THERAPIES FOR TREATING EPILEPSY OTHER THAN DRUGS

(Advanced Neuropharmacology)

INTRODUCTION

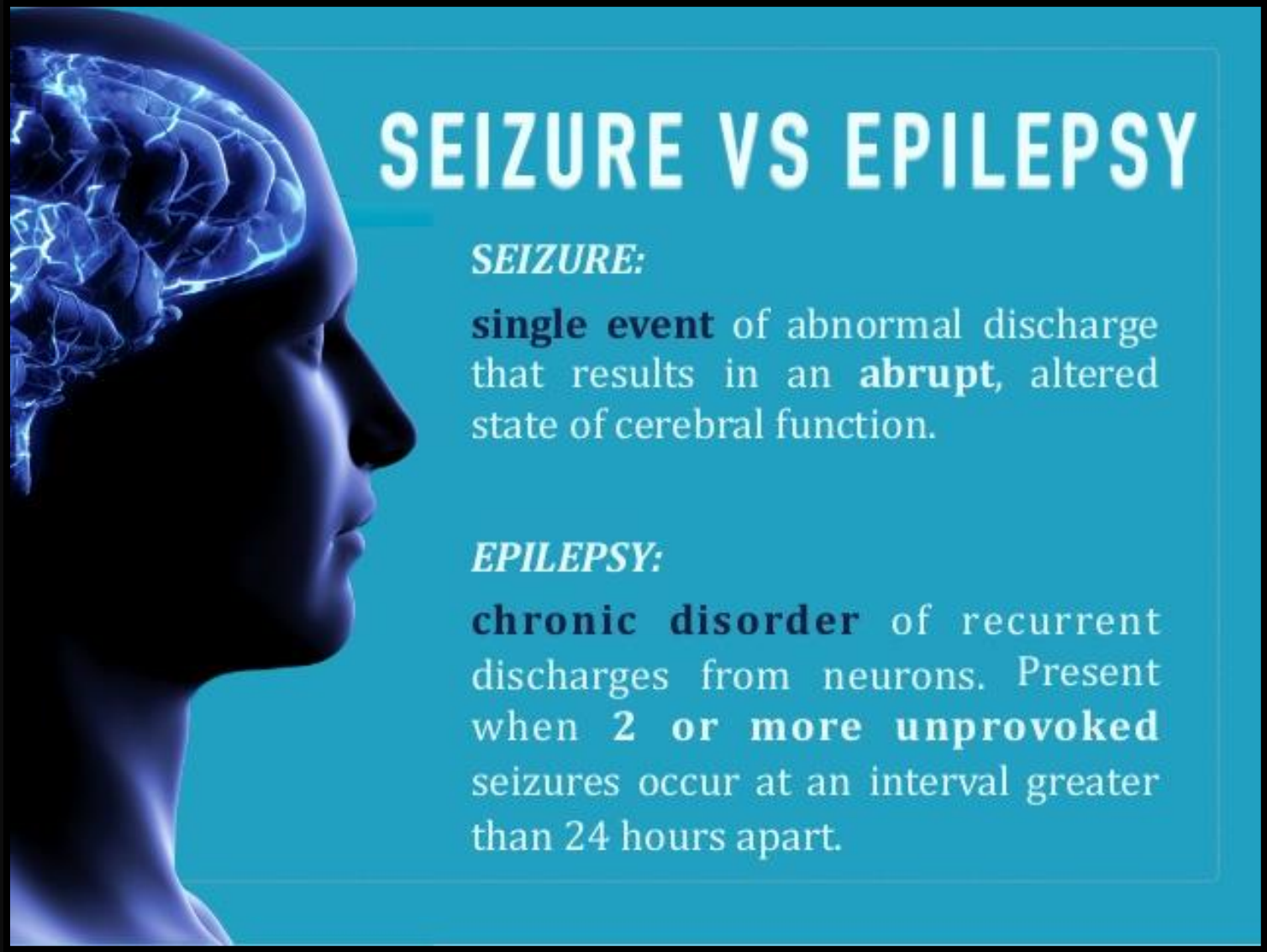
*The term "**Epilepsy**" describes a syndrome of neurological disorders, characterized by unpredictable, recurrent and periodic seizures.*

(Brunton, Randa, & C., 2018) (H P Rang, 2012)

An *epileptic seizure* occurs due to *abnormal* or *excessive* neuronal activity in the brain.

(Brunton, Randa, & C., 2018)

INTRODUCTION



INTRODUCTION

The International League Against Epilepsy (ILAE) defines epilepsy as the occurrence of;

1. Two or more seizures occurring more than 24 hours apart.

2. A seizure, accompanied with > 60% possibility of another seizure in the next 10 years.

3. Diagnosis of an epilepsy syndrome. (based on clinical features and investigations)

(Harris & Angus-Leppan, 2020)

PREVALENCE

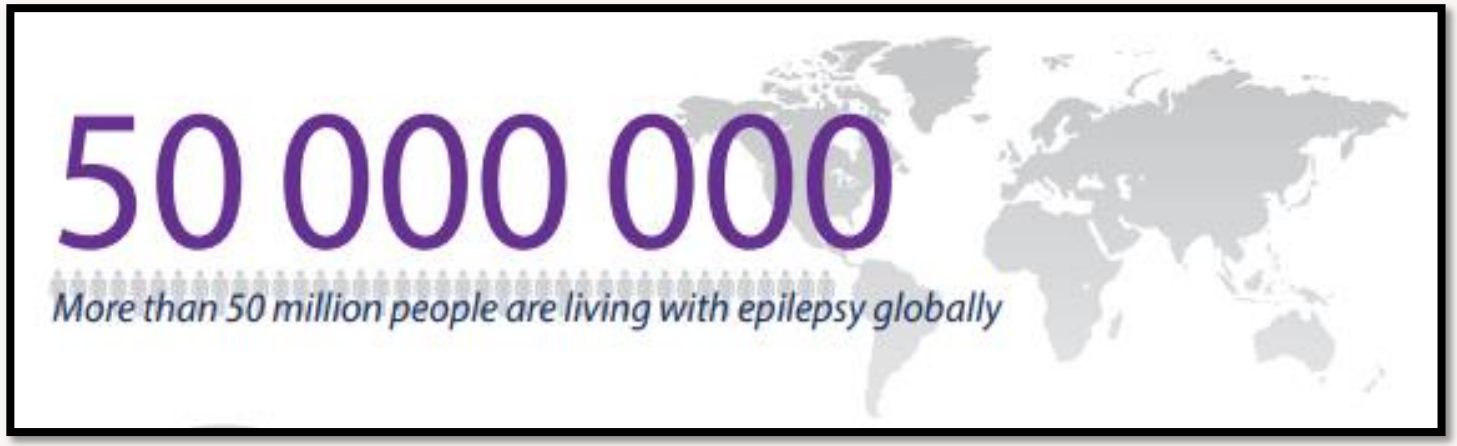
Infographic by the World Health Organization, in 2015,

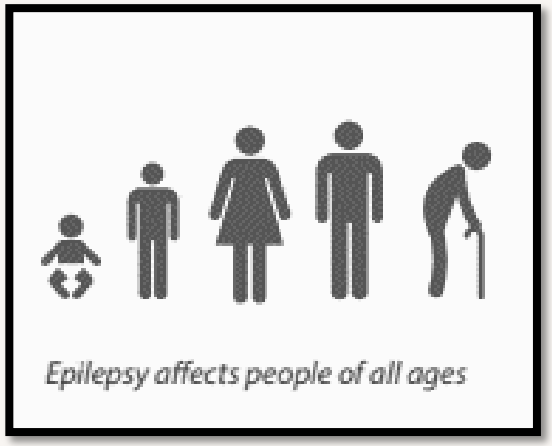
found epilepsy to have effected more than 50 million people,

throughout the world, regardless of age and gender.

85% belong to the middle and low-income countries. (World Health Organization, 2015)

In Pakistan the prevalence has been roughly estimated to be 9.99 per thousand. (Siddiqui, et al., 2015)





(World Health Organization, 2015)

ETIOLOGY

Factors that may be responsible for epilepsy:

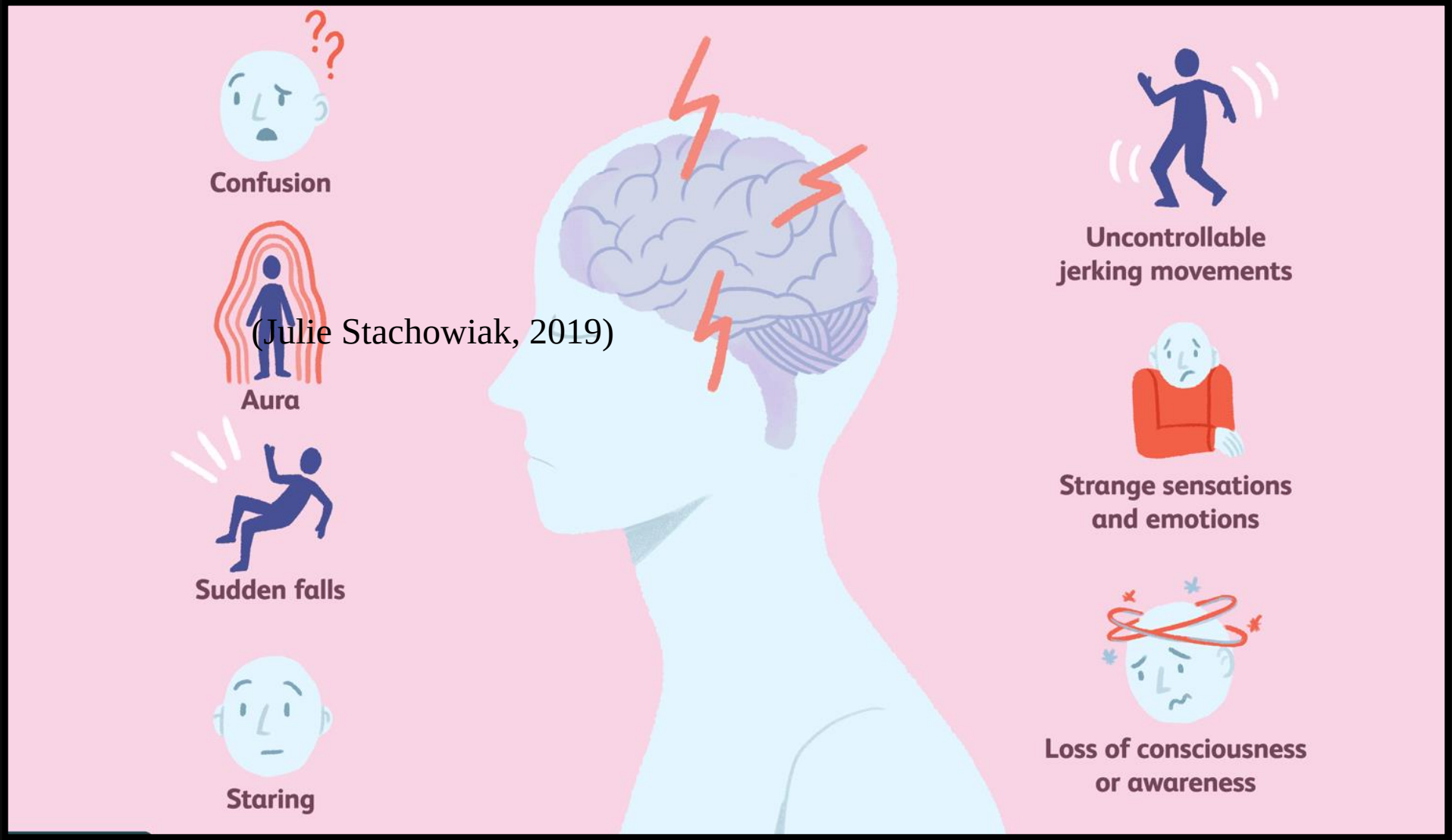
- Structural abnormalities (genetic or acquired)
- Genetic mutations
- Infections
- Neurodegenerative disease / Stroke / Tumors
- Provoking factors (fever /toxins /drugs /alcohol / auditory or visual triggers)
- Unknown causes

in most cases the cause cannot be identified. (Whalen, Finkel, & Panavelil, 2015)

MECHANISM OF EPILEPSY

(UCBEAction, 2015)

CLINICAL SIGNS AND SYMPTOMS OF A SEIZURE



(Julie Stachowiak, 2019)

(Julie Stachowiak, 2019)

PATHOPHYSIOLOGY OF EPILEPSY

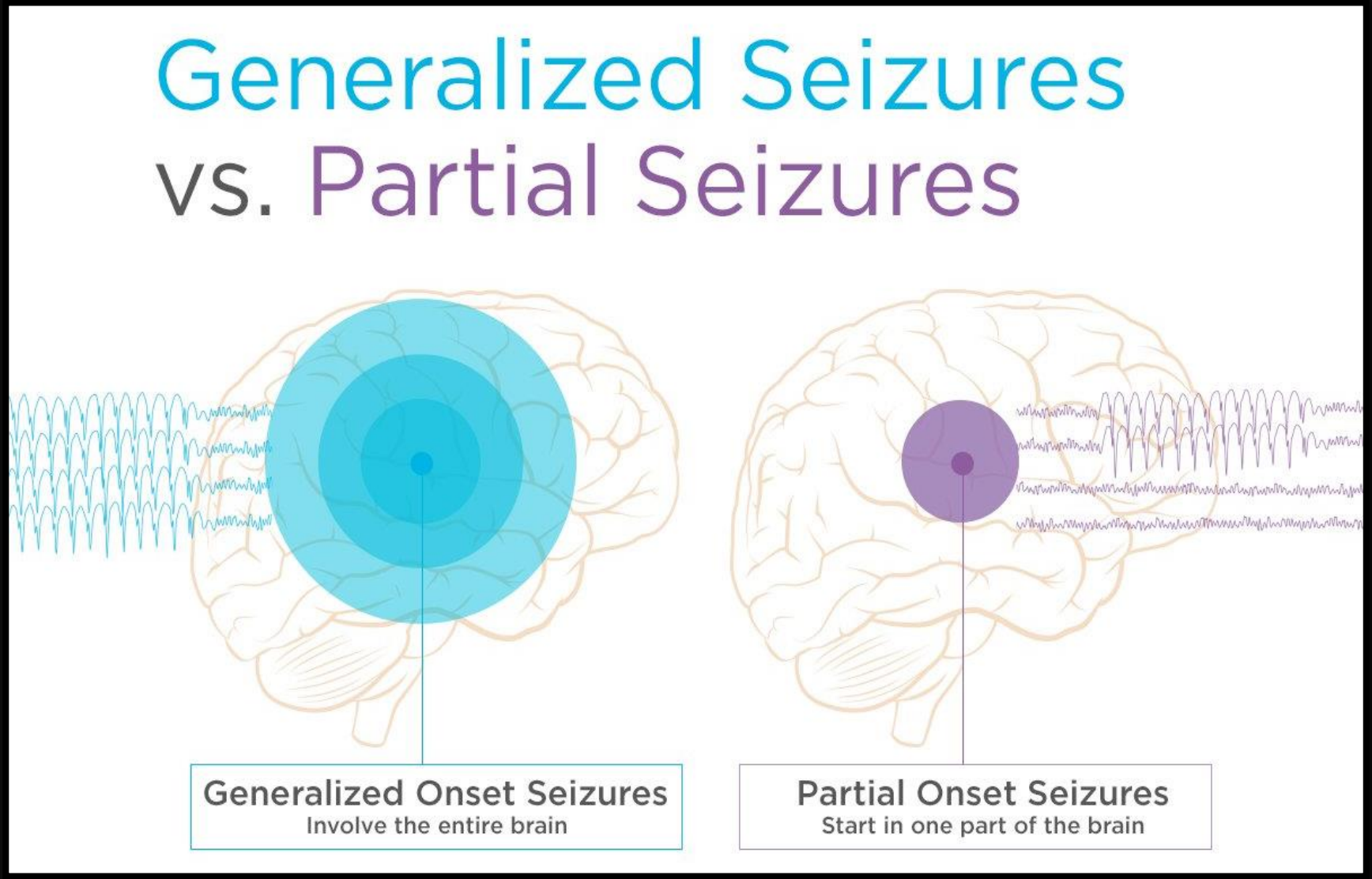
Epileptic seizures are produced by abnormal discharges of neurons that may be caused by any pathological process which affects the cortical layer of the brain. (Brunton, Randa, & C., 2018)

Exact pathophysiology of epilepsy remains unknown, there exist many hypotheses for the underlying mechanisms, including;

- Neurodegeneration
- Disturbances in the blood-brain barrier
- Hypoxia
- Oxidative stress.

(Kobylarek, et al., 2019)

TYPES OF SEIZURES



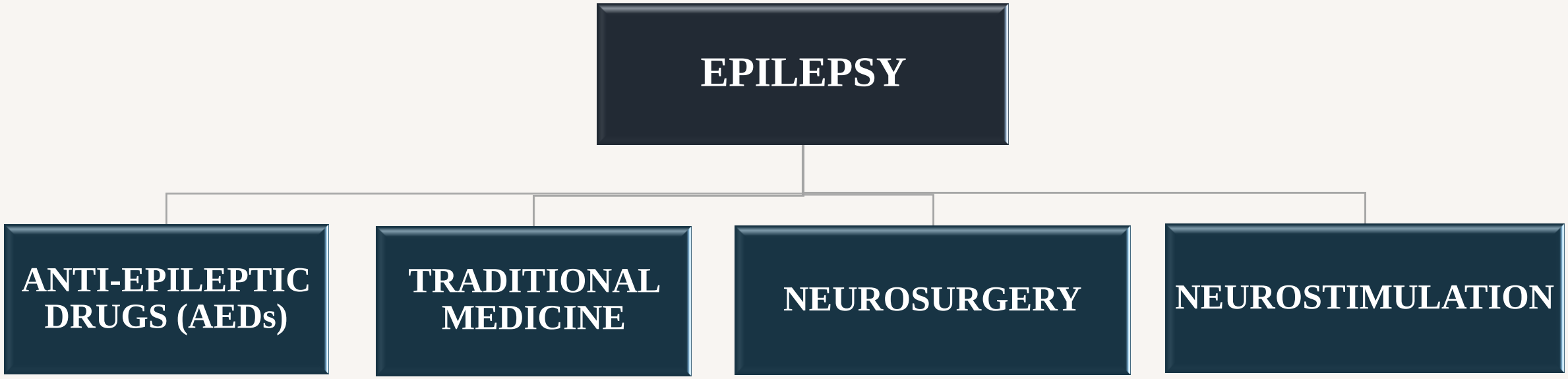
(NeuroPace, 2017)

TYPES OF SEIZURES

Classification of epileptic seizures according to The International League Against Epilepsy (ILAE)

- Focal / Partial Onset Seizures
  - Simple partial seizures
  - Complex partial seizures
- Generalized Onset Seizures
  - Absence seizures
  - Tonic-clonic seizures
  - Myoclonic seizures
- Unknown Onset Seizures

TREATMENT & MANAGEMENT



1. ANTI-EPILEPTIC DRUGS (AEDs)

- The most common treatment
- Effective in approximately **70%** of the cases
- Prolonged use of the drugs, possess many side effects which limit their use. (H P Rang, 2012)

The drug therapy for epilepsy is usually long term, lasting for a minimum of three years and possibly lasting for a lifetime, depending upon the requirements of the patient.

(Brunton, Randa, & C., 2018)

1. ANTI-EPILEPTIC DRUGS (AEDs)

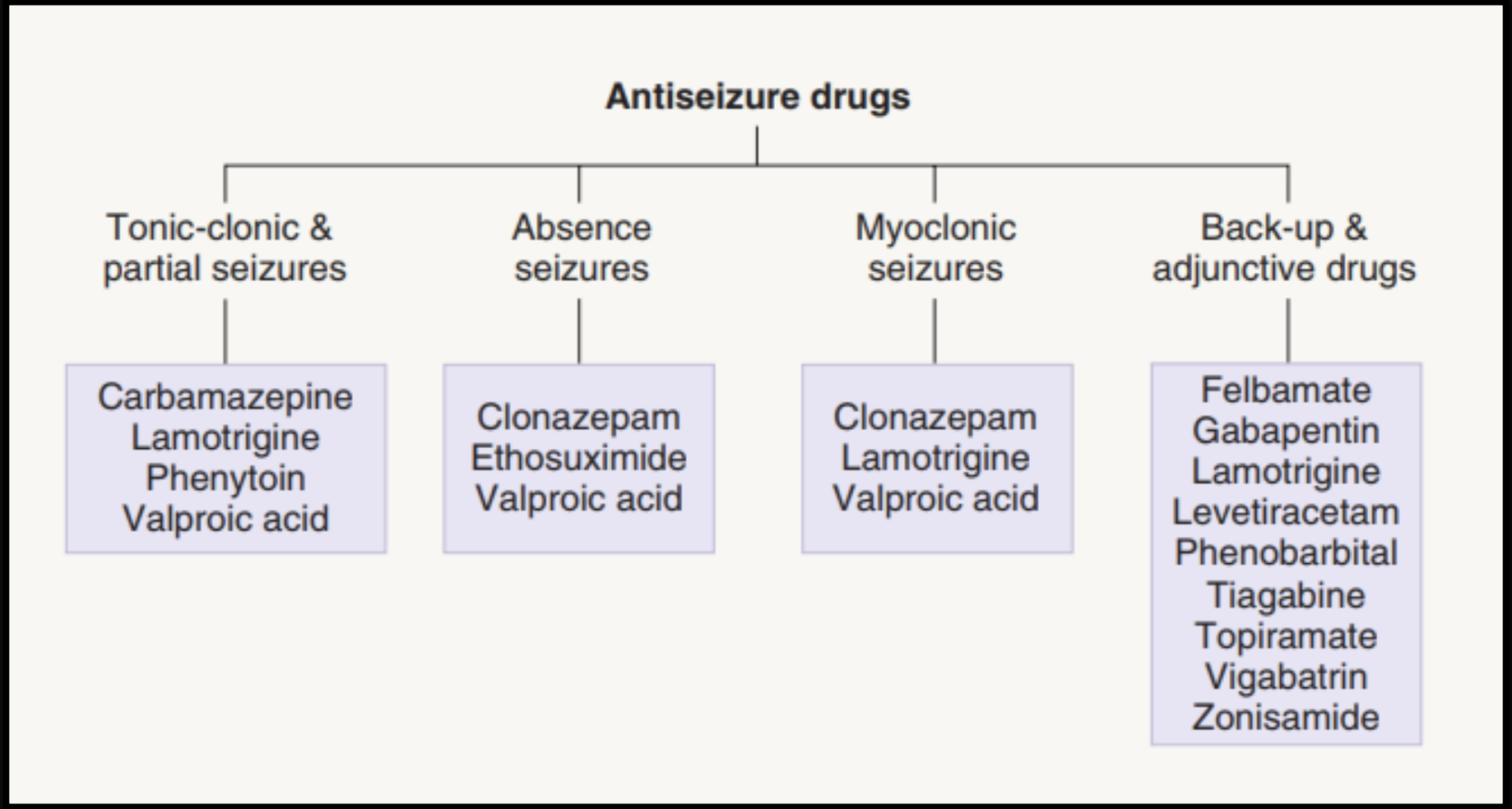


Fig: Classification of Antiseizure drugs (Trevor, Katzung, & Kruidering-Hall, 2015)

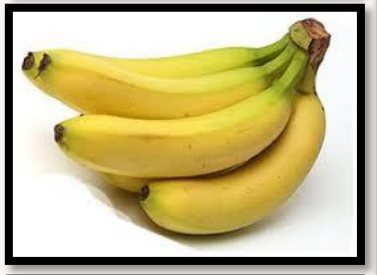
2. TRADITIONAL / NATURAL MEDICINES

In the recent decades, people have been searching for alternatives, for the existing chemicals and seeking those from the herbal origin formulations. Herbs with antioxidative and anti-inflammatory activities evidently play an essential role in protecting neurons as per the recent studies.

Some plants that can been used and investigated for their use in Epilepsy are mentioned. (Merish & Essakkypandian, 2020)

2. TRADITIONAL / NATURAL MEDICINES

BOTANICAL NAME	OTHER NAME	FAMILY
Abies webbiana	Talisparta	Pinaceae
Musa sapientum	Banana	Musaceae
Sphaeranthus indicus	East Indian Globe Thistle	Asteraceae
Terminalia chebula	Black/ chebulic myrobalan	Combretaceae



2. TRADITIONAL / NATURAL MEDICINES

BOTANICAL NAME	OTHER NAME	FAMILY
Ginkgo biloba L.	Ginkgo/ Maidenhair tree	Ginkgoaceae
Chrysanthemum trifurcatum	Chrysanthemum	Asteraceae
Ocimum sanctum	Tulasi/ Tulsi / Holy Basil	Lamiaceae
Glycyrrhiza glabra	Liquorice	Febaceae




NEUROSURGERY

In case of seizures that occur despite drug treatment, surgical treatments are considered.

(Harris & Angus-Leppan, 2020)

Epileptic surgery is to be considered in

- Epilepsies of structural origin
- Children and young people who have failed two antiepileptic drugs.

40% to 80% seizure freedom, depending on age and type of surgery. (Varadkar, 2020)

The optimal age for surgery has been previously considered to be between 12-30 years, surgery in adults between 45-60 has been cautioned. (Ichikawa, Fujimoto, Okanishi, Sato, & Enoki, 2020)

NEUROSURGERY

- Resection

  One of the most common neurosurgeries for treatment is the temporal lobectomy,

  80% successful in controlling the seizures.

- Disconnection

  A procedure used if the eloquent cortex of the brain is involved,

  or for the separation of the neuronal activity of two cerebral hemispheres.

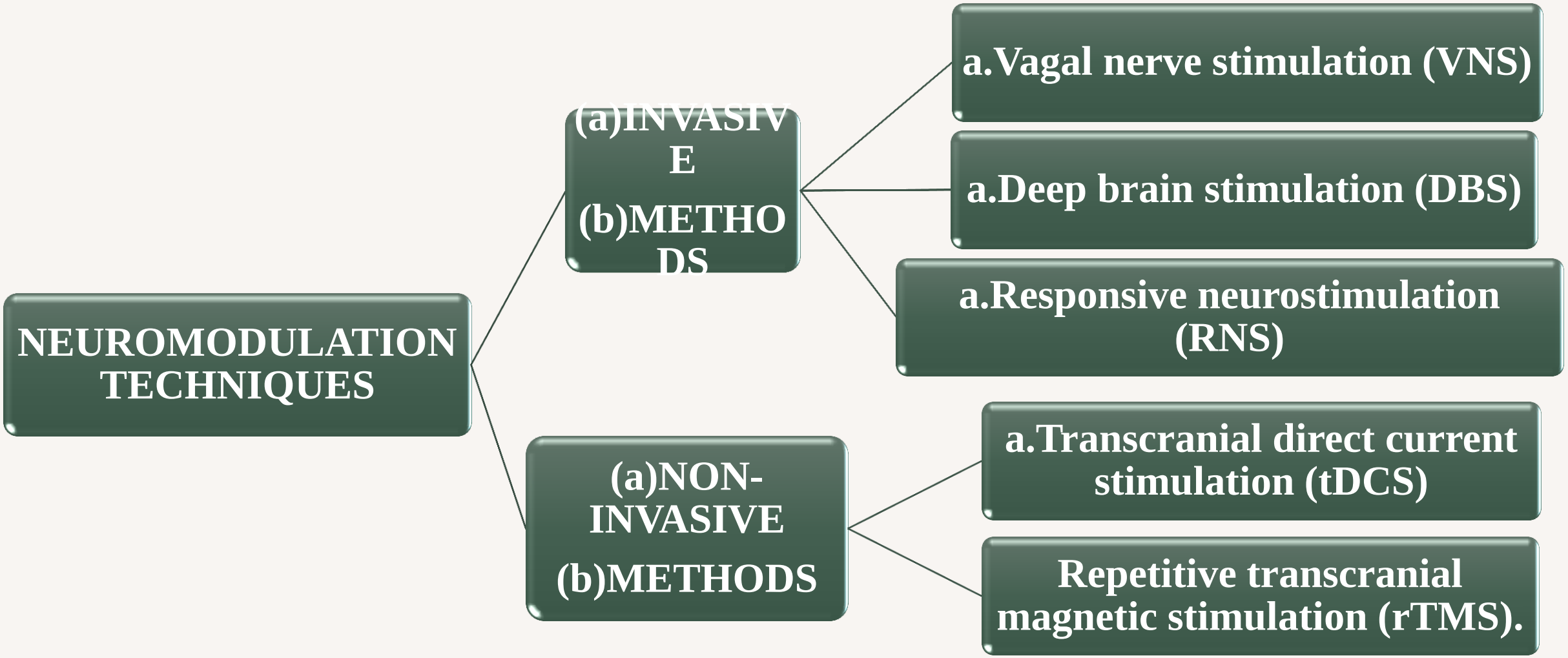
- Neurostimulation

  Stimulation is a reversible and adjustable procedure, that is considered for patients unsuitable for resection surgery. (Harris & Angus-Leppan, 2020)

NEUROSURGERY

(Atlanta, 2014)

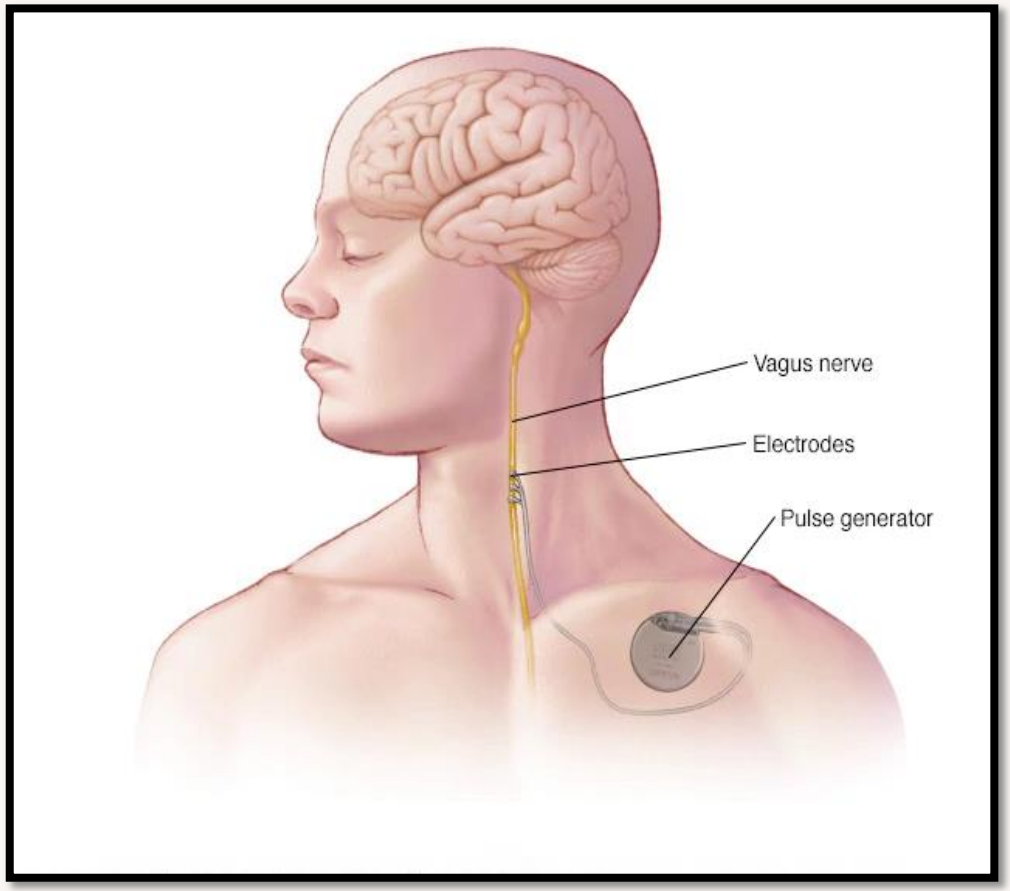
NEUROMODULATION



VAGUS NERVE STIMULATION (VNS)

VNS requires subcutaneous implantation of

- The generator in the left sub-clavicular region
- with an electrode around the left vagus nerve.



The implantation procedure usually takes 30 min - 2 h, typically performed under general anesthesia.

Nearly **>50%** seizure reduction with VNS, in various patients having different epilepsy syndromes. (Sondhi & Sharma, 2020)

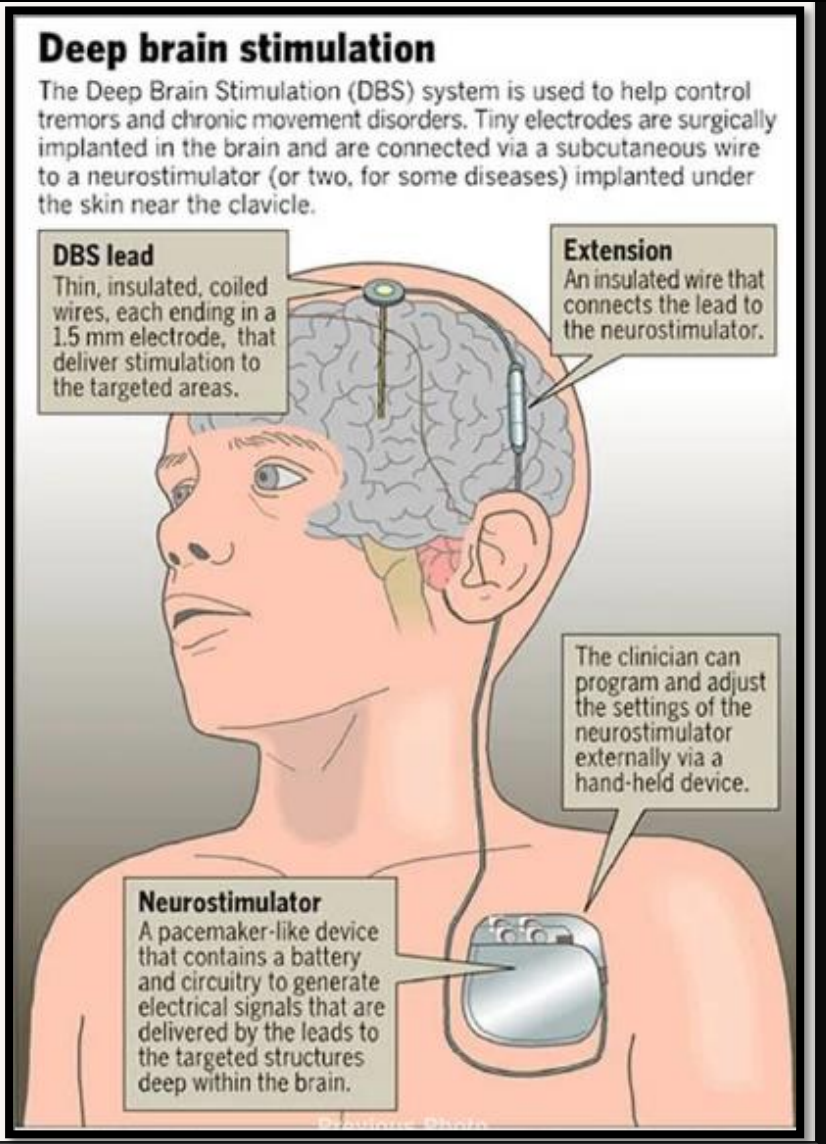
VAGUS NERVE STIMULATION (VNS)

(Padhya, 2018)

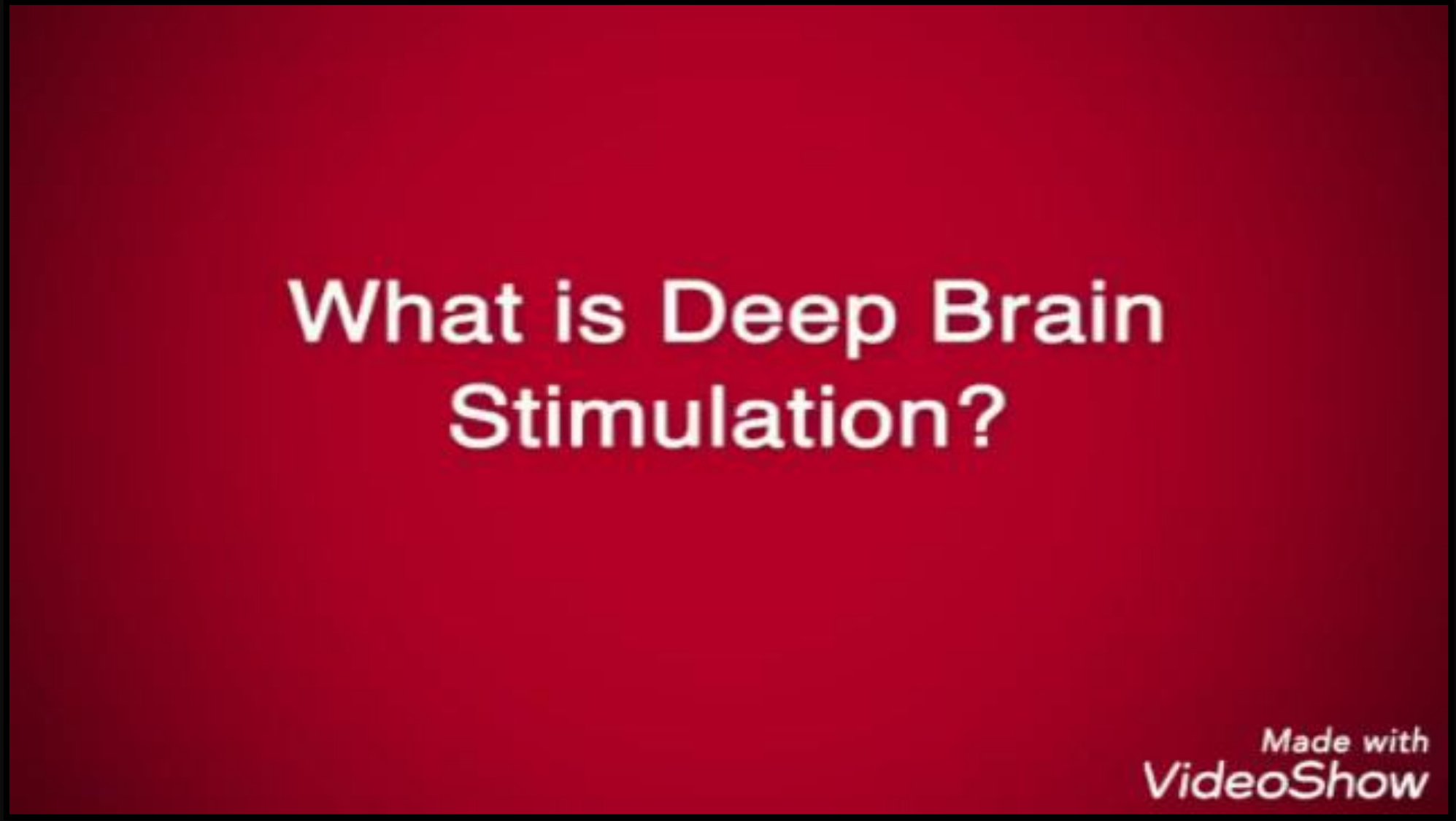
DEEP BRAIN STIMULATION (DBS)

DBS involves subcutaneous implantation of the generator in the left sub-clavicular region with bilateral depth electrodes in the anterior nucleus of the thalamus.

The anterior nucleus of the thalamus is a core component of the Papez circuit. It serves as a relay station for outflow from the amygdala and hippocampus, and is a suitable target for seizure reduction/ control. Seizures were reduced by a median 56% in a 2 year study. (Sondhi & Sharma, 2020)



DEEP BRAIN STIMULATION (DBS)



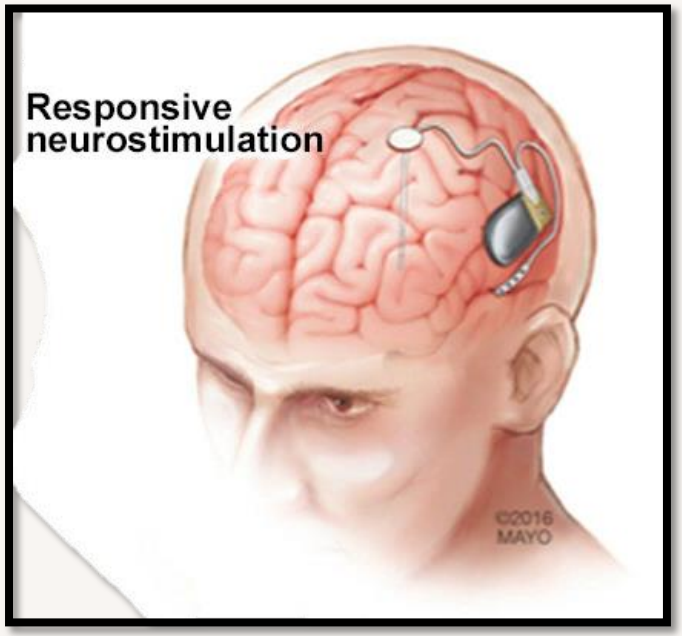
RESPONSIVE NEUROSTIMULATION (RNS)

Responsive cortical stimulation

using the RNS system has been approved by the FDA

for use as adjunctive therapy in reducing

the frequency of seizures in individuals ≥18 years.



(Sondhi & Sharma, 2020)

RNS involves placing of one or two electrodes, directly over the epileptic focus.

The system aims to detect electrocortical signatures that predict an imminent seizure,

and programmatically delivering cortical stimulation to aborts the predicted seizure.

(Harris & Angus-Leppan, 2020)

RESPONSIVE NEUROSTIMULATION (RNS)

In a study, an estimated 70% reduction in seizures was reported. (Alqahtani, et al., 2020)

Concurrent electrical stimulation is automatically delivered, ***only*** when abnormal electrographic activity is detected, hence arresting evolving seizure propagation.

Delivering stimulation only when necessary,

↓ amount of current dispensed ↑ battery life, and ↓ unwanted side effects.

The lack of stimulation during normal brain activity prevents disturbance of normal function in eloquent areas, and stimulation is delivered below a perceptible threshold to the patient.

(Kwon, Jetté, & Ghatan, 2019)

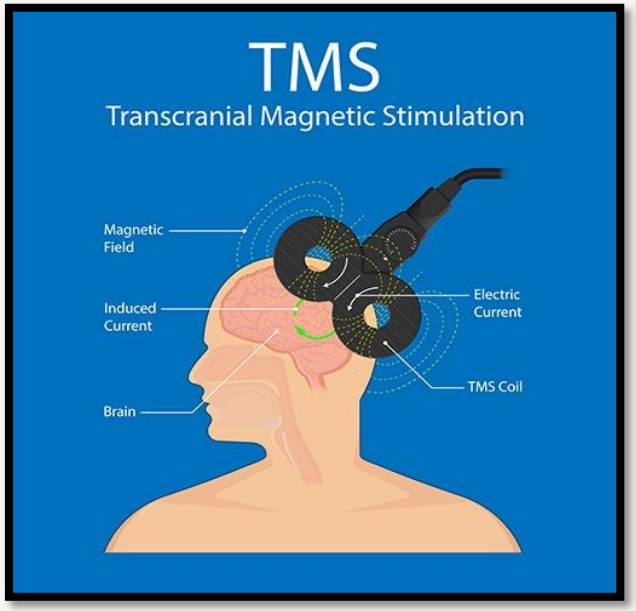
RESPONSIVE NEUROSTIMULATION (RNS)

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

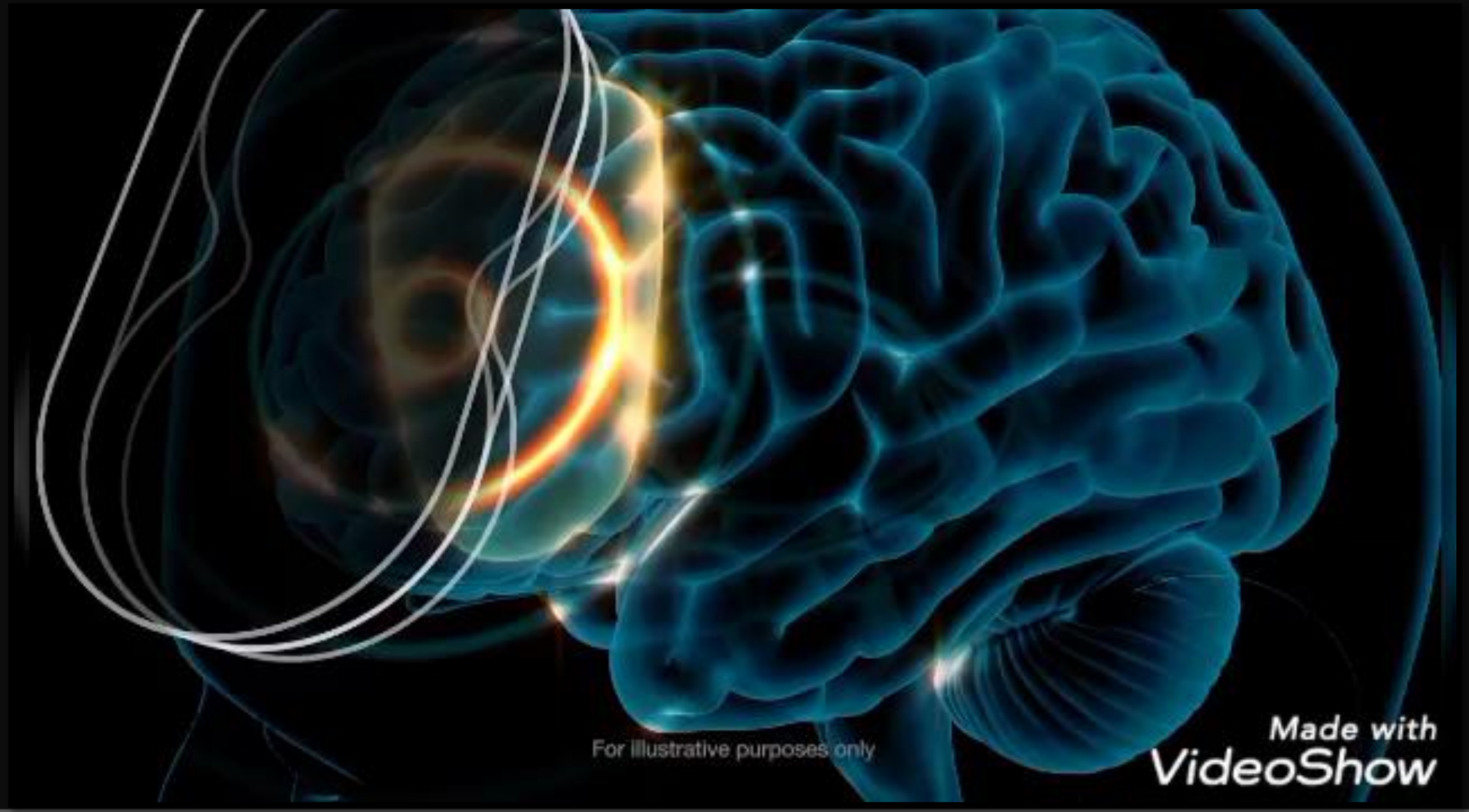
Transcranial magnet stimulation (TMS) is a non-invasive approach, which uses an external electromagnetic coil to induce an electrical current in the underlying brain tissue.

There are various mechanisms through which TMS suppress the epileptic discharges or modify the neuronal activity i.e.,

- Modifying the excitability of the neurons
- Modifying the function of the ion-channels
- Altering the synaptic transmission
- Interrupting the communication between two neurons using an electrical field that is generated locally. (Alqahtani, et al., 2020)

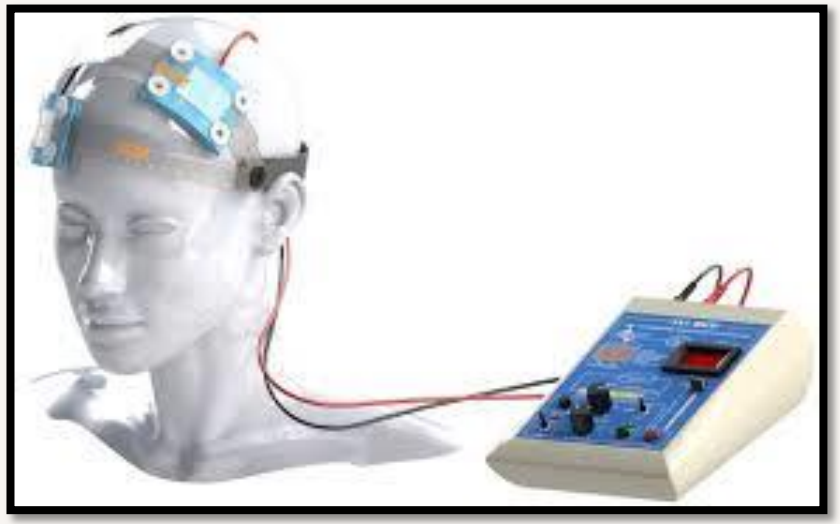


TRANSCRANIAL MAGNETIC STIMULATION (TMS)



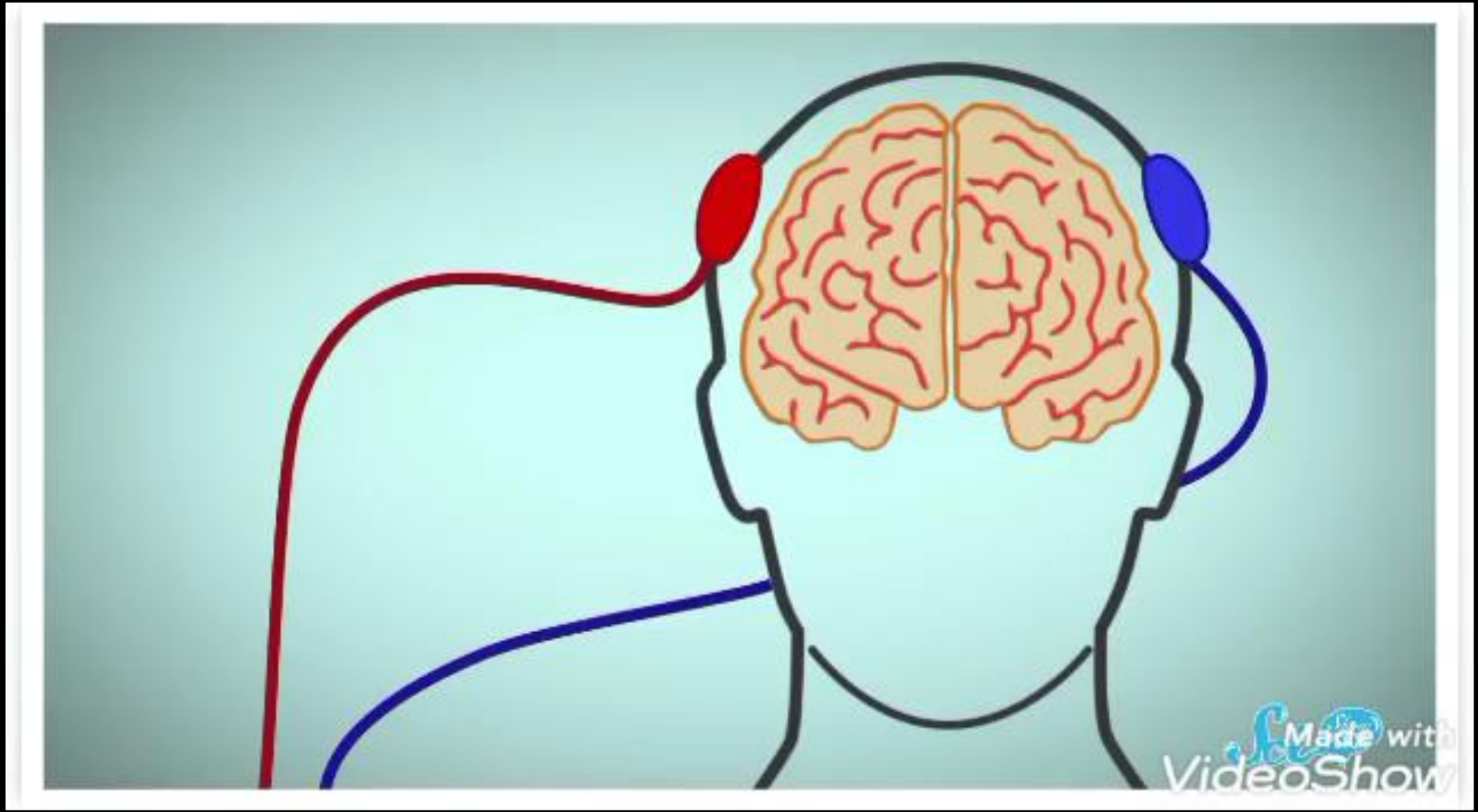
Transcranial DIRECT CURRENT STIMULATION (tDCS)

tDCS is an entirely non-invasive technique, applied through two electrodes (anode and cathode) over the skull, scalp via metal or conductive rubber electrodes using an electrolyte-based contact medium (Gschwind & Seeck, 2016) to induce widespread changes of cortical excitability through a weak constant electric current.



Cortical excitability ↑following anodal stimulation & ↓ following cathodal stimulation. Based on this principle, hyperpolarization using cathodal tDCS has been proposed as therapy to suppress epileptic neuronal discharges and clinical seizures in basic and clinical studies. (San-juan, et al., 2015)

Transcranial DIRECT CURRENT STIMULATION (tDCS)



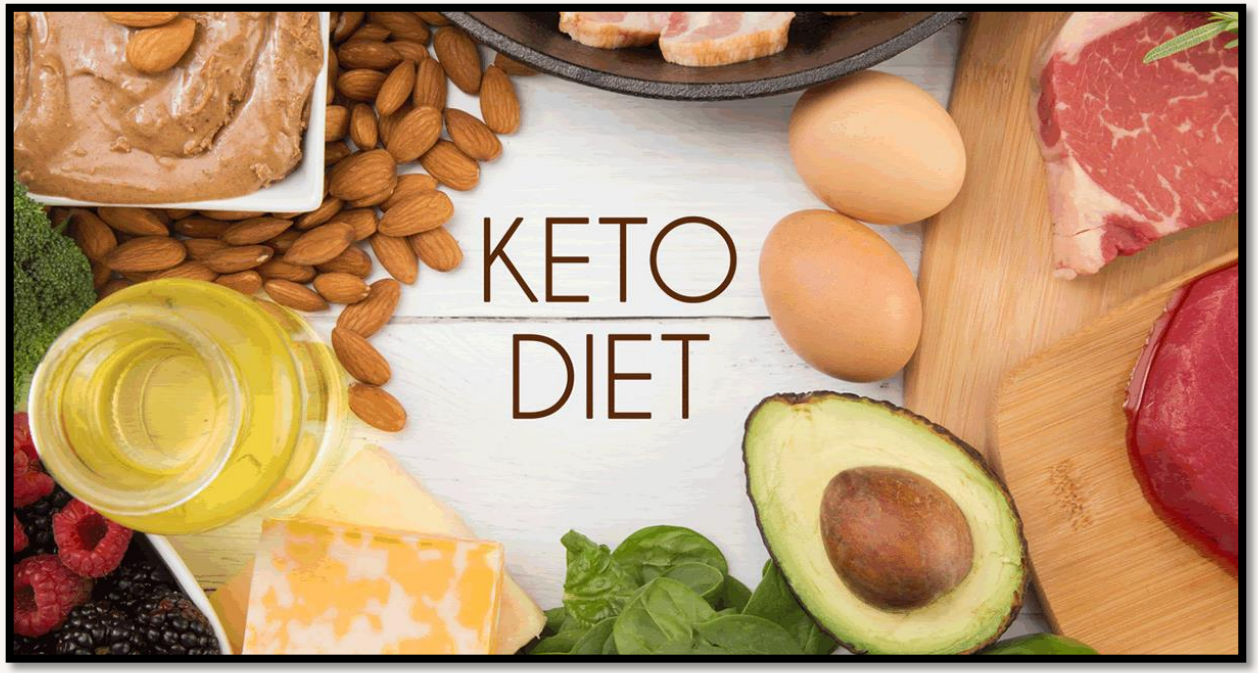
DIETARY INTERVENTIONS

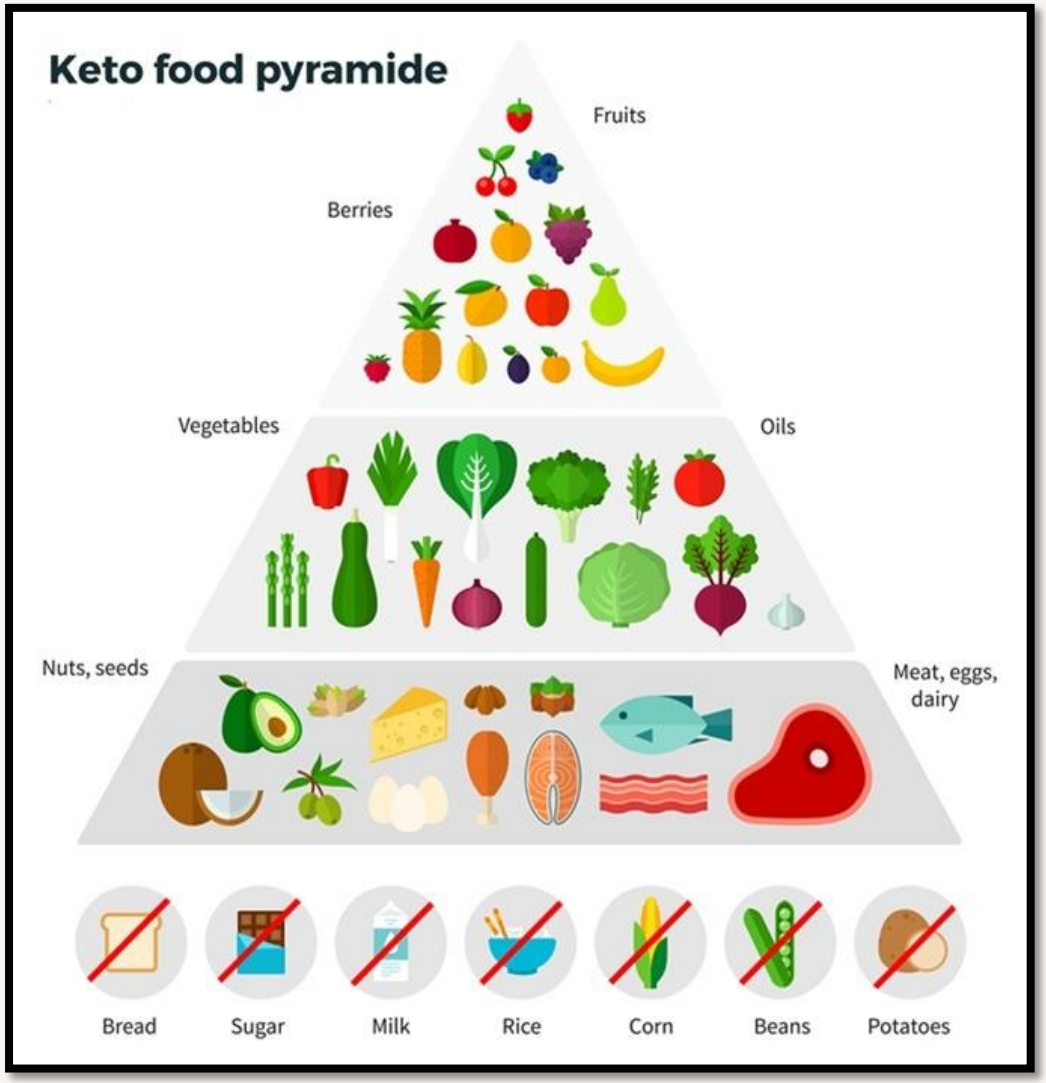
Diets have been used to control seizures through centuries,

the most common diets employed include;

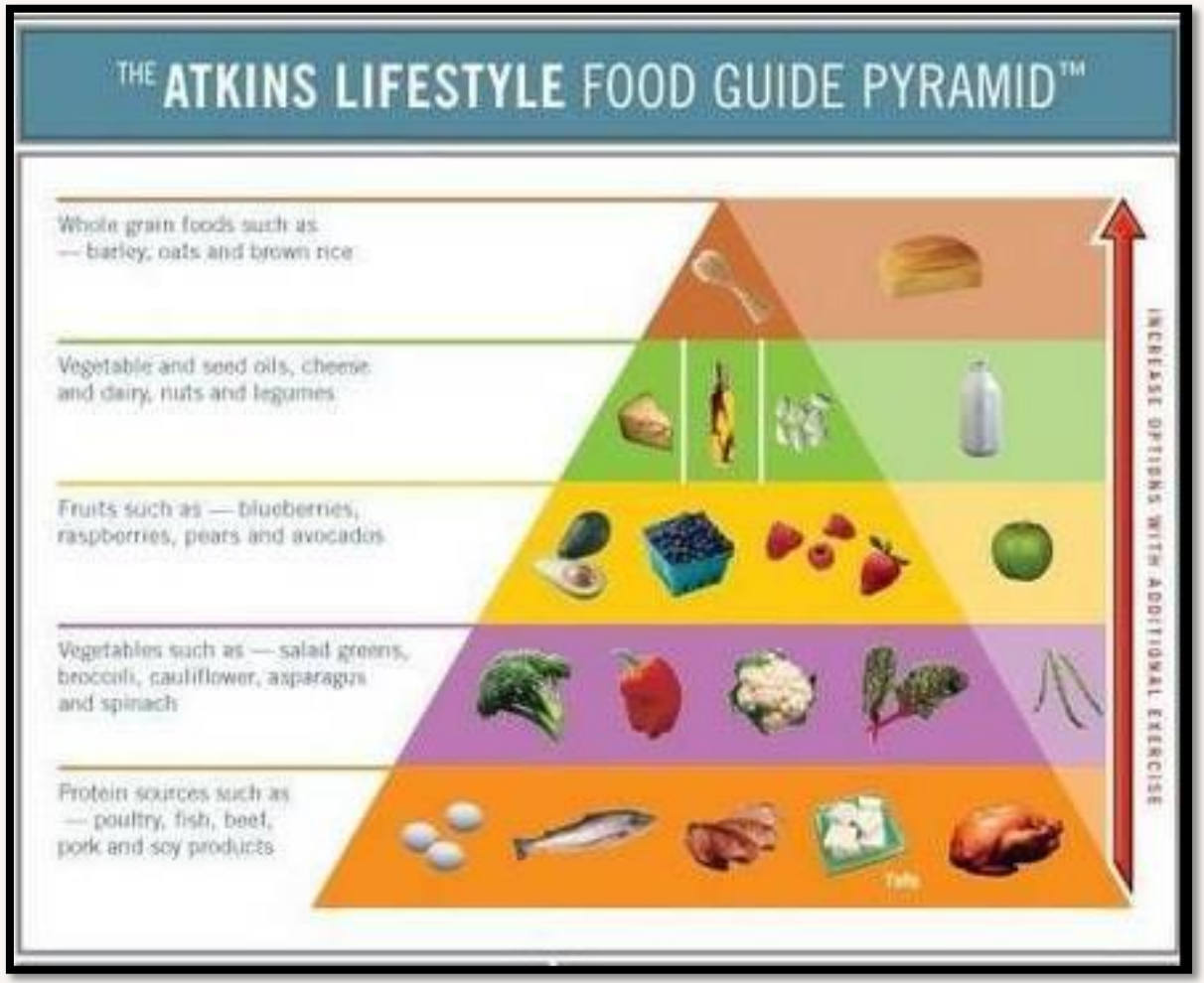
- Ketogenic Diet
- Modified Atkin’s Diet
- Low Glycemic Index Diet (Sondhi & Sharma, 2020)

KETOGENIC DIET

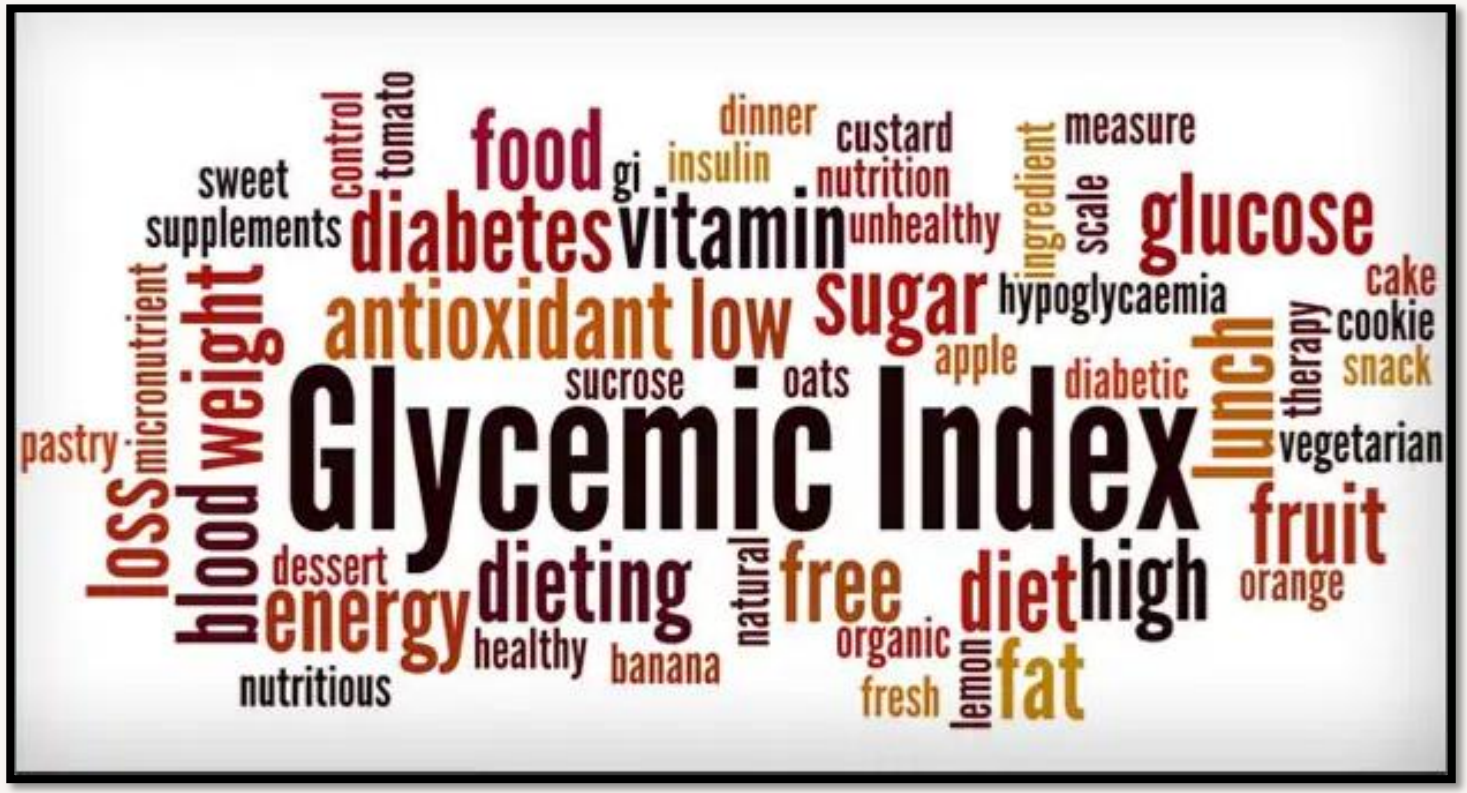


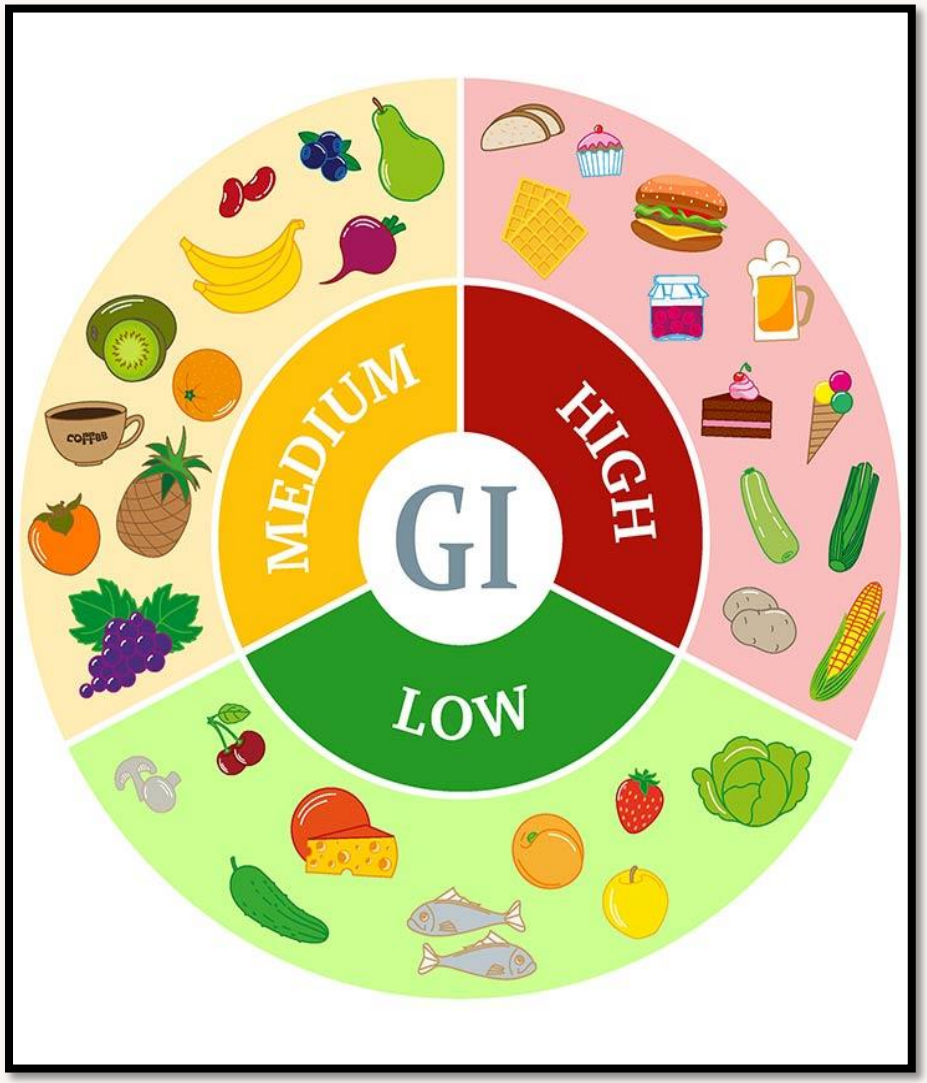


MODIFIED ATKIN'S DIET



LOW GLYCEMIC INDEX DIET





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