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Newer therapeutic advances in Epilepsy

(TC-54)-Novel Treatments In Neurology

DISCLAIMER

No conflict of interest.

Learning objective(s): This presentation will help to understand the recent advances in the field of epilepsy and update knowledge about evolution in the therapeutic armamentarium of epilepsy.

Plan of my talk

- Therapeutic modalities in epilepsy
- Evolution of Antiepileptic Drugs
- What is new in the management of epilepsy?
- Alternative modalities in Epilepsy Treatment
- Future Hope for Epilepsy

EPILEPSY

- Diagnosis in different age groups
- Classification
- Medical Management
  - »Conventional AEDs
  - »Newer AEDs
- Surgical Management
- Rehabilitation
- NEWER DEVELOPMENTS

AED	Ist Year of Clinical Trial	Author
Bromide	1857	Friedlander W.J
Phenobarbital	1912	Hauptmann
Mephobarbital	1932	Heyde
Phenytoin	1937	Merrit & Putnam
Carbamazepine	1963	Large M
Valproic Acid	1964	Carraz G
Clonazepam	1969	Gastaut H
Chlorazepate	1974	Booker H.E

LIST OF CONVENTIONAL ANTIEPILEPTIC DRUGS

DRUG NAME	ABBREV. USED
u CARBAMAZEPINE*	CBZ
u CLONAZEPAM*	CZP
u DIAZEPAM*	DZP
u ETHOSUXIMIDE	ESM
u ETHOTOIN	EHN
u MEPHENYTOIN	MHT
u METHYLPHENOBARBITAL	MPB
u MATHARBITAL	MTB
u MESUXIMIDE	MSM

**** DRUGS COMMONLY USED.***

CONVENTIONAL ANTIEPILEPTIC DRUGS

- **PARAMETHADIONE** — **PMD**
- **PHENACIMIDE** — **PAC**
- **PHENOBARBITAL*** — **PB**
- **PHENSUXIMIDE** — **PSM**
- **PHENYTOIN*** — **PHT/DPH**
- **PRIMIDONE** — **PRM**
- **PROGABIDE** — **PGB**
- **TRIMETHADIONE** — **TMD**
- **VALPROATE(ACID OR SALT) *** — **VPA**

DRUGS COMMONLY USED

There has been an explosion of new antiepileptic drug availability for physicians to treat patients with recurrent seizures. Principal antiepileptic drugs consisted of 6 key agents for both generalized and partial epilepsy for nearly 8 decades. **Since 1993, the availability of newer "second-generation" agents** has nearly doubled the armamentarium available for the millions of patients who have recurrent seizures.

Newer Antiepileptic Drugs

- LAMOTRIGINE* (1995) LTG
- **LEVETIRACETAM (1999) LTM**
- NAFIMIDINE NFM
- OXCARBAZEPINE* (Jan. 2000) OCZ
- STIRIPENTOL STP
- TIAGABIN (1997)
- TOPIRAMATE** (1997) TPM
- VIGABATRIN* GVG
- ZONISAMIDE* (1998) ZMS

Newer Antiepileptic Drugs

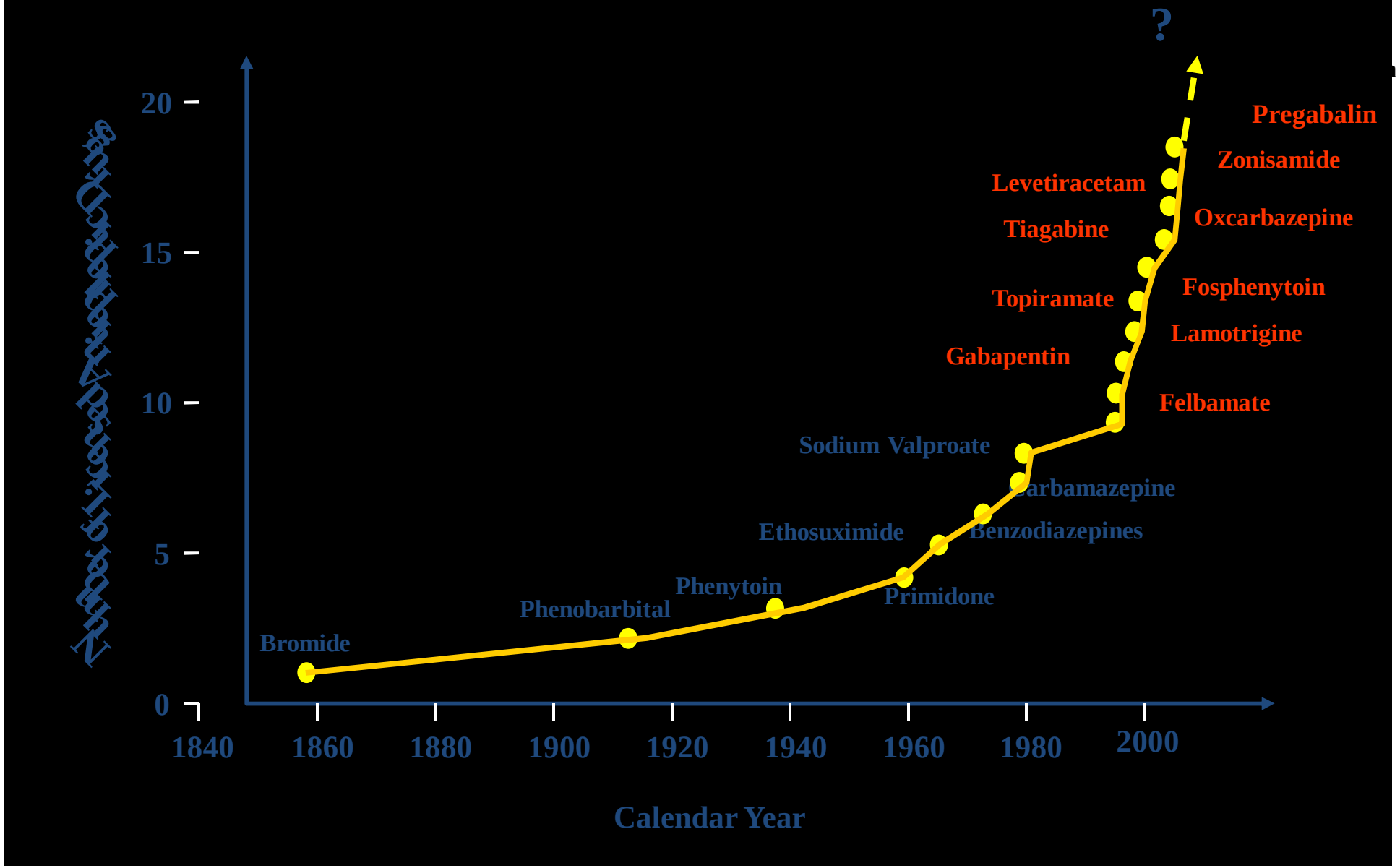
- **CLOBAZAM**** — **CLB**
- **DENZIMOL** — **DNZ**
- **FELBAMATE** — **FBM**
- **FLUNANIZINE** — **FNR**
- **FLUZINAMIDE** — **FXN**
- **GABAPENTIN**** — **GBP**

****drugs which hold promise**

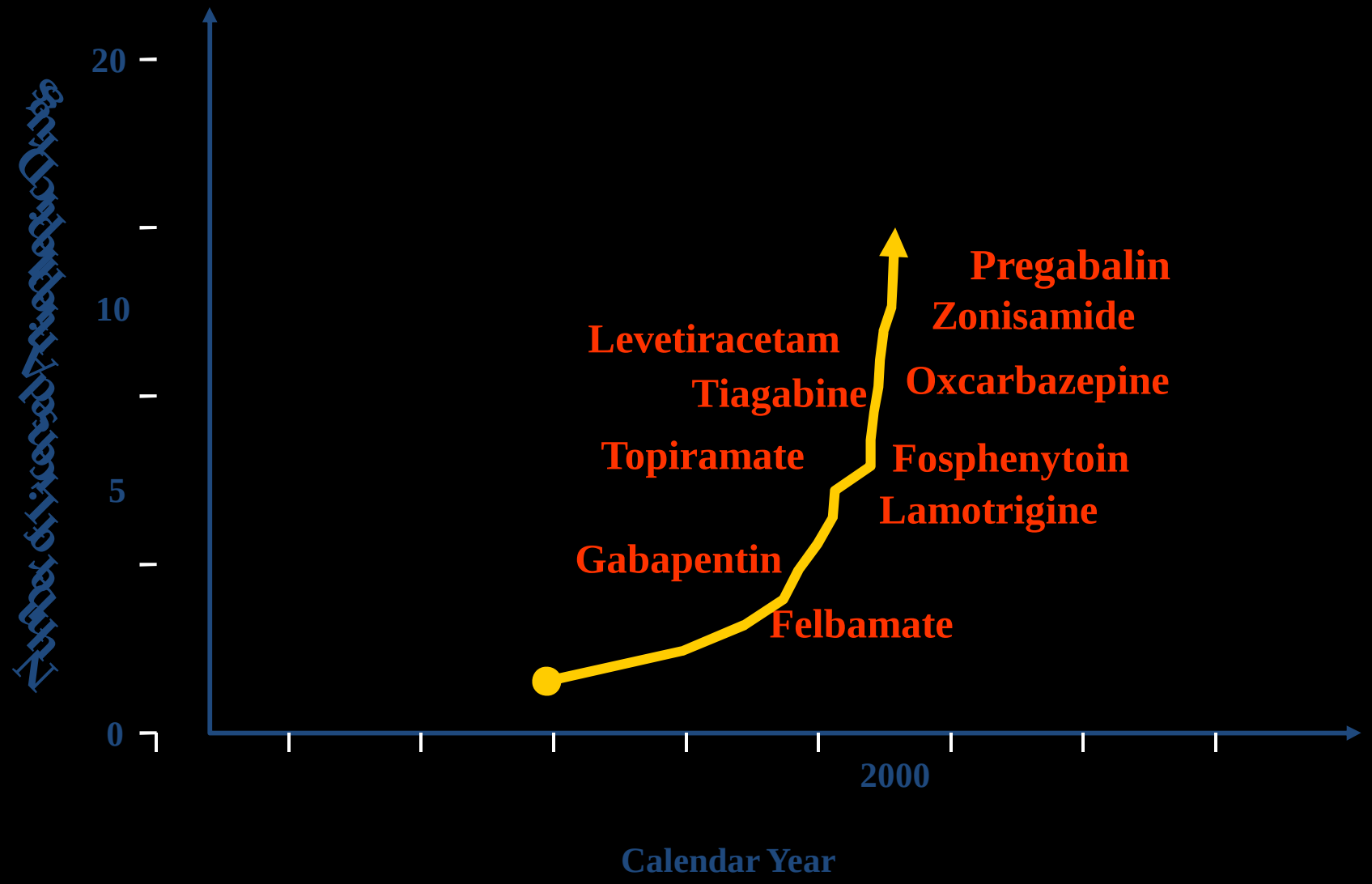
NEWER AEDs

- **LAMOTRIGINE*** **LTG**
- **NAFIMIDINE** **NFM**
- **OXCARBAZEPINE*** **OCBZ**
- **STIRIPENTOL** **STP**
- **TOPIRAMATE**** **TPM**
- **VIGABATRIN*** **GVG**
- **ZONISAMIDE*** **ZMS**

ANTIEPILEPTIC DRUG DEVELOPMENT



SINCE 1998


20
10
5
0
2000
Calendar Year
Pregabalin
Zonisamide
Levetiracetam
Oxcarbazepine
Tiagabine
Topiramate
Fosphenytoin
Lamotrigine
Gabapentin
Felbamate

Newer Treatments
Medications in Development

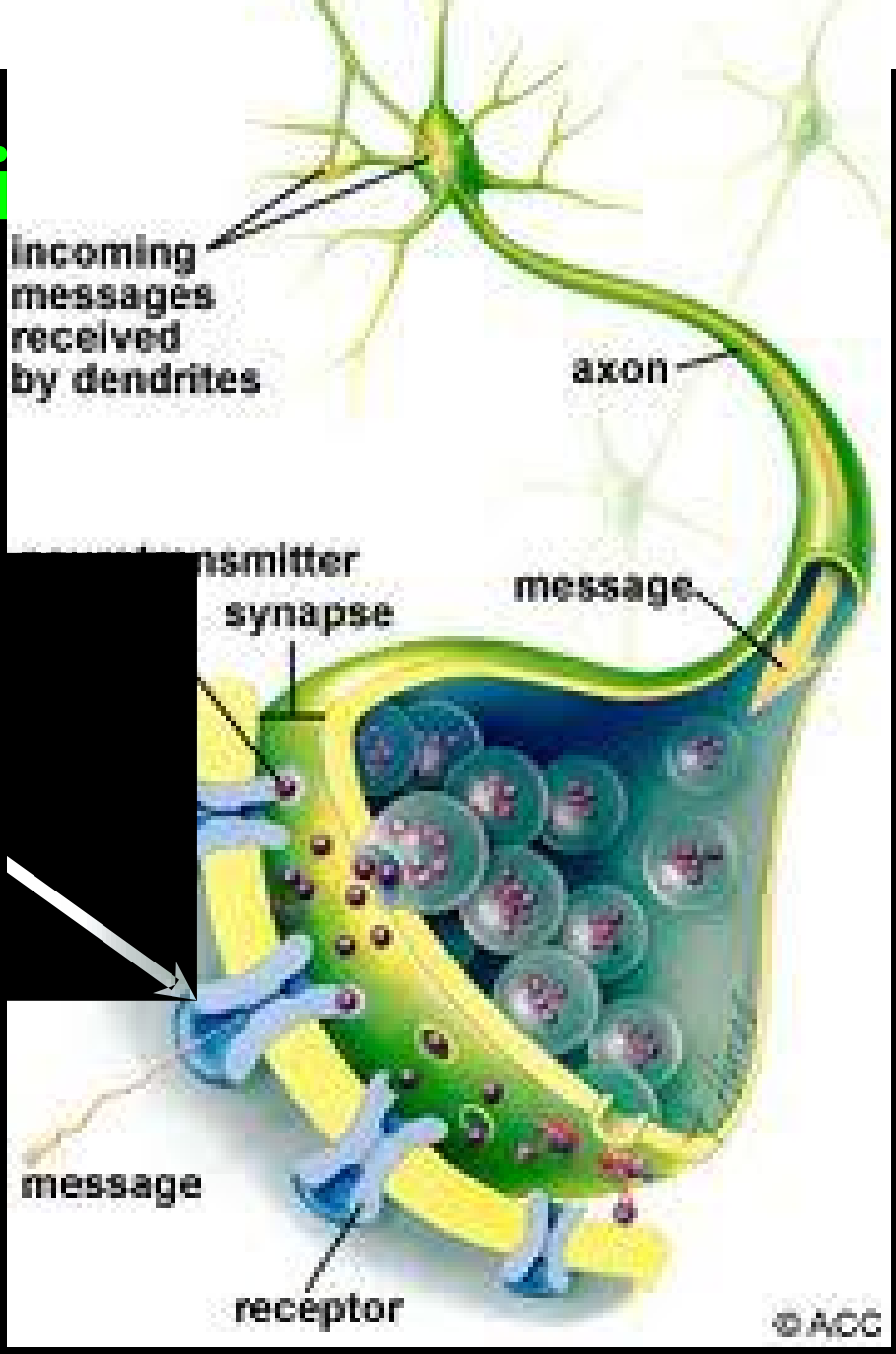
- Carisbamate (Partial seizures)
- Retigabine (Partial seizures)
- Eslicarbazepine (Partial seizures)
- Perampanel (Partial seizures)
- Brivaracetam (Generalized tonic seizures)
- Fluorofelbamate
- JZP-4, PID, Valrocemide, Ganaxolone

What Are Promising New Medical Treatments?

- **Maintenance Treatment**
  - **Ezogabine (Potiga)**
  - **Perampanel**
  - **Vertex**
- **Emergency Treatment**
  - **Intranasal Midazolam**

Poti

- Potassium Channel Opener
- Partial Sei
- Rare but serious side effects



Peramapanel

- **Glutamate Blocker**
- **Effective in trials for partial seizures**
- **Side effects: Dizziness, Sleepiness**

Vx-765 for Partial Epilepsy

- New approach to Epilepsy Rx
  - Anti-Inflammatory
  - Short Duration of therapy (weeks instead of years)
  - Oral Medicine
- Early Clinical Trials Completed
  - Early results encouraging but longer treatment duration to be studied
  - Headache, dizziness, GI most common side effects

Options for the Intractable Seizure Patient

- Medications (combinations)
- Diets
- Surgical procedures
  - √ **Stimulators**
  - –Resections

Vagus nerve stimulation

Mechanism of action of VNS is unknown

- Stimulation of vagal nuclei leads to widespread activation of cortical & subcortical pathways
- Increased seizure threshold

- Rarely works if Pts. is refractory to the first 2 - 3 drugs.

- Patients have seizures arising from more than one site
  - risk of ongoing seizures
  - harm from the surgery high

- Side effects - transient hoarseness , cough & dyspnea

Neuromodulatory Treatments

- Device implanted to alter instead of destroy brain tissue
- Range of treatment possible: Electrical, Cooling, local medications
  - Limit body/brain side effects
- Improve brain function

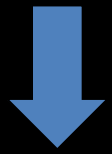
Deep brain stimulation (DBS)

Action - bilateral & symmetrical ablation

- stimulation of given target.

- **Para sagittal hole ~ 15 mm diameter made 2 cm lateral to mid line just anterior to the coronal suture**

microelectrode implanted



neurological pacemaker (infraclavicular)

Visualase

- Implant
- Treatment
- Follow up

NeuroPace

- Implant
- Treatment
- Follow up

Trigeminal nerve stimulation

Can be delivered noninvasively in humans

In a small open-label pilot study, bilateral stimulation of the ophthalmic branch produced a mean reduction in seizure frequency of 59% at 12 months

DeGiorgio et al., 2009

Repetitive transcranial magnetic stimulation (rTMS)

- **Noninvasive cortical stimulation method**
- **RTMS modulates cortical excitability with high-frequency rTMS enhancing and low-frequency rTMS decreasing cortical excitability in most individuals**
- **low-frequency rTMS is moderately beneficial, with more improvement in subjects who have cortical dysplasia or neocortical epilepsy**

(Hsu et al., 2011).

Open Loop Neurostimulation

Stimulation delivered continuously or on a clock cycle

Examples: VNS and DBS*

*DBS is not FDA approved for epilepsy

Responsive Neurostimulation

Stimulation delivered in response to detected epileptiform activity

Examples: RNS™ System*

*The RNS™ System is not FDA approved for epilepsy

- *Closed-loop stimulation*

  The generator is implanted in the skull and connected to either depth or subdural strip electrodes to deliver stimulation directly to one or two seizure onset zones

- ***0pen-loop stimulation* to various cortical and subcortical structure and *Bilateral stimulation* of the anterior nucleus of the thalamus has been proven effective (*Fisher et al., 2010).***

- **Responsive stimulation -a suitable treatment option for patients with bilateral independent seizure foci or with an epileptogenic zone in eloquent cortex not suitable for surgical resection.**

Radiosurgery

- uses a stereotactic frame to immobilize the head while radiation beams are precisely directed from different angles to a target.

- delivers radiation to the target with a steep gradient so that regions within a few millimeters of the target receive a substantially reduced radiation dose

- **used successfully for hypothalamic hamartoma, AVM and MTLE**

- **Neuropsychological testing showed no definite change in cognitive measures from baseline at 2 years after radiosurgery *(Quigg et al., 2011).***

- **Radiosurgery may have a place in the treatment of drug-resistant mesial temporal epilepsy for patients who are opposed to or at greater risk for complications with standard epilepsy surgery.**

Alternative Treatments Biofeedback

- Method of using relaxation or imagery to change body functions such as breathing, heart rate, and blood pressure
- These functions are monitored
- A stressful situation is presented and relaxation techniques are utilized
- Patient is able to view these functions and the see the differences between stressed and relaxed states

Alternative Treatments Biofeedback

- Has been shown to help people with high blood pressure, headaches, and pain.
- Patients who have seizures triggered by anxiety or stressful situations may benefit

Alternative Treatments
Relaxation Techniques

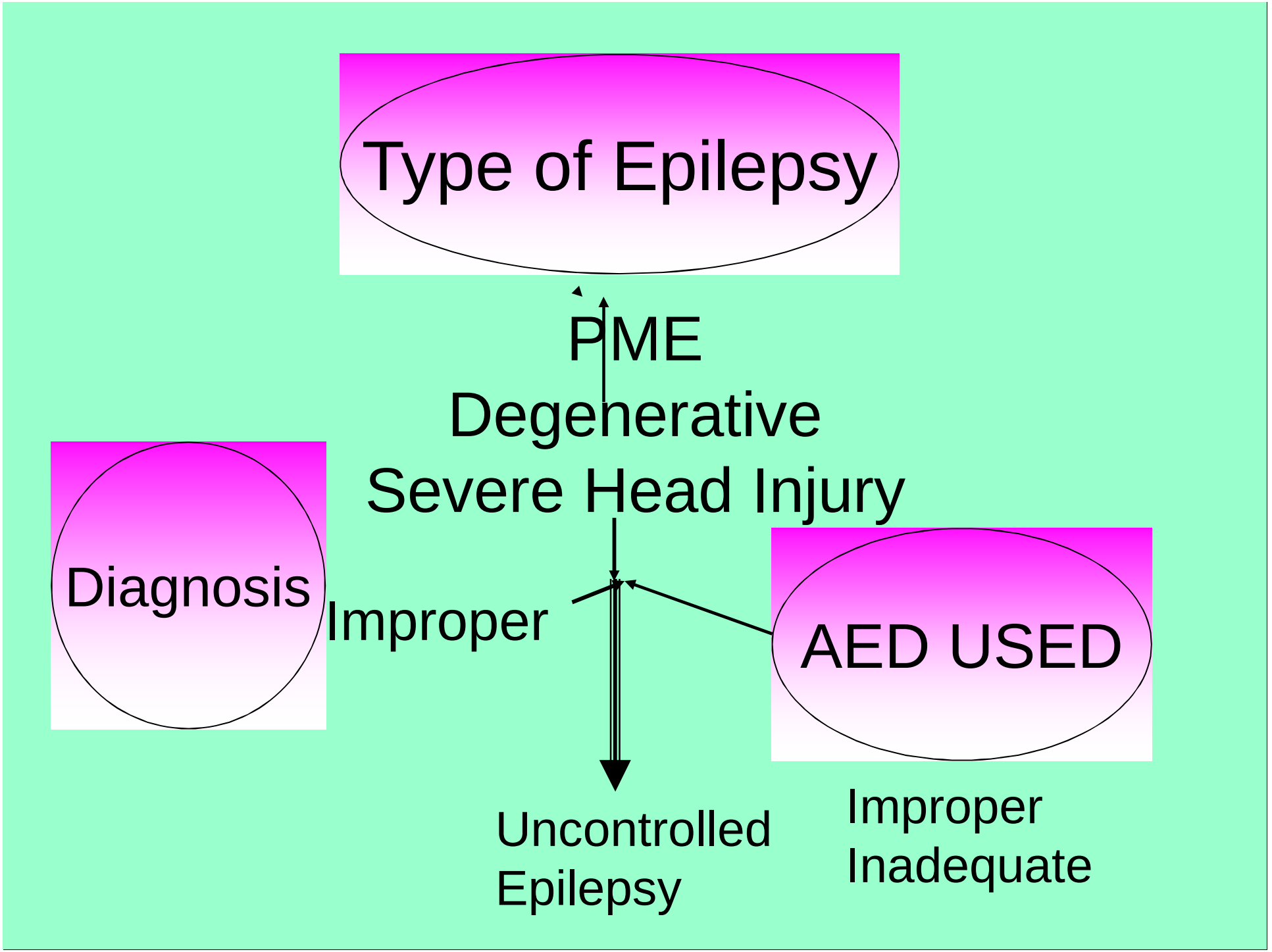
- Reiki
- Yoga
- Hypnosis
- Deep breathing exercises
- Massage therapy
- Meditation
- Muscle relaxation techniques

Alternative Treatments Melatonin

- Natural hormone produced by the pineal gland in the brain
- Frequently used as a sleep aid
- Study results with respect to helping seizures have been inconclusive.

Alternative Treatments Vitamins

- **Necessary for good health, however……**
- **Large doses of vitamins have not been shown to be of any benefit in reducing seizure frequency**
- **Patients on seizure medication may require supplements of calcium and Vitamin D for bone health.**


Type of Epilepsy
PME
Degenerative
Severe Head Injury
Diagnosis
Improper
AED USED
Uncontrolled
Epilepsy
Improper
Inadequate

EPILEPSY

- **HISTORY** DETAILS TO BE ENQUIRED FROM ALL POSSIBLE SOURCES.
- PERSONAL OBSERVATION IS VERY USEFUL.
- THERE IS NO SUBSTITUTE FOR A GOOD HISTORY.

Future Hope for Epilepsy

- **Instrument based system**
  - ***More smart stimulation device***
    - » ***Brain computer interface***
  - ***Focal cortical cooling***
  - ***Focal drug delivery***
    - » ***The seizure focus, The trigger site***
    - » ***Propagation pathways, Seizure stimulated drug release***

- **Neuronal grafting, gene therapy**
  - ***Noradrenergic modification, Cholinergic modification***
  - ***Serotonergic modification, GABAergic modification***
  - ***Hippocampal repair***

第十四届亚洲及大洋洲神经病学大会
14th Asian & Oceanian Congress of Neurology (AOCN 2014)

2 - 5 March 2014 • Macao, China
Venue: The Venetian® Macao

Organizer: Asian and Oceanian Association of Neurology

Host Organizer: The Hong Kong Neurological Society

Supported by: Chinese Society of Neurology

Important Dates

Deadline for Submission of Abstracts
15 September 2013

Deadline for Early-Bird Registration
1 December 2013

Website: **www.aocn2014.org**

SAVE THE DATE

XXII World Congress of Neurology

Santiago - Chile 2015

Changing Neurology Worldwide

THANKS