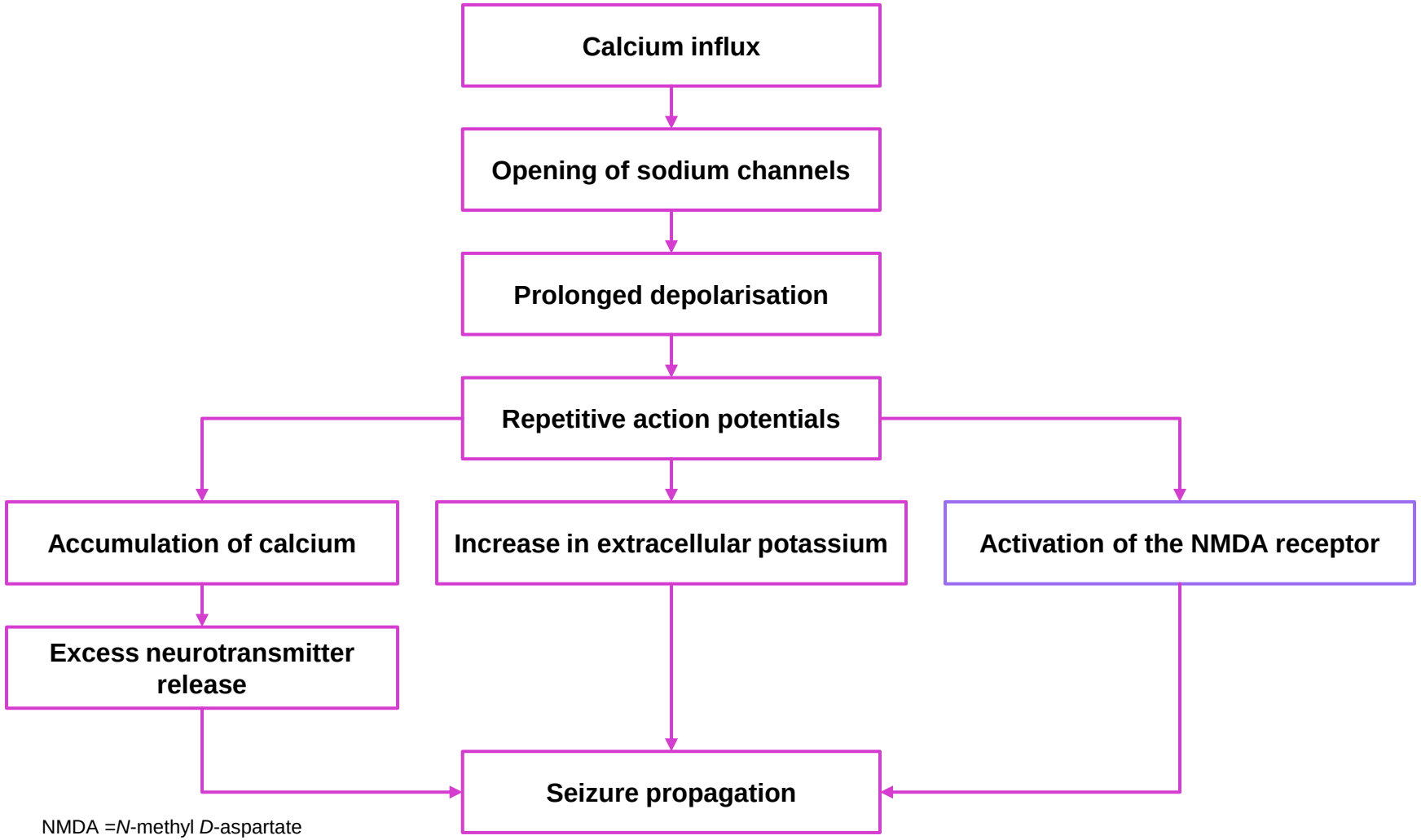




- Abnormality in any of these components can affect the neuronal excitation-inhibition balance

Lowenstein. *Harrison's Principles of Internal Medicine*; 2008; Trescher. *Neurology in Clinical Practice*; 2008.

Seizure Initiation and Propagation



NMDA =*N*-methyl *D*-aspartate

Lowenstein. *Harrison's Principles of Internal Medicine*. 2008.

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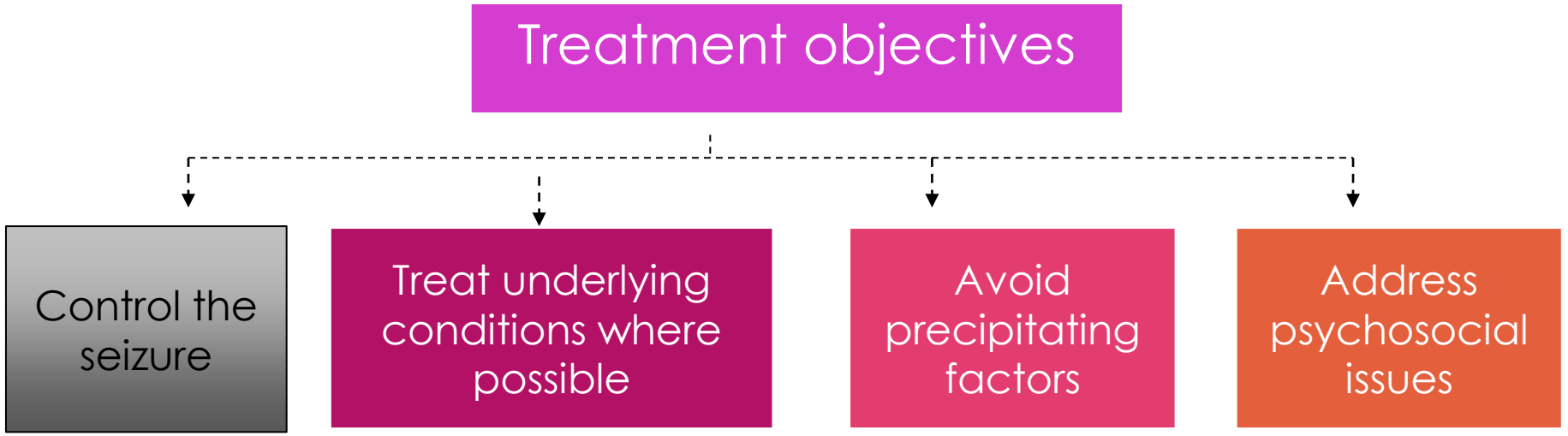
  - **How to choose an AED**
  - **Mechanism of action of AEDs**
  - **Rationale for polytherapy**

Management of Epilepsy



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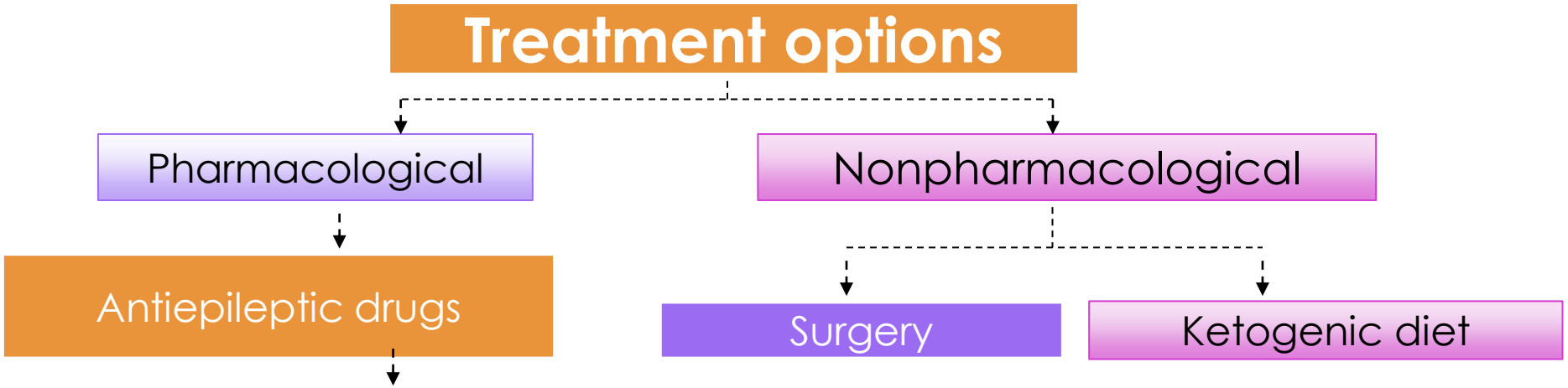
Management of Epilepsy



- Effective in controlling seizures in 60% to 70% of patients
- Persistent seizures are treated by
  - Switching over to another agent
  - Optimizing the dosage
  - Combination of antiepileptic agents (poly-therapy)

Lowenstein. Harrison's Principles of Internal Medicine. 2008; Duncan. Lancet. 2006; Trescher. Neurology in Clinical Practice. 2008.

Non-pharmacological Management: Surgery

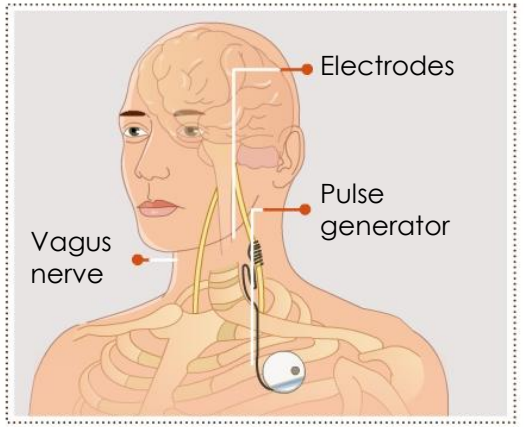
- About 20% to 40% of patients with epilepsy may not respond to antiepileptic drug treatment
- The cause for unresponsiveness should be determined and the option of surgery should be evaluated
- Seizures arising from more than one site may not be amenable to surgery
- Surgery is beneficial in about 1% to 5% of patients with intractable epilepsy and cases of medial temporal lobe epilepsy.
- Seizures secondary to brain tumours or hydrocephalus also benefit from surgery
- Usually surgery aims to remove the epileptogenic focus

Trescher. *Neurology in Clinical Practice*. 2008; Lowenstein. *Harrison's Principles of Internal Medicine*. 2008.

Surgical Procedures and Vagal Nerve Stimulation

- **Procedures That Remove Epileptogenic Focus**
  - Anterior temporal lobectomy
  - Focal cortical resection and lesionectomy
  - Lesionectomy
  - Hemispherectomy
- **Palliative Procedures That Interrupt the Pathways of Seizure Spread**
  - Corpus callosotomy
  - Multiple subpial transections

Vagus Nerve Stimulation



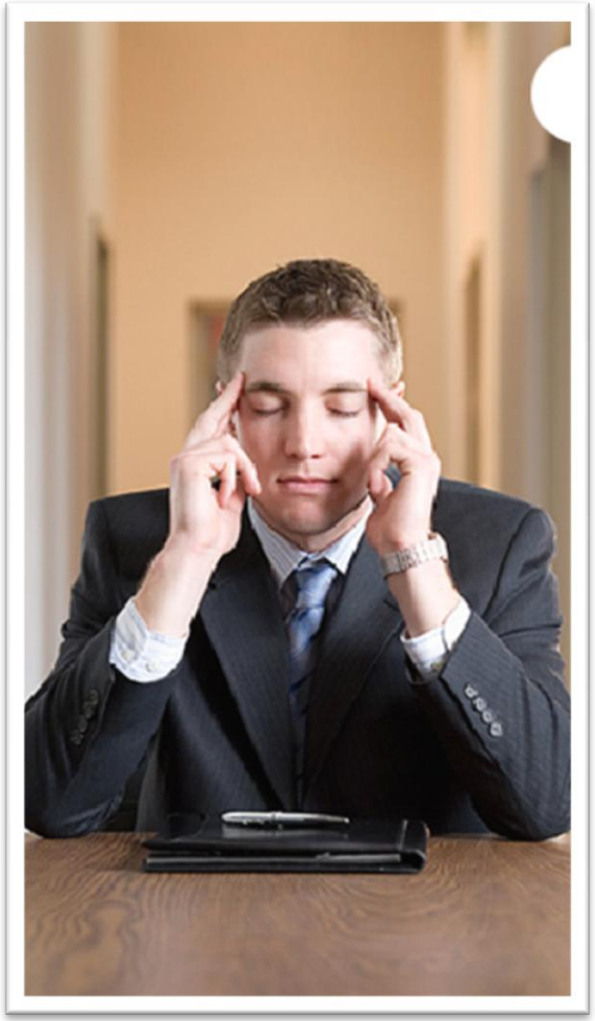
- Adjunctive treatment for refractory partial epilepsy
- Although complete control is rare, seizure frequency reduces
- The patient may be put on lower doses of antiepileptic drugs

Trescher. *Neurology in Clinical Practice*. 2008.

Non-Pharmacological Treatment

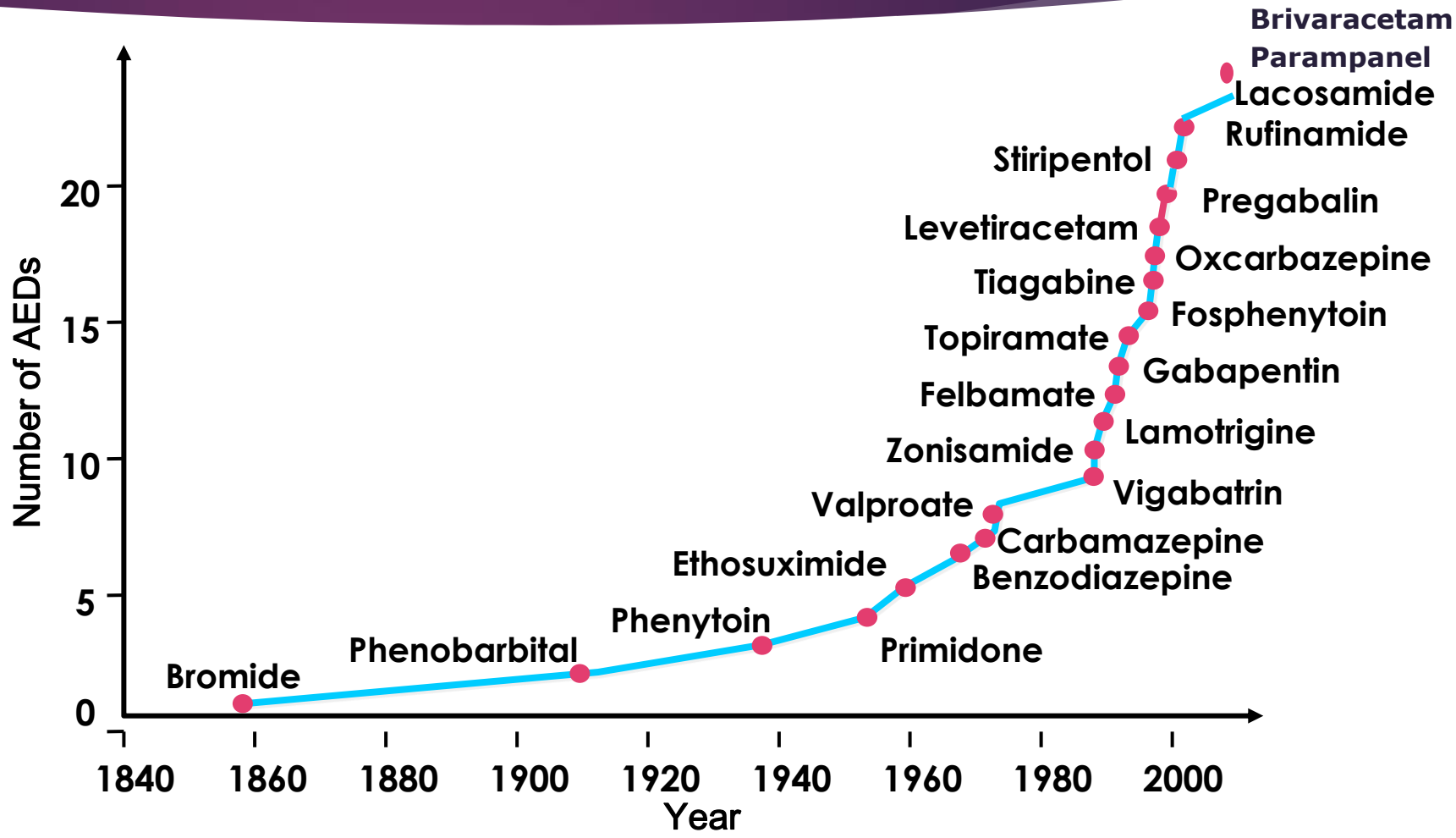
- **Prevention of Provoking Factors**
  - Maintain a good sleep schedule
  - Limit alcohol intake
  - Adopt stress reduction techniques
  - Avoid specific sensory stimuli that precipitate epilepsy
  - Avoid use of medications that lower the seizure threshold

- **Ketogenic diet**
  - Diet rich in fatty acid
  - Beneficial in children

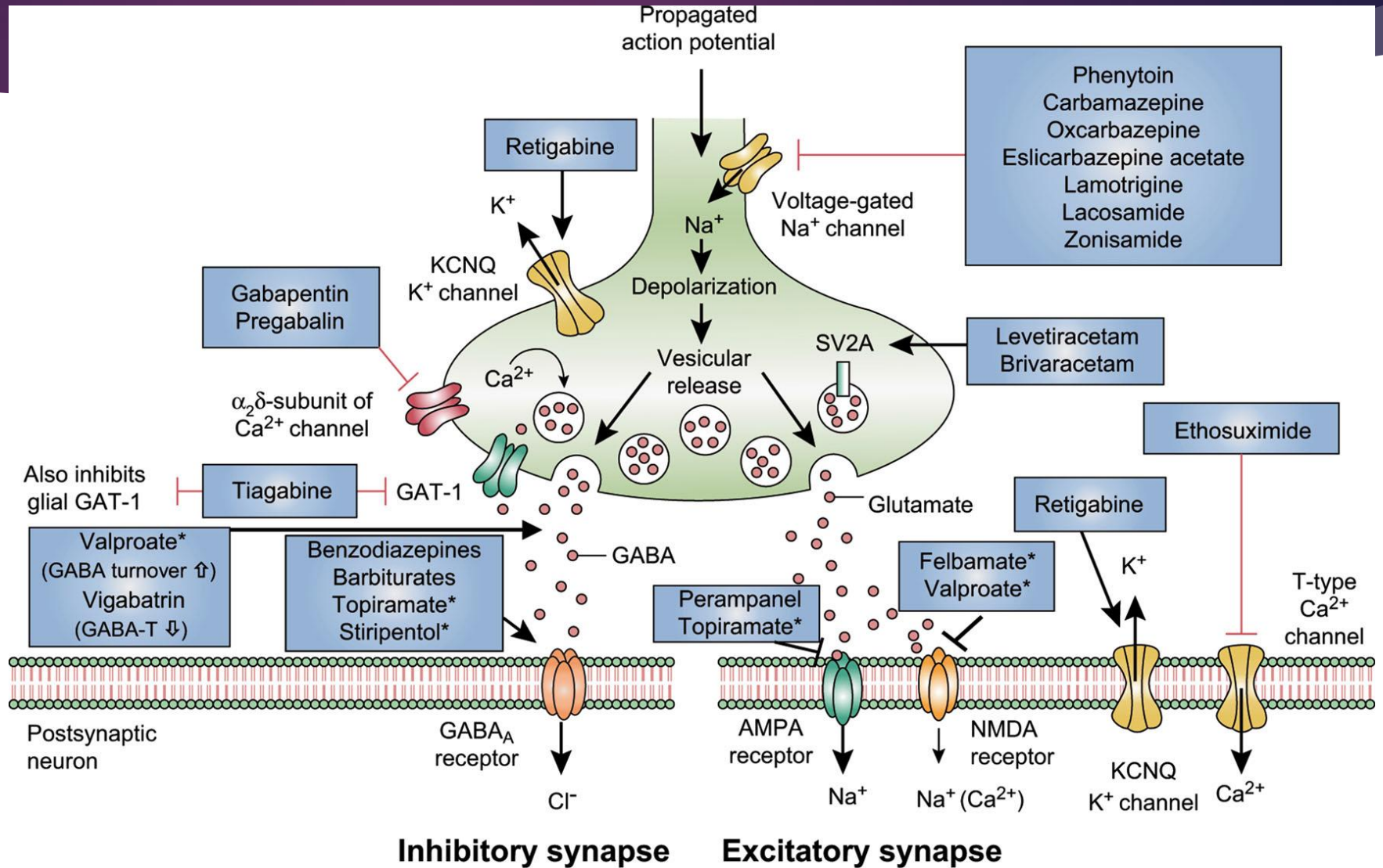


Lowenstein. *Harrison's Principles of Internal Medicine*. 2008. Duncan, et al. Adult epilepsy. *Lancet*. 2006

Introduction of AEDs in clinical practice



AEDs: Mechanism of action



Characteristics of clinically approved AEDs

AED	Companies	Year of approval	Presumed main mechanisms of action	Approved indications	Main utility	Main limitations
First-generation drugs						
Potassium bromide	Dow	1857‡	GABA potentiation?	GTCS, myoclonic seizures	Broad use for focal and generalized seizures	Currently for adjunctive use only, not in wide use anymore; acts as a sedative
Phenobarbital	Bayer	1912‡	GABA potentiation	PGCS, sedation, anxiety disorders, sleep disorders	Broad use for focal and generalized seizures	Enzyme inducer; skin hypersensitivity; no absence seizures
Phenytoin	Parke-Davis/ Pfizer	1938	Sodium channel blocker	PGCS	First-line AED, i.v. use	Enzyme inducer; skin hypersensitivity; NLPK; not useful for absence or myoclonic seizures
Trimethadione	Abbott	1946	T-type calcium channel blocker	Absence seizures	Rare use for absence seizures	Not in wide use anymore; teratogenic
Primidone	Imperial Chemical Industries	1954	GABA potentiation	PGCS	Broad use for focal and generalized seizures	Enzyme inducer; skin hypersensitivity; no absence seizures; acts as a sedative
Ethosuximide	Parke-Davis/ Pfizer	1958	T-type calcium channel blocker	Absence seizures	First-line AED, no skin hypersensitivity	Somnolence, loss of appetite, nausea, vomiting, singultus, depression, psychotic episodes, insomnia, rare aplastic anaemia

Löscher, W et al. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov 2013;12: 757–776 (2013)

Characteristics of clinically approved AEDs

AED	Companies	Year of approval	Presumed main mechanisms of action	Approved indications	Main utility	Main limitations
First-generation drugs						
Diazepam	Roche	1963	GABA potentiation	Convulsive disorders, status epilepticus, anxiety, alcohol withdrawal	Broad use for focal and generalized seizures, i.v. use, no clinical hepatotoxicity, no skin hypersensitivity	Currently for adjunctive use only; emergency use only; acts as a sedative; leads to tolerance (loss of efficacy)
Carbamazepine	Novartis	1964	Sodium channel blockade	PGCS, trigeminal pain, bipolar disorder	First-line AED	Enzyme inducer; skin hypersensitivity; not useful for absence or myoclonic seizures
Valproate	Sanofi/Abbott	1967	Multiple (for example, GABA potentiation, glutamate (NMDA) inhibition, sodium channel and T-type calcium channel blockade)	PGCS, absence seizures, migraine prophylaxis, bipolar disorder	Broad use for focal and generalized seizures, first-line AED, i.v. use, no skin hypersensitivity	Enzyme inhibitor; substantial teratogenicity; weight gain
Clonazepam	Roche	1968	GABA potentiation	Lennox–Gastaut syndrome, myoclonic seizures, panic disorders	Broad use for focal and generalized seizures, no clinical hepatotoxicity	Currently for adjunctive use only; acts as a sedative; leads to tolerance (loss of efficacy)
Clobazam	Hoechst Roussel/ Lundbeck/Sanofi	1975	GABA potentiation	Lennox–Gastaut syndrome, anxiety disorders	Broad use for focal and generalized seizures, no clinical hepatotoxicity	Currently for adjunctive use only; acts as a sedative; leads to tolerance (loss of efficacy)

Löscher, W et al. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov 2013;12: 757–776 (2013)

Characteristics of clinically approved AEDs

Second-generation drugs						
Progabide	Synthelabo	1985	GABA potentiation	PGCS, Lennox–Gastaut syndrome, myoclonic seizures, muscle hypertonia	Rarely used for focal seizures	Clinical hepatotoxicity, not in wide use anymore
Vigabatrin	Sanofi/Lundbeck	1989	GABA potentiation	Infantile spasms, complex partial seizures (currently for adjunctive use only)	No clinical hepatotoxicity	Not useful for absence or myoclonic seizures; vision loss; weight gain
Lamotrigine	GlaxoSmithKline	1990	Sodium channel blocker	PGCS, Lennox–Gastaut syndrome, bipolar disorder	Broad use for focal and generalized seizures, first-line AED	Enzyme inducer; skin hypersensitivity
Oxcarbazepine	Novartis	1990	Sodium channel blocker	Partial seizures	First-line AED	Enzyme inducer; skin hypersensitivity; not useful for absence or myoclonic seizures
Felbamate	Carter-Wallace/ MedPointe Pharmaceuticals	1993	Multiple (GABA potentiation, glutamate (NMDA) inhibition, sodium and calcium channel blockade)	PGCS, Lennox–Gastaut syndrome	Broad use for focal and generalized seizures	Currently for adjunctive use only; aplastic anaemia; clinical hepatotoxicity; skin hypersensitivity; clinical hepatotoxicity; not in wide use anymore
Gabapentin	Parke-Davis/ Pfizer	1993	Calcium channel blocker (α2δ subunit)	PGCS, postherpetic and diabetic neuralgia, restless legs syndrome	No clinical hepatotoxicity	Currently for adjunctive use only; weight gain; not useful for absence or myoclonic seizures

Löscher, W et al. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov 2013;12: 757–776 (2013)

Characteristics of clinically approved AEDs

AED	Companies	Year of approval	Presumed main mechanisms of action	Approved indications	Main utility	Main limitations
Second-generation drugs						
Topiramate	Janssen/Johnson & Johnson	1995	Multiple (GABA potentiation, glutamate (AMPA) inhibition, sodium and calcium channel blockade)	PGCS, Lennox–Gastaut syndrome, migraine prophylaxis	Broad use for focal and generalized seizures, first-line AED, no clinical hepatotoxicity	Somnolence, dizziness, cognitive impairment, speech problems, kidney stones, weight loss
Tiagabine	Novo Nordisk	1996	GABA potentiation	Partial seizures	No clinical hepatotoxicity	Currently for adjunctive use only; not useful for absence or myoclonic seizures
Levetiracetam	UCB Pharma	2000	SV2A modulation	PGCS, partial seizures, GTCS, JME	First-line AED, i.v. use, no clinical hepatotoxicity	Not useful for absence or myoclonic seizures
Zonisamide	Elan/Eisai	2000	Sodium channel blocker	Partial seizures	Broad use for focal and generalized seizures, no clinical hepatotoxicity	Currently for adjunctive use only; acts as a sedative
Stiripentol	Biocodex	2002	GABA potentiation, sodium channel blocker	Dravet syndrome	No clinical hepatotoxicity	Currently for adjunctive use only
Pregabalin	Pfizer	2004	Calcium channel blocker (α2δ subunit)	Partial seizures, neuropathic pain, generalized anxiety disorder, fibromyalgia	No clinical hepatotoxicity	Currently for adjunctive use only; not useful for absence or myoclonic seizures; weight gain

Löscher, W et al. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov 2013;12: 757–776 (2013)

Characteristics of clinically approved AEDs

Third-generation drugs						
Rufinamide	Eisai	2004	Sodium channel blockade	Lennox–Gastaut syndrome	No clinical hepatotoxicity	Currently for adjunctive use only
Lacosamide	UCB Pharma	2008	Enhanced slow inactivation of voltage-gated Na^+ channels	Partial seizures	No clinical hepatotoxicity	Currently for adjunctive use only
Eslicarbazepine acetate	Bial/Eisai	2009	Sodium channel blocker	Partial seizures	Adjunctive drug for partial seizures	Enzyme inducer; currently for adjunctive use only
Retigabine (ezogabine)	GlaxoSmithKline	2011	Potassium channel activator	Partial seizures	Adjunctive drug for partial seizures, only when other suitable AEDs have failed	Currently for adjunctive use only; blue colouration of lips and nails; retinal dysfunction; not useful for absence or myoclonic seizures; not in wide use anymore
Perampanel	Eisai	2012	Glutamate (AMPA) receptor antagonist	Partial seizures	Adjunctive drug for partial seizures	Currently for adjunctive use only; not useful for absence or myoclonic seizures
Brivaracetam	**UCB Pharma**	**2016**	**SV2A Modulator**	**Partial Seizures**	**Adjunctive drug for partial seizures, Monotherapy in US**	

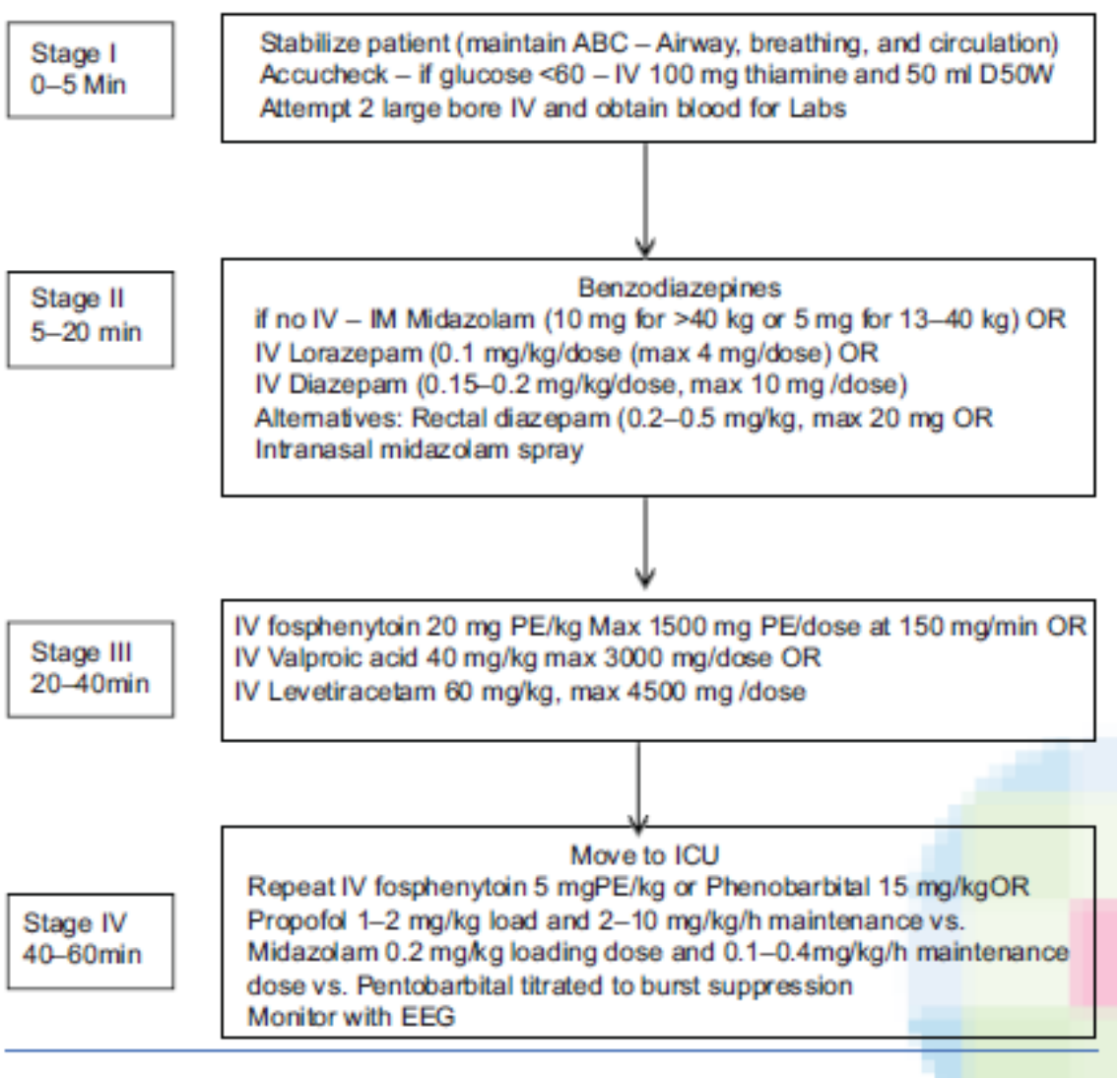
Löscher, W et al. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov 2013;12: 757–776 (2013)

Common side effects of AEDs

Antiepileptic drug	Common side effects	Enzyme induction
Phenobarbital	Sedation, depression, and paradoxical hyperactivity	Yes
Phenytoin	Nystagmus, ataxia, diplopia, gingival hyperplaysia, hirsutism, hepatoxicity,	Yes
Carbamazepine	Nausea, rash, hyponatremia, leukopenia, and rare, hepatotoxicity	Yes
Oxcarbazepine	Hyponatremia, fatigue, headaches, dizziness, ataxia, and rash	Yes
Lamotrigine	Stevens-Johnson syndrome, hypersensitivity, and rash	No
Topiramate	Impaired language fluency and cognitive dysfunction, paresthesias, metabolic acidosis, weight loss, renal calculi, and acute glaucoma	Yes (weak)
Zoniasamide	Rash, Stevens-Johnson syndrome, renal calculi, fatigue, and dizziness	No
Levetiracetam	Irritability and behavior problems	No
Lacosamide	Dizziness and nausea	No
Eslicarbazepine	Dizziness, nausea, fatigue, and ataxia	Yes (weak)
Rufinamide	Fatigue, vomiting, and loss of appetite	Yes
Clobazam	Sedation	No
Perampenel	Dizziness, irritability, severe mood and behavior changes, and homicidal ideations	No

Singh SP,Neurol India 2017;65:S6-11.

Treatment of convulsive status epilepticus in adults



Singh SP,Neurol India 2017;65:S6-11.

To choose an AED

- Not a "one size fits all" scenario
- Major considerations:
  - Type of seizure
  - Type of epileptic syndrome
  - Efficacy
  - Adverse effect profile
  - Age & gender
  - Ease of use (fast and easy dose titration)
  - Specific co-morbidities
  - Personal experience with the AED
  - Affordability

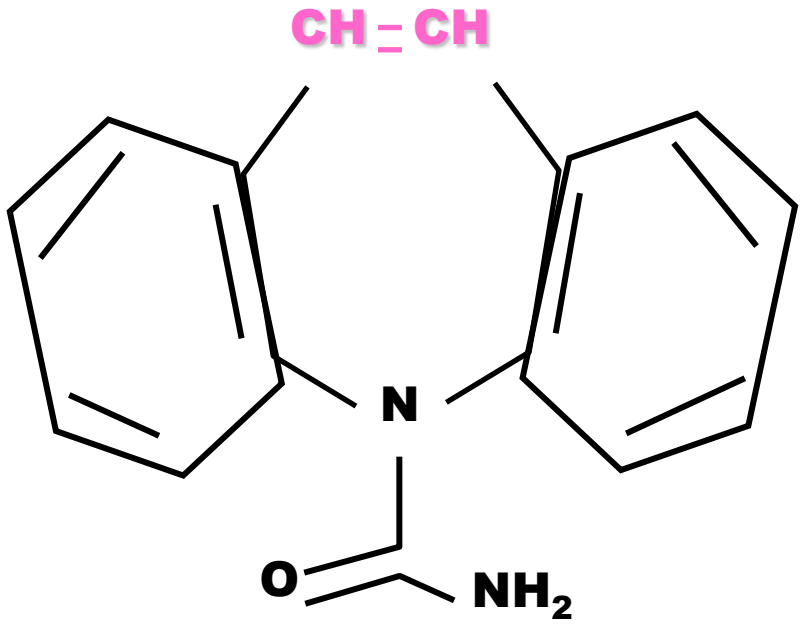
Carbox

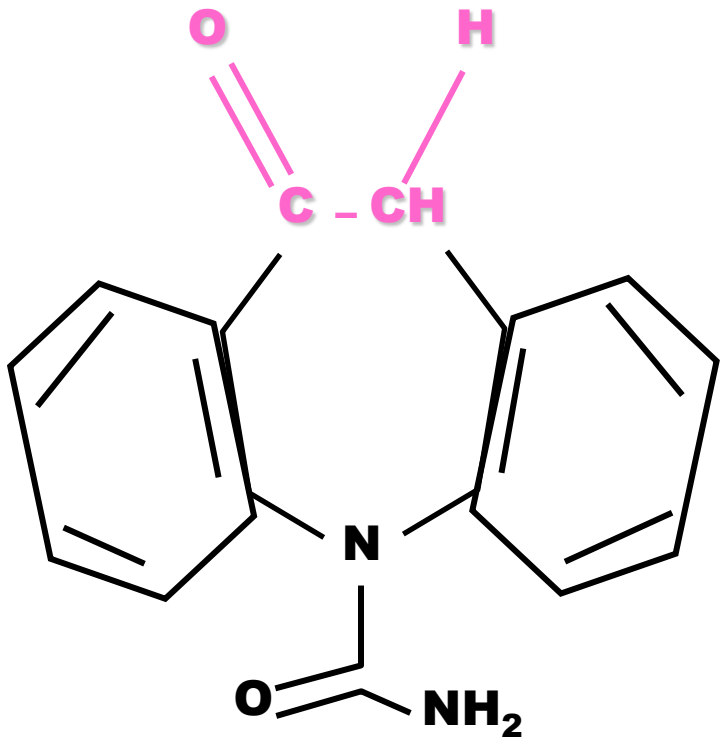
(Oxcarbazepine)

Introduction to Oxcarbazepine

- Keto analogue of carbamazepine
- Shares most of the pharmacological effects of Carbamazepine

Structures of carbamazepine and oxcarbazepine



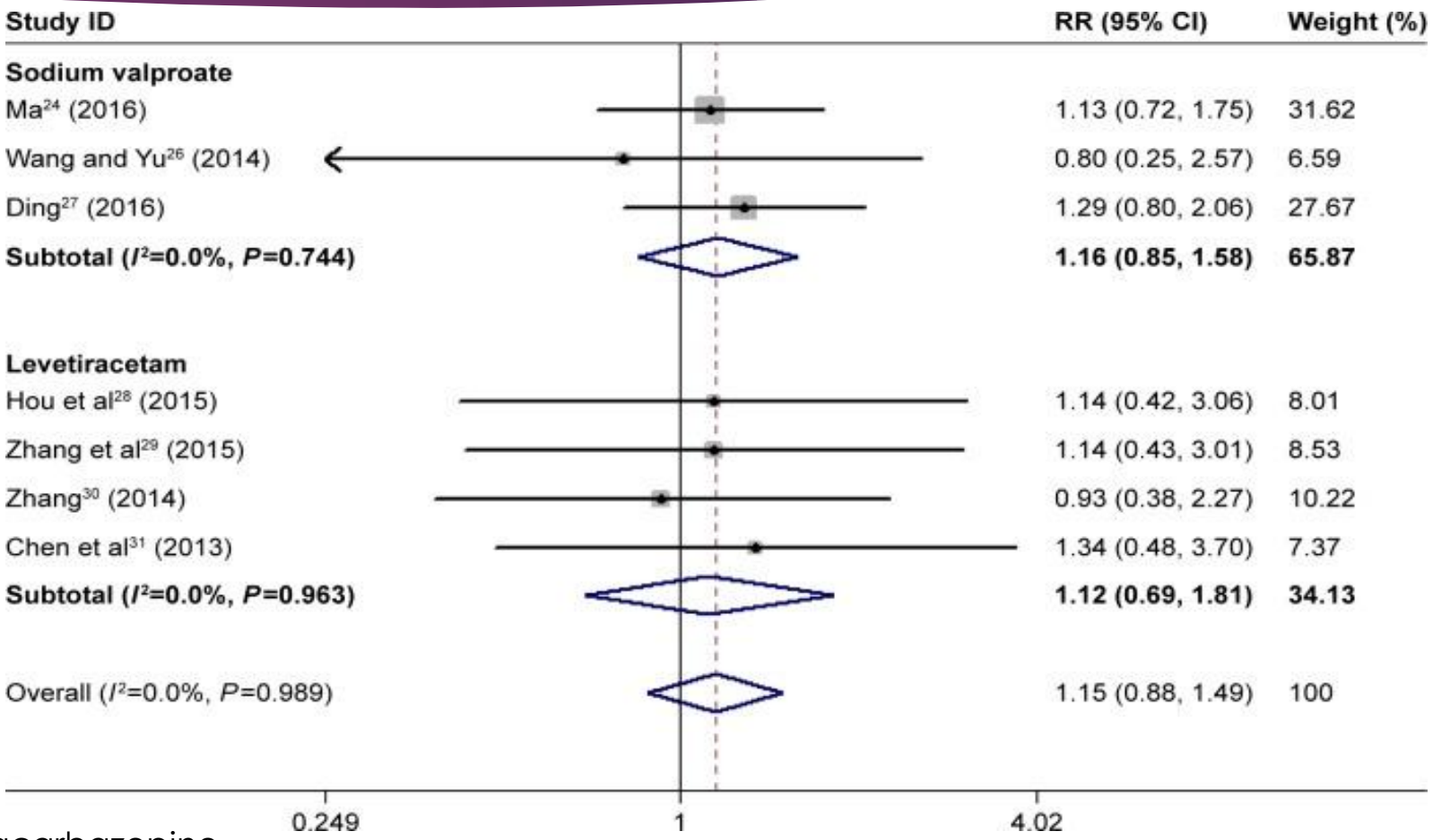


International brand prescribing information

The clinical profile of oxcarbazepine: first-line and first-choice

- First-line: first antiepileptic drug (AED) monotherapy ever
- First-choice: preferred drug for any change of epilepsy treatment, either as substitution monotherapy or adjunctive therapy
- Long-term experience in more than 250,000 patient-years

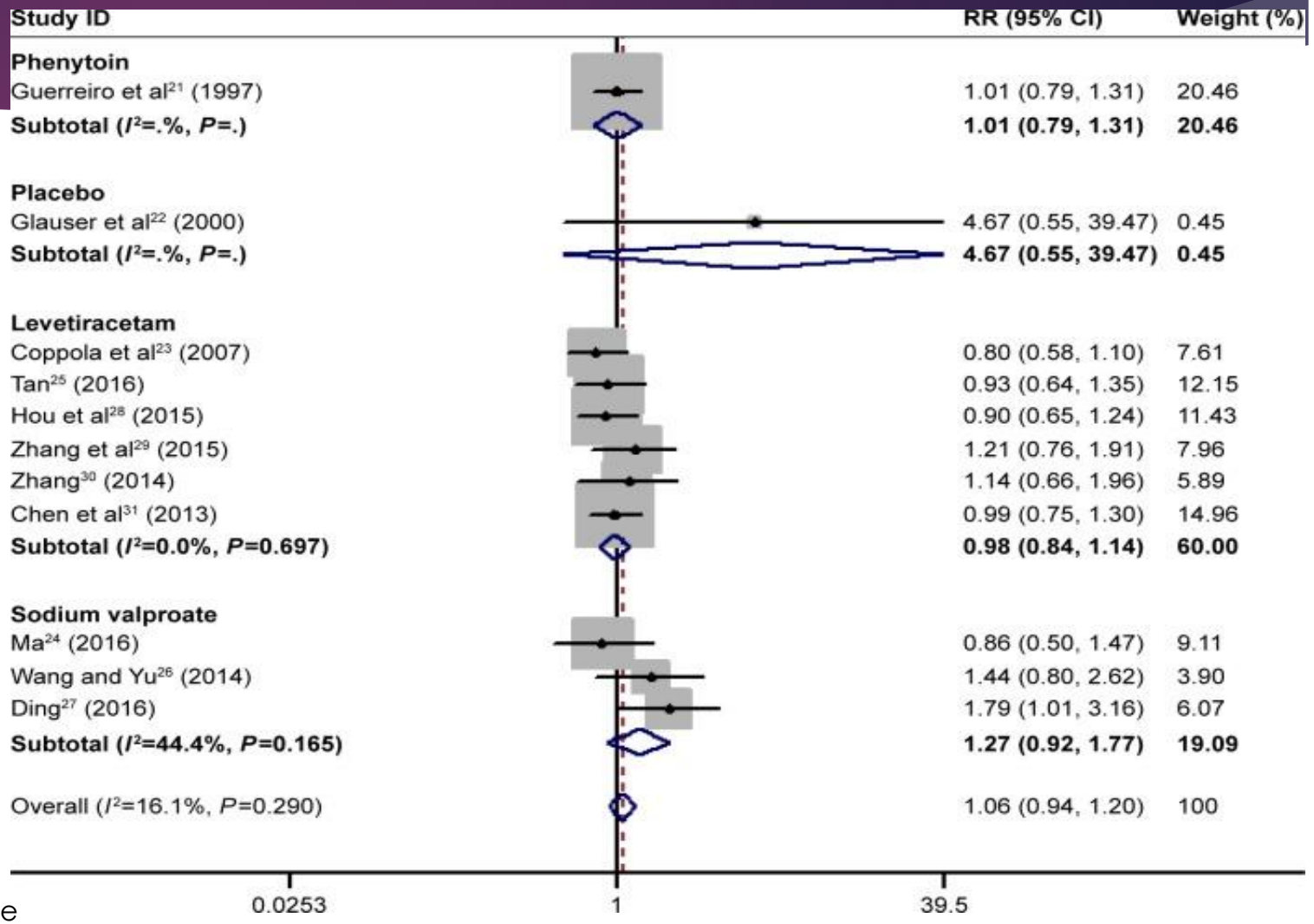
Seizure frequency : ≥75% reduction from baseline in



CI, confidence interval; RR, risk ratio; OXC, oxacarbazepine.

Geng H et al. Neuropsychiatr Dis Treat. 2017; 13: 685–695.

Effects of OXC on seizure-free rate



CI, confidence interval; RR, risk ratio; OXC, oxacarbazepine

Geng H et al. Neuropsychiatr Dis Treat. 2017; 13: 685–695.

Oxcarbazepine vs Sodium valproate/ Levetiracetam/Phenytoin

- OXC was associated with similar seizure-free rate as the other first line agents
- Percentage reduction from baseline in seizure frequency was comparable to Sodium valproate, Levetiracetam, Phenytoin

Geng H et al. Neuropsychiatr Dis Treat. 2017; 13: 685–695.

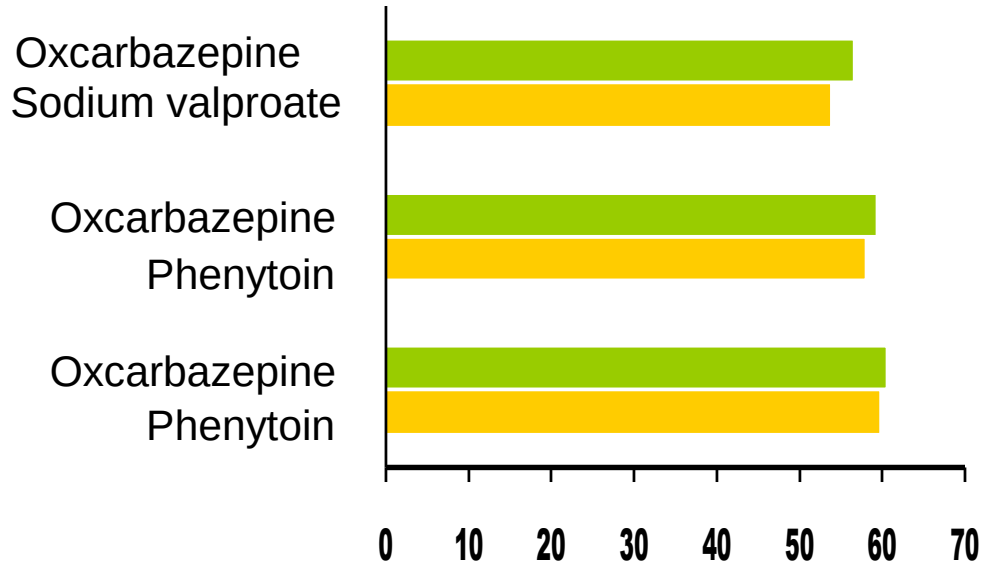
Oxcarbazepine is better tolerated than Carbamazepine

- Oxcarbazepine does not form an epoxide metabolite (associated with many of the adverse effects seen with carbamazepine)
- In a survey of 260 patients, 70% who experienced adverse effects with carbamazepine improved when switched to oxcarbazepine
- No loss of seizure control
- Fewer drug-drug interactions than carbamazepine because of its minimal interaction with the CYP450 system

Dam et al, Epilepsy Res 1989

Carbox

For newly diagnosed patients…



OCBZ demonstrated comparable efficacy to comparator AEDs like PHT, CBZ & VALP

Geng H et al. Neuropsychiatr Dis Treat. 2017; 13: 685–695.

For poorly controlled patients…

Poor tolerability beforehand:

- OCBZ improved tolerability in 48% in addition efficacy improved in 21%

Suboptimal efficacy beforehand:

- OCBZ improved efficacy in 56%

Offers better tolerability & efficacy than CBZ

Geng H et al. Neuropsychiatr Dis Treat. 2017; 13: 685–695.

Carbox-Mechanism of Action

- Blocks voltage-sensitive Na^+ channels
- Modulation of voltage-activated Ca^{2+} currents
- Increases K^+ conductance
- Thus reduces high-frequency repetitive firing of action potentials in the epileptic focus

Carbox-Composition

- Each film coated sustained release Carbox OD 150 Tablet Contains Oxcarbazepine Extended release 150mg.
- Each film coated sustained release Carbox OD 300 Tablet Contains Oxcarbazepine Extended release 300mg.
- Each film coated Carbox 150 Tablet Contains Oxcarbazepine150mg.
- Each film coated Carbox 300 Tablet Contains Oxcarbazepine300mg.
- Each film coated Carbox 600 Tablet Contains Oxcarbazepine600mg.

Carbox OD- Indications

- **Adults :** Monotherapy or adjunctive therapy in the treatment of partial seizures
- **Pediatrics:**

- Monotherapy in the treatment of partial seizures in children 4–16 years

- Adjunctive therapy in the treatment of partial seizures in children 2–16 years

Carbox-Additional Benefits

Carbox is efficacious, safe and well tolerated as adjunctive therapy in children with inadequately controlled partial seizures

Carbox- Target dose by body wt -children

Weight (kg)	Oxcarbazepine (mg/day)*
20.0-29.0	900
29.1-39.0	1200
39.1->60.0	1800

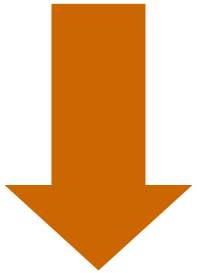
***Actual median daily dose 31.4 mg/kg/day (6.4-51.4 mg/kg/day)**

International brand prescribing information

Oxcarbazepine- Dosage

Start 300 mg/day

(given 150mg bid)



Increase by

300 mg/day weekly
(based on clinical response)

Target dose of 900-1200 mg/day

International brand prescribing information

CARBOX - Dosage

In poorly controlled patients

Start--- • 300 mg/day (given 150 mg bid)

Add--- • 300 mg/day at week 2 and 300 mg weekly increments thereafter

Switching to OCBZ therapy

Reduce original AED over 3-6 weeks

Step 1	Step 2	Step 3	Step 4
75% of original dose	50% of original dose	25% of original dose	Discontinue

International brand prescribing information

Carbox- Side effects

- Drowsiness
- Dizziness
- Headache
- Diplopia
- Ataxia
- Nystagmus
- Dysarthria
- Nausea
- Vomiting
- Diarrhoea

International brand prescribing information

Carbox –Contraindications

- Hypersensitivity to oxcarbazepine
- Pregnancy & lactation

Carbox-drug interaction

Plasma Concentrations of the active monohydroxy of oxcarbazepine may be reduced by strong inducers of cytochrome P450 isoenzymes, such as Carbazepine, pheytoin, phenobarbitol.

Carbox - Features

- Proven efficacy in the management of partial seizures including seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures
- Improved tolerability as compared CBZ due to the absence of epoxide metabolite
- Predictable pharmacokinetics and dose/concentration related effects
- Low risk of drug-drug interactions

Carbox- Features (contd.)

- Rated as Good and Excellent by more physicians and patients than PHT, VPA and CBZ
- Tolerability far superior to PHT and CBZ
- Convenient bid dosing
- Proven safety for more than 250,000 patient years

Carbox-key strengths

- Easy switch from other AEDs to oxcarbazepine
- Very good efficacy in refractory cases
- Few AED interactions - few side effects
- Wide therapeutic range - Proven long-term efficacy
- Low potential for allergic reactions

Oxcarbazepine vs Carbamazepine

Carbamazepine	Oxcarbazepine(CARBOX)
• Very effective in treatment of epilepsy • Limited potential for chronic toxicity	• Very effective • Limited toxicity • Rapid dose escalation • Limited enzyme induction • May be tolerated by Cbz-hypersensitive patients


THANK YOU
FOR LISTENING!