Special Lecture
"Update in Epilepsy"
Prof. Sirichai Chayasirisobhon
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Update in Epilepsy

Sirichai Chayasirisobhon, M.D., FAAN
Director Emeritus, Adult Epilepsy Program,
Kaiser Permanente Medical Center,
Orange County, California,
USA

Conceptual Definition of Epilepsy (2005)

- Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological and social consequences of this condition.
- The definition of epilepsy requires the occurrence of at least one epileptic seizure.

Fisher RS et al. 2005

Definition of Epilepsy

Operational (Practical) Clinical Definition of Epilepsy (2013)

Epilepsy is the disease of the brain defined by:

- At least two unprovoked seizures occurring >24 hours apart.
- One unprovoked seizure and a probability of further seizures similar to the generalized recurrence risk after two unprovoked seizures (approximately 75% or more).
- At least two seizures in a setting of reflex epilepsy.

Fisher RS et al. 2013

Operational (Practical) Clinical Definition of Epilepsy (2013)

Epilepsy is no longer present for individuals who had an age-dependent epilepsy syndrome, but are now past the applicable age or those who have remained seizure-free for at least 10 years off anti-seizure medicines, provided that there are no known risk factors associated with a high probability (>75%) of future seizures.

Fisher RL et al. 2013

One Unprovoked Seizure - treat or not treat

Treat if:

- the patient has brain lesion or abnormal EEG.
- the patient has partial seizure.
- the physician feels that the patient may risk a recurrent seizure

One Unprovoked Seizure - treat or not to treat

Not to treat:

- Because about 50% of the patients may not have another seizure
- Not to treat if
  -the patient has generalized seizure with a normal EEG and no risk factor.
  AND
  -the patient is willing not to drive at least 6 months

Recurrent Seizure – Treat or Not Treat

- The risk of recurrent seizure after a first unprovoked seizure range from 4% to 46%. (Berg A. et al. Neurology 1991;41:965-972)
- The risk increases to 70% after two or more seizures. (Shinnar et al. Ann Neurol 2000;48:140-147)
- 50% of patients with first seizure have normal EEG (Brodie MJ et al. Lancet 2000; 356; 323-329)
- Seizure recurrence is more likely if the patient has focal neurological deficits, mental retardation, an epileptiform EEG and a structural brain lesion

Risk factors for recurrent seizures

- Prolonged period before seizures are controlled
- High frequency of seizures before control
- Neurological abnormalities
- Mental retardation
- Partial seizures
- Consistent abnormal EEGs

Classification of Epilepsy

Report of ILAE Commission on Classification and Terminology, 2005-2009

- Generalized seizures are seizures occurring in and rapidly engaging bilaterally distributed networks.
- Focal seizures are seizures limiting to one hemisphere or either discretely localized or more widely distributed (focal)

Classification of Epileptic Seizures

Criteria are determined by clinical and EEG

- Partial seizure (focal, local)
  - Simple
  - Complex
  - Evolving to secondarily generalized
- Generalized (convulsive or nonconvulsive)
  - Absence
  - Myoclonic
  - Clonic
  - Tonic
  - Tonic-clonic
  - Atonic
- Unclassified

Epilepsia 1981;22:489-501

Revised terminology and concept for organization of seizures and epilepsies: Report of ILAE Commission on Classification and Terminology, 2005-2009

- Focal epilepsy
  - Simple
  - Complex
  - Evolving to secondarily generalized
- Generalized epilepsy
  - Absence
  - Myoclonic
  - Clonic
  - Tonic
  - Tonic-clonic
  - Atonic
- Unclassified

Berg AT. et al. Epilepsia 2010;51:676-685

Classification of Epilepsies and Epileptic syndromes

Criteria are determined by clinical, EEG, age, cause, prognosis

- Localization-related epilepsies
  - Idiopathic
  - Symptomatic
- Generalized epilepsies
  - Idiopathic
  - Idiopathic+/-symptomatic
  - Symptomatic
- Undetermined
  - With both focal and generalized
- Special syndromes
  - Situation-related: febrile seizure

Epilepsia 1985;26:268-278, Epilepsia 1989;30:389-399

Revised terminology and concept for organization of seizures and epilepsies: Report of ILAE Commission on Classification and Terminology, 2005-2009

- Genetic has played an important role in the new proposed classification and terminology.

Berg AT. Et al. Epilepsia 2010;51:676-685

Idiopathic Epileptic Syndromes

Syndrome	Gene	Chromosome
Benign epilepsy of centrotemporal spike		15q14
Benign familial neonatal convulsion	KCNQ2	20q13
	KCNQ3	8q24
Benign familial neonatal-infantile seizure	SCN2A	2q24
Myoclonic epilepsy of infancy	SCN1A	2q24
Chilhood absence epilepsy w. febrile sz	GABRG2	5q31
Juvenile myoclonic epilepsy	EFHC1	6p21
Generalized epilepsy w. febrile seizure plus	SCN1A	2q24
	SCN2A	2q24
	GABRG2	5q34

Symptomatic Epilepsy

- Symptomatic epilepsy used to described a seizure with a cause: structural or metabolic cause
- Structural causes are scar, stroke, tumor, etc.
- Metabolic causes are drug, alcohol, hyperglycemia, etc.

Report of ILAE Commission on Classification and Terminology, 2005-2009

- Cryptogenic epilepsy was defined in 1989 as presumed symptomatic. For example: Nocturnal frontal lobe epilepsy that is believed to have a "lesion", but imaging is normal. It is found to be autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)

Report of ILAE Commission on Classification and Terminology, 2005-2009

- Idiopathic epilepsy is replaced by genetic epilepsy.
- Symptomatic epilepsy is replaced by structural/metabolic epilepsy.
- Cryptogenic epilepsy is replaced by unknown.

Revised terminology and concept for organization of seizures and epilepsies: Report of ILAE Commission on Classification and Terminology, 2005-2009

- Focal epilepsies
  - Genetic
  - Structural/metabolic
- Generalized epilepsies
  - Genetic
  - Genetic+/-structural/metabolic
  - Structural/metabolic
- Undetermined
  - With both focal and generalized
- Special syndromes
  - Situation-related: febrile seizure

Epilepsia 1985;26:268-278, Epilepsia 1989;30:389-399

Antiepileptic Drugs

HLA-B*15:02 Screening in Thailand

- It is estimated that without HLA-B*15:02 screening, 187 patients will develop SJS/TEN annually
- Universal HLA-B*15:02 screening can reduce this number to approximately 23 patients per year.
- 343 patients need to screen to prevent one case of SJS/TEN.
- Universal HLA-B*15:02 represents good value for the money in term of preventing SJS/TEN in CBZ-treated patients

Rattanavipapong Waranya et al. Epilepsia 2013;54:1628-1638.

Mechanism of Action of AEDs

- Sodium channel blockade
- Calcium channel blockade
- Glutamate antagonism
- GABA potentiation

First Generation Antiepileptic Drugs

- 1912 phenobarbital (PB)
- 1938 phenytoin (PHT)
- 1954 primidone (PRM)
- 1960 ethosuximide (EZM)
- 1968 diazepam (DZP)
- 1974 carbamazepine (CBZ)
- 1975 clonazepam (CZP)
- 1977 lorazepam (LZP)
- 1978 valproate (VPA)
- 1981 clorazepate (CRZ)

Second Generation Antiepileptic Drugs

- 1993 Felbamate (FBM)
- 1994 Lamotrigine (LTG)
- 1995 Fosphenytoin (FOS)
- 1997 Topiramate (TPM)
- 1997 Tiagabine (TGB)
- 1999 Levetiracetam (LEV)
- 2000 Zonisamide (ZNS)
- 2000 Oxcarbazepine (OXC)
- 2005 Pregabalin (PGB)
- 2011 Vigabatrin (VGB)
- 2011 Clobazam (CLZ)

Mechanism of Action of 2nd generation AEDs

AED	*Na+ blockade*	*Ca++ blockade*	*GABA potentiation*	*Glutamate Antagonism*
Felbamate	x	x (T)	x	x
Gabapentin		x (L)	x	
Lamotrigine	x	x (T)		x
Topiramate	x	x (T,L)	x	x
Tiagabine			x	
Oxcarbazepine	x	x (N/P)		
Zonizamide	x	x (L,T)	x	
Levetiracetam		x (N)	x (Zn, bc)	
Pregabalin			x	
Vigabatrin			x	
Clobazam			x	

Third Generation AEDs

- 2011 Rufinamide (RNM)
- 2011 Lacosamide (LCM)
- 2011 Ezogabide (EGB)
- 2012 Perampanel (PRP)
- 201? Eslicarbazepine (ECP)
- 201? Brivaracetam (BVC)

Mechanism of Action of AEDs

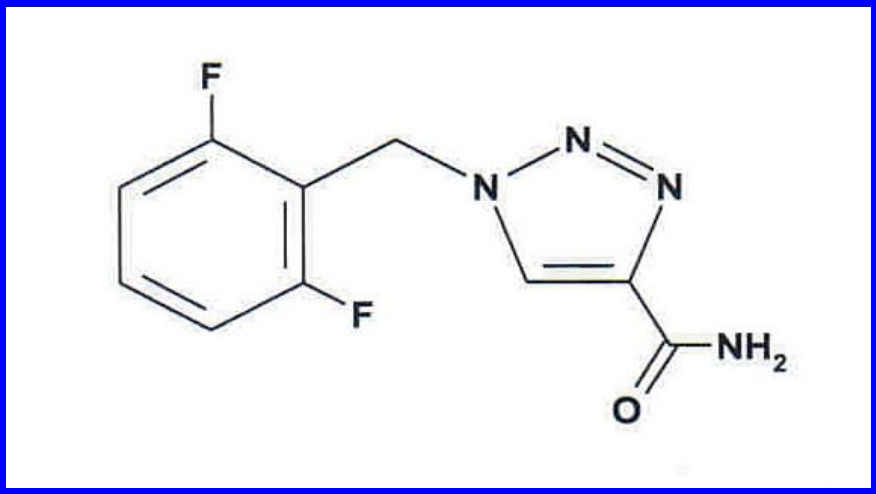
- Sodium channel blockade
- Calcium channel blockade
- Glutamate antagonism
- GABA potentiation
- Potassium channel opener

Mechanism of Action of 3rd generation AEDs

AED	*Na+ blockade*	*Ca++ blockade*	*GABA potentiation*	*Glutamate Antagonism*	*K+ potentiation*
Rufinamide	x				
Lacosamide	x				
Ezogabine					x
Perampanel				x (AMPA)	
Eslicarbazepine	x				
Brivaracetam			x(SV2A)		

Rufinamide (Banzel)

Triazole derivative



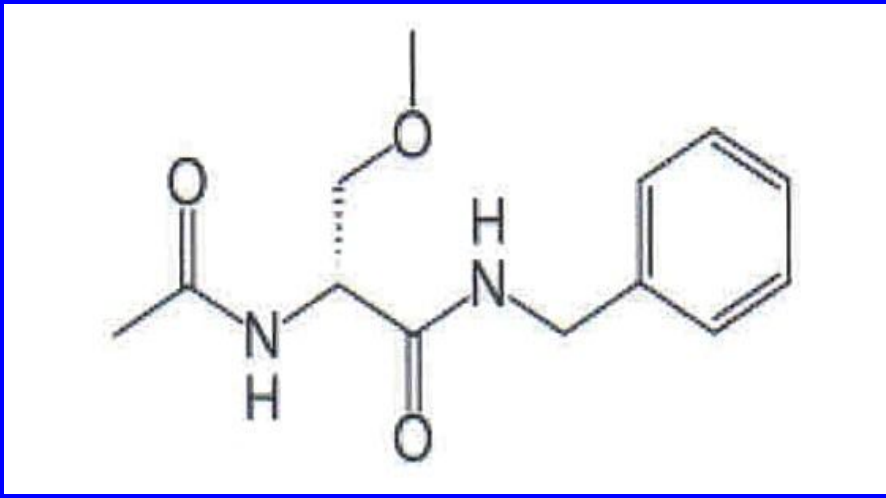
Rufinamide

- Rufinamide is indicated for adjunctive treatment of seizures associated with lennox-Gastaut syndrome in children 4 years and older and adults.
- Mechanism is to modulate the activity of sodium channels and in particular, prolongation of the inactive state of the channel and slow sodium channel recovery from inactivity and limit sustained repetitive firing of sodium-dependent action potentials.

Rufinamide

- Half-life is approximately 6-10 hours.
- Metabolism: weak enzyme inhibitor of CYP 2E1 and weak enzyme inducer of CYP 3A4.
- Adverse reactions: somnolence, dizziness, ataxia, suicidal ideation (1 per 500)
- Precaution: shorten QT interval
- Dosage: 10 mg per kg per day to a target dose of 45 mg/kg/day or 3200 mg per day in BID.

Lacosamide (Vimpat)



Lacosamide (Vimpat)

- Indication: Lacosamide is indicated for adjunctive treatment of partial-onset seizures.
- Mechanism: it enhances slow inactivation of voltage-gated sodium channels resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal

Rogawski MA 2006; Errington AC 2008

Lacosamide (Vimpat)

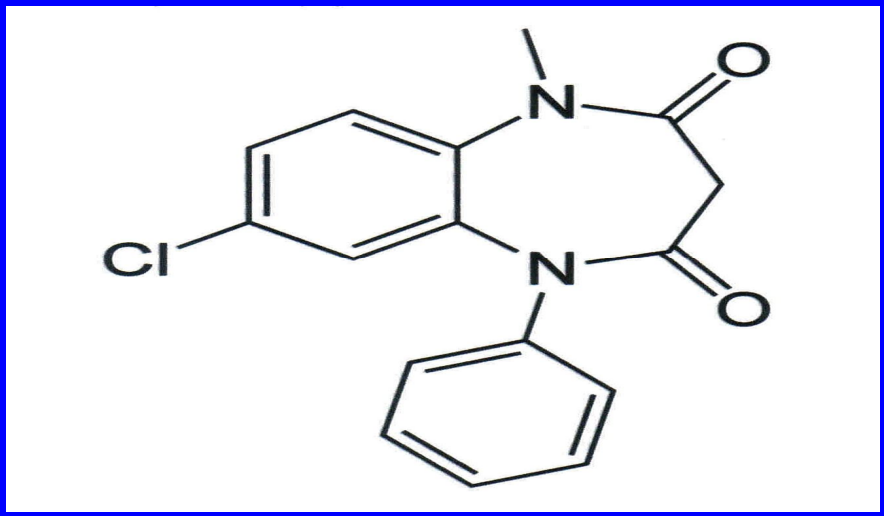
- Metabolism: Linear kinetics; less drug interaction due to less protein binding (<15%) and does not induce or inhibit cytochrome 450 in vitro except inhibiting CYP2C19.
- Half-life: 13 hours
- Adverse reactions: somnolence, dizziness, ataxia, suicidal ideation, cardiac arrhythmia, syncope
- Dosage: oral/IV 400-600 mg per day (BID)

Lacosamide (Vimpat)

- Lacosamide and oral contraceptive Levonorgestrel plus ethinylestradiol have low potential for drug-drug interaction.
- Therefore coadministration of the two drugs is unlikely to result in contraceptive failure or loss of seizure control.

Cawello W, et al. Epilepsia 2013;54:530-536.

Clobazam (Onfi)



Clobazam (Onfi)

1,5 benzodiazepine

- Clobazam is indicated for adjunctive treatment for seizures associated with Lennox Gastaut syndrome in patients two years and older.
- It has agonist activity at GABA-A receptors.
- Metabolism: oxidation in liver and largely protein bound.

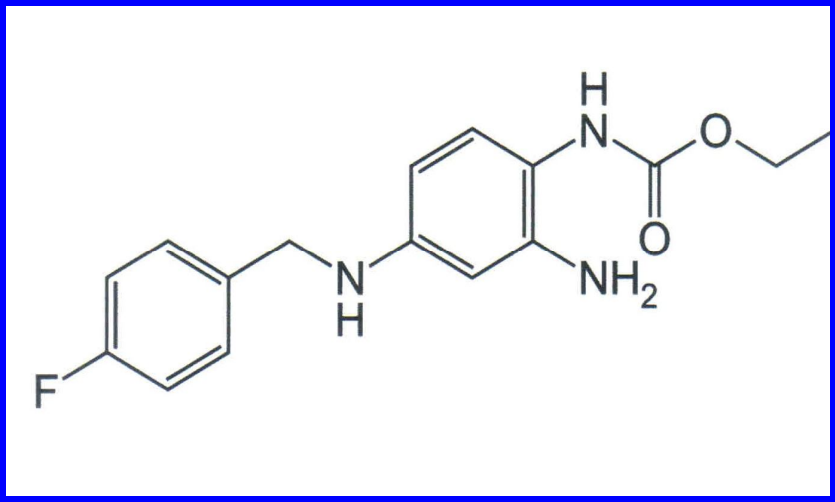
Clobazam (Onfi)

- Half-life: 10 -50 hours
- Dosage: start dose 5 mg and increase slowly in 14 days to 20 mg (weight ≤30 kg) or to 40 mg (weight ≥30 kg).
- Adverse reaction: Somnolence, drooling, ataxia, diplopia, dysarthria, constipation, cough, pain with urination, fever, behavioral change, suicidal ideation (1:500)

Mechanism of Action of AEDs

- Sodium channel blockade
- Calcium channel blockade
- Glutamate antagonism
- GABA potentiation
- Potassium channel opener

Ezogabine (Potiga)



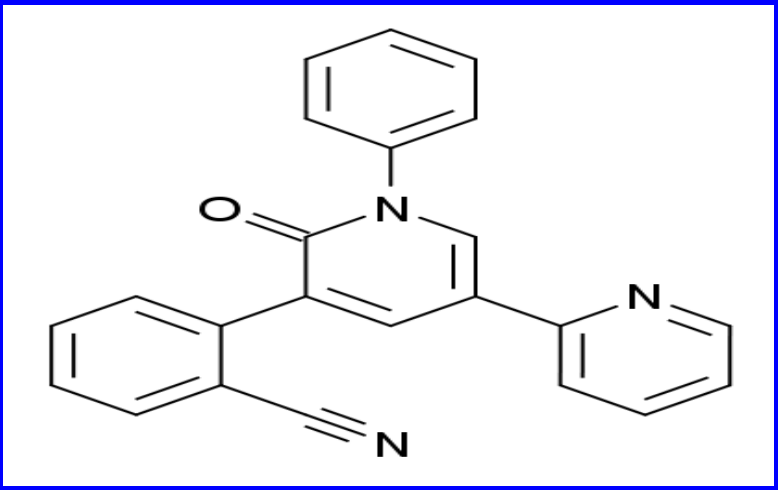
Ezogabine (Potiga)

- It is known in Europe as Retigabine (Trobalt).
- Mechanism:
  - They work through the KCNQ2/3 or Kv7-channels which modulate the M current, affecting cell excitability.
  - These voltage-dependent K channels turn on during the period of excessive hyperexcitability of the neuron.

Ezogabine (Potiga)

- Adverse reactions: dizziness, fatigue, confusion vertigo, tremor, incoordination, diplopia, inattention, memory impairment, urinary retention, psychotic symptoms.
- Warning: Blue skin discoloration on and around the lips, nail beds of the fingers or toes, face and legs, and scleral and conjunctival discoloration pigment changes in the retina.
- Dosage: 600 mg to 1200 mg per day.

Perampanel (Fycompa)



Perampanel (Fycompa)

- Perampanel is a potent, orally active, noncompetitive and highly selective α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonist.
- It blocks AMPA receptor at the postsynaptic membrane of excitatory synapses in the brain binding glutamate and transducing glutamate-mediating postsynaptic signaling.

Perampanel (Fycompa)

- Protein binding 95%
- Metabolism: hepatic, mostly via CYP3A4 and/or CYP3A5.
- Half life: 105 hours.
- Excretion: bowel 70%, urine 30%

Perampanel

- Approved for partial-onset seizures in patients who are 12 years of age or older.
- Dosage: 4 mg once daily, may increase to 8 to 12 mg per day.
- Responder rates (seizure reduction ≥ 50%) was 35% for 12-mg/day doses
- Adverse events: dizziness, somnolence, sedation, fatigue.

Steinhoff BJ Et al.Epilepsia 2013;54:1481-1489.
French JA et al. Epilepsia 2013;54:117-125.
Krauss GL et al. Epilepsia 2013;54:126-134.

Eslicarbazepine (Aptiom)

Eslicarbazepine Acetate (Aptiom)

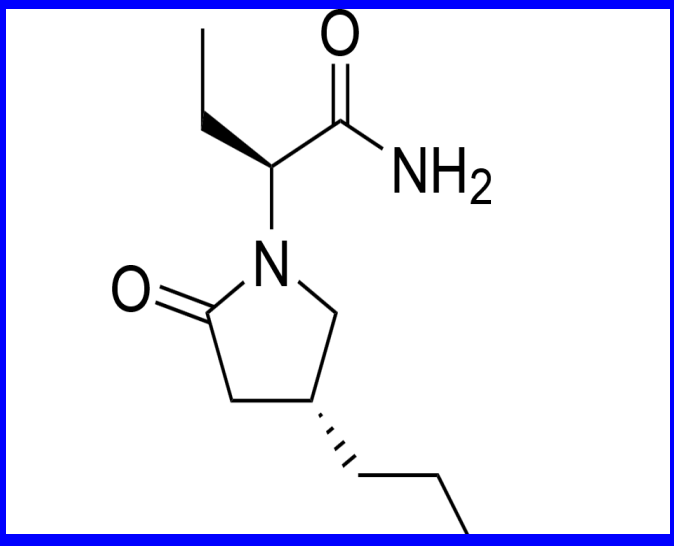
- ESL is a prodrug of eslicarbazepine ([S]-licarbazepine and the active metabolite of oxcarbazepine.
- Block voltage-gated sodium channels in rapidly firing “epileptic”neurons.

Eslicarbazepine Acetate (Aptiom)

- Dosage: 400 – 1200 mg once daily.
- The responder rate (seizure reduction ≥ 50%) was 42% per 12 week interval.
- Adverse events: dizziness, headache and somnolence

Gil-Nagel A et al. Epilepsia. 2013;54:98-107;
Nunes T et al. Epilepsia 2013;54:108-116.

Brivaracetam



Brivaracetam

- Is chemically related to levetiracetam.
- Its binding affinity for the synaptic vesicle protein 2A (SV2A) is 10-fold higher than that of levetiracetam
- It inhibits sodium channels.
- Treatment: adjunctive therapy for focal epilepsy
- Dosage: 100 mg/day to 200 mg /day.

Paesschen WY, et al. Epilepsia 2013;54:89-97

AEDs and Contraceptive Drugs Lower hormone level

- Carbamazepine
- Felbamate
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Primidone
- Rufinamide
- Topiramate (≥200 mg/day)

AEDs and Contraceptive Drugs
No significant effect

- Clonazepam
- Ethosuximide
- Ezogabine
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam
- Pregabalin
- Tiagabine
- Topiramate (<200 mg/d)
- Valproate
- Vigabatrin
- Zonisamide

AEDs and Pregnancy
The North American Antiepileptic Drug 1997-2011

AED	Enrolled Pregnancy	Total Malformations	Prevalence of Malformation
Carbamazepine	1033	31	3.0%
Clonazepam	64	2	3.1%
Gabapentin	145	1	0.7%
Lamotrigine	1562	31	2.0%
Levetiracetam	450	11	2.4%
Oxcarbamazepine	182	4	2.2%
Phenobarbital	199	11	5.5%
Phenytoin	416	12	2.9%
Topiramate	359	15	4.2%
Valproate	323	30	9.3%
Zonisamide	90	0	0.0%
Unexposed	442	5	1.1%

AEDs and special populations

Seizure in elderly	Levetiracetam
Seizure and migraine	Topiramate, Valproate
Seizure and pregnancy	Lamotrigine , Levetiracetam
Seizure and over-weight	Topiramate, Zonesamide

AEDs and important side effects

AED	Side effects
Carbamazepine	Rash, leucopenia, low sodium
Ezogabine	Blue skin discoloration, pigment changes in the retina
Lamotrigine	Rash
Levetiracetam	Mood changes
Oxcarbamazepine	Hyponatremia
Phenytoin	Rash, gum swelling
Topiramate	Cognitive dysfunction, tingling, weight loss, kidney stone
Valproate	Weight gain, hair loss
Vigabatrin	Permanent visual field defect

Do antiepileptic Drugs lead to suicide?

- US Food and Drug Administration (FDA) has warned linking AEDs to suicidal-related behavior in January 2008.
- Since the FDA warning, at least 4 large studies yielded contradictory results.
- Suicidal-related behavior may have previous history of psychiatric disorder.

AEDs and Suicidal Risks

- A recent study found that individuals with a first AED exposure had increased risk of suicide-related behavior both before and after initiating of AED; the rate of suicide-related behavior gradual reduced after.

  Pugh MJV et al. Neurology 2013;81:1900-1908

Surgical Approach in Epilepsy

- Temporal lobectomy
- Amygdalohippocampectomy
- Extratemporal cortical resection
- Hemispherectomy
- Corpus callosotomy
- Multiple subpial transections
- Vagus nerve stimulation (VNS)
- Deep brain stimulation
- Responsive Neuropace Stimulator System (RNS)

Vagus Nerve Stimulation

- The efferent fibers mainly originate from neurons located in the medulla oblongata. They are parasympathetic projections to the heart, lung, stomach and intestine, liver, pancreas and kidney
- The afferent fibers compose about 80% of the fibers in the cervical portion of the vagus. They project to spinal trigeminal nucleus and nucleus of tractus solitarius .

Vagus Nerve Stimulation

- Spinal trigeminal nucleus projects to ventral postero-lateral nucleus of thalamus, post-central gyrus, and inferior parietal lobe

Vagus Nerve Stimulation

- Nucleus of tractus solitarius projects to
  - locus coeruleus
  - parabrachial plexus nucleus
  - Kolliker-Fuse nucleus
  - raphe magnus nucleus
  - inferior cerebellar hemisphere

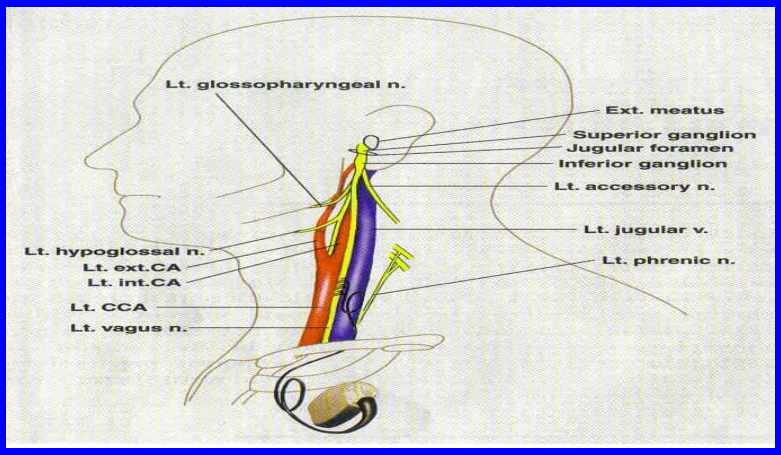
Vagus Nerve Stimulation

- Nucleus of tractus solitarius projects to parabrachial plexus nucleus, then to periaqueductal gray, then to central nucleus of amygdala, then to periventricular nucleus of hypothalamus and then to ventro posteromedial nucleus of thalamus.

Vagus Nerve Stimulation - Mechanism

- Stimulation of Nucleus of tractus solitarius increases GABA and decreases glutamate. (Walker BR et al 1999)
- Locus coeruleus involved in anticonvulsant effect of VNS. Lesion in locus ceruleus eliminates VNS to suppress seizures. (Krahl et al 1998)
- VNS decreases activity in left and right medial thalamus (Ring HA et al 2000)

Vagus Nerve Stimulation



VNS Generators

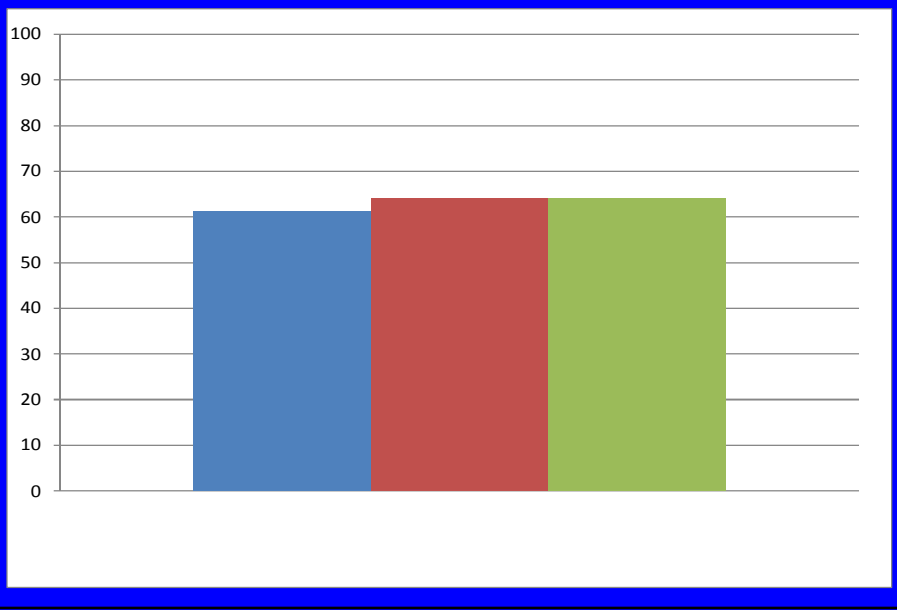
Single electrode **Dual electrodes**

VNS patients studied at 6 months, one year and 2 years with no change in AEDs

- 18 patients or 43.9% improved seizure frequency throughout 3 periods.
- 15 patients or 36.6% showed partial improvement.
- 8 patients or 19.5% showed no change

(pending in peer review journal)

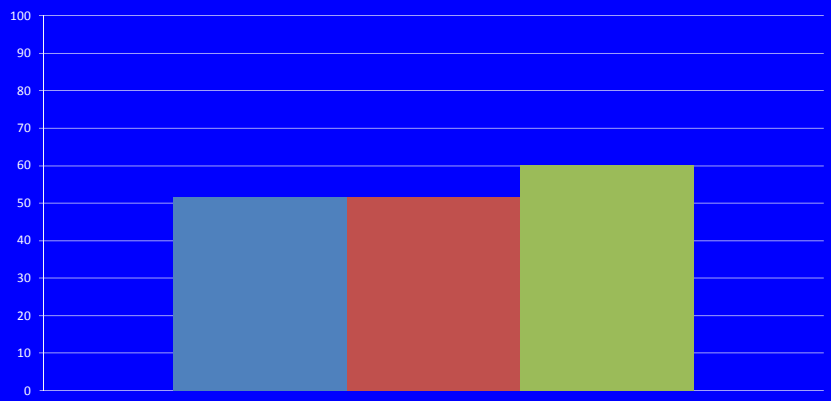
Efficacy of VNS ≥50% reduction in seizure frequency at 6-month, 12-month and 24-month



VNS patients < 12 years old studied at 6 months, 12months and 24 months

- 15 patients or 42.9% improved seizure frequency throughout 3 periods.
- 8 patients or 22.8% showed partial improvement.
- 12 patients or 34.3% showed no change

Efficacy of VNS ≥50% reduction in seizure frequency in all three periods in children under 12 years old at 6-months, 12-months and 24-months



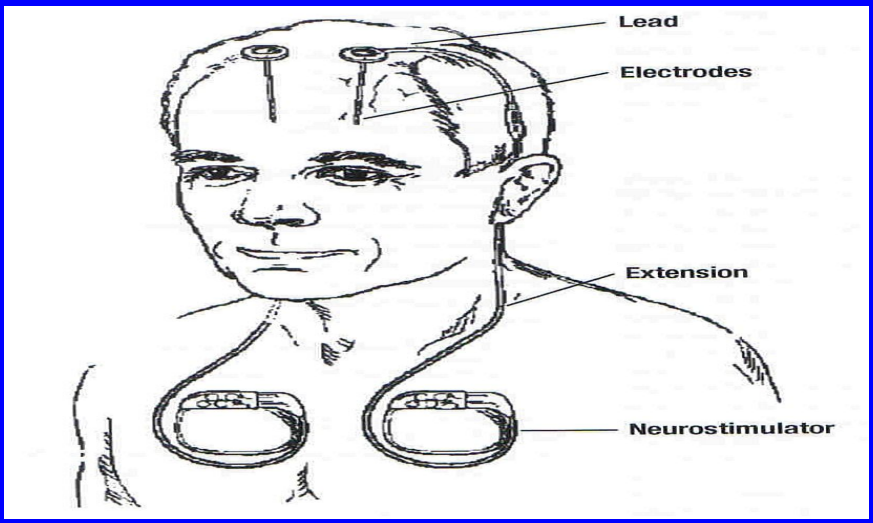
Deep Brain Stimulation

Deep brain stimulation:

- Anterior thalamic nucleus in limbic seizure
  Andrade DM, et al Neurology 2006;66:1571-1573; Lee KJ et al 2006
- Subthalamic nucleus in focal motor epilepsy.
  Chabardes S, et al 2002
- Centrmedian thalamic nucleus in generalized form: Lennox Gastaut syndrome.
  Velasco AL, et al 2006
- Hippocampal electrical stimulation
  Tellez-Zenteno JF, et al Neurology 2006;66:1490-1494
- Responsive NeuroPace Neurostimulator (RNS)
  Morrell MJ, et al. Neurology 2011;77;1295-1304

Deep Brain Stimulation of Thalamus

Courtesy by Dr. M.Tagliati



Anterior Nucleus of Thalamus

- Thalamus can serve as a relay station through thalamocortical networks, thereby inhibiting or disrupting rhythmic depolarization signals from spreading and causing overt seizures
- Stimulation of anterior nucleus of thalamus has been shown to reduce synchrony and increase inhibition in hippocampus or neocortex

Kerrigan JF et al. Epilepsia 2004;45:346-354.

Efficacy of Anterior Nucleus of Thalamus Stimulation

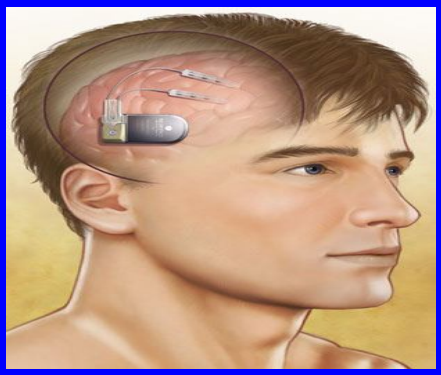
- From SANTE (stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy)
- At the end of 3-month period, controls showed 14.9% median reduction od seizures, while the active group showed 40.5% median reduction of seizures.
- Follow-up for 2 years, the active group showed 56% median reduction. 14 patients were seizure free for 6 months.

Fisher R. et al. Epilepsia 2010;51:899-908.

Responsive NeuroPace Neurostimulator (RNS)

- The RNS system is surgically implanted under the scalp and connected to one or two leads (insulated wires with 4 small electrodes at the end).
- These leads are implanted within the patient's brain and/or places on the brain surface, in the area of the presumed seizure origin.
- The RNS continuously monitors the patient's brain waves.
- When seizure activity is detected, the device delivers brief and mild electrical stimulation through the leads in an attempt to suppress seizures.

Responsive NeuroPace Stimulator



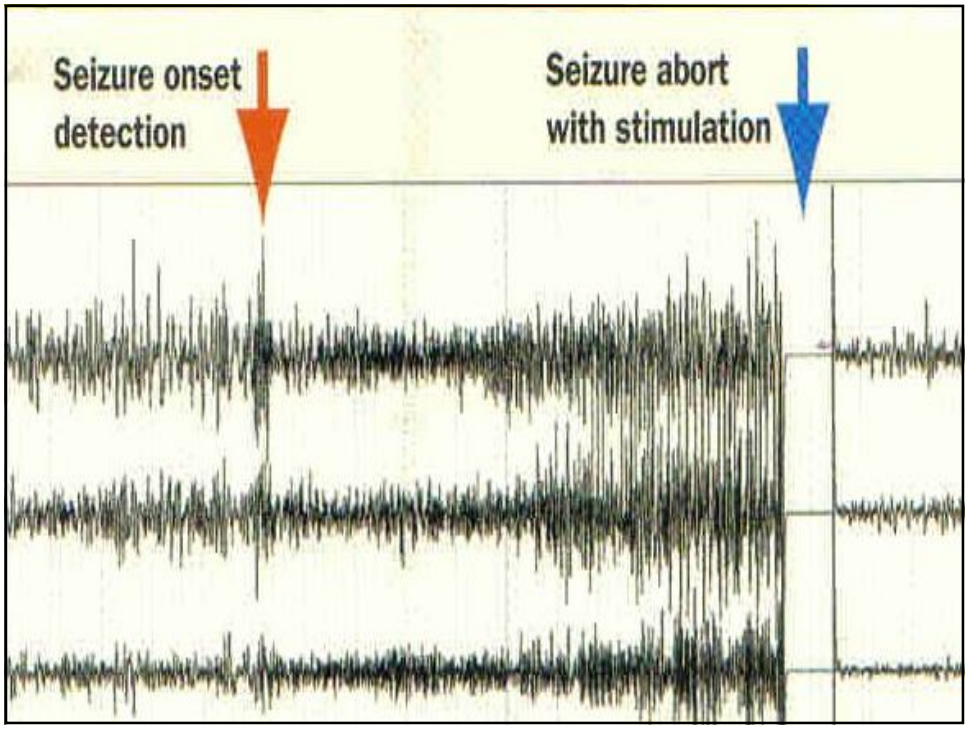
Responsive NeuroPace Stimulator

Responsive NeuroPace Stimulator

- The RNS System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than two epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/or secondarily generalized seizures

Responsive NeuroPace Stimulator

- The RNS System also comes with a programmer for physicians to non-invasively set the detection and stimulation parameters for the implanted device, and has the ability to view the patients electrocorticogram (ECoG) in real time and upload previously recorded ECoGs stored on the RNS implant.



Responsive NeuroPace Neurostimulator (RNS)

- 97 patients or 37.9% treated with RNS showed significant reduction in seizures comparing to 94 patients or 17.3% showed improvement during the blind period.
- No difference in adverse reactions between the two groups.
- The RNS treatment group showed improvement in quality of life.

Morrell MJ et al. Neurology 2011;77;1295-1304.

Responsive NeuroPace Stimulator

- Results from clinical studies show significant benefits for patients, with a 37.9% reduction in seizure frequency for subjects with active implants. Follow up with patients two years post-implant showed that over half experienced a reduction in seizures of 50% or more.

Smart Neuro-Stimulator

- The technique is similar to Responsive NeuroPace Neurostimulator (RNS) except that the stimulator will fire at the onset of spike activity recorded in the epileptic focus.
- This technique is under developed by Barrow Neurological Institute.

Predicting Seizures?

- A system called a long term implanted seizure advisory system is used to predict impending seizures.
  Cook MJ et al. Lancet Neurol 2013;12:563-571
- This system consists of cortical electrodes placed in the most epileptogenic areas (unilateral or bilateral).
- The lead are tunneled down the neck and connect to the telemetry unit placed subclavicularly similar to VNS.

Predicting Seizures?

- 15 patients with refractory seizures were studied with long term device for 4 month.
- 11 patients had adverse events of which 4 were considered serious requiring procedural intervention. Units were explanted in 2 patients.
- 2 of 10 subjects completed the study with excellent prediction.