Epilepsy Pharmacotherapy

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Choosing an Antiepileptic Drug (AED)

- Seizure type
- Epilepsy syndrome
- Drug Mechanism of Action (MOA)
- Pharmacokinetics
  - Drug interactions
  - formulation
- Concomitant medical/psychiatric conditions
- Adverse effects
- Cost

Treatment Goal:

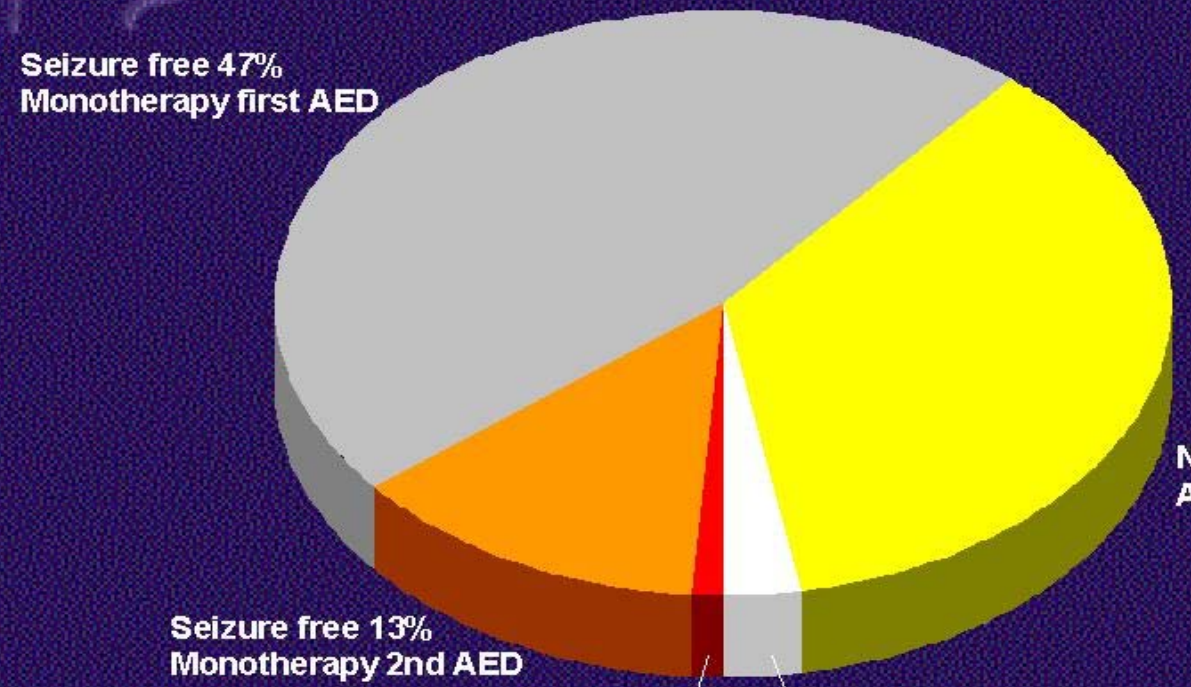
No Seizures, No Side effects

Currently Available AEDs: Generic Names & Trade Names

Generic	Trade
Briveracetam (BRV)	Briviact
Carbamazepine (CBZ)	Carbatrol, Tegretol
Cenobamate	Xcopri
Clobazam (CLB)	Onfi
Cannabidiol (CBD)	Epidiolex
Eslicarbazepine (ESL)	Aptiom
Ethosuximide (ETH)	Zarontin
Felbamate (FBM)	Felbatol
Fosphenytoin (FOS)	Cerebyx
Gabapentin (GBP)	Neurontin
Lamotrigine (LTG)	Lamictal

Generic	Trade
Perampanel (PER)	Fycompa
Phenobarbital (PB)	
Phenytoin (PHT)	Dilantin
Pregabalin (PGB)	Lyrica
Primidone (PRM)	Mysoline
Tiagabine (TGB)	Gabitril
Topiramate (TPM)	Topamax
Valproate (VPA)	Depakote
Vigabatrin (VGB)	Sabril
Zonisamide (ZNS)	Zonegran
Lacosamide (LCM)	Vimpat
Vigabatrin (VGB)	Sabril

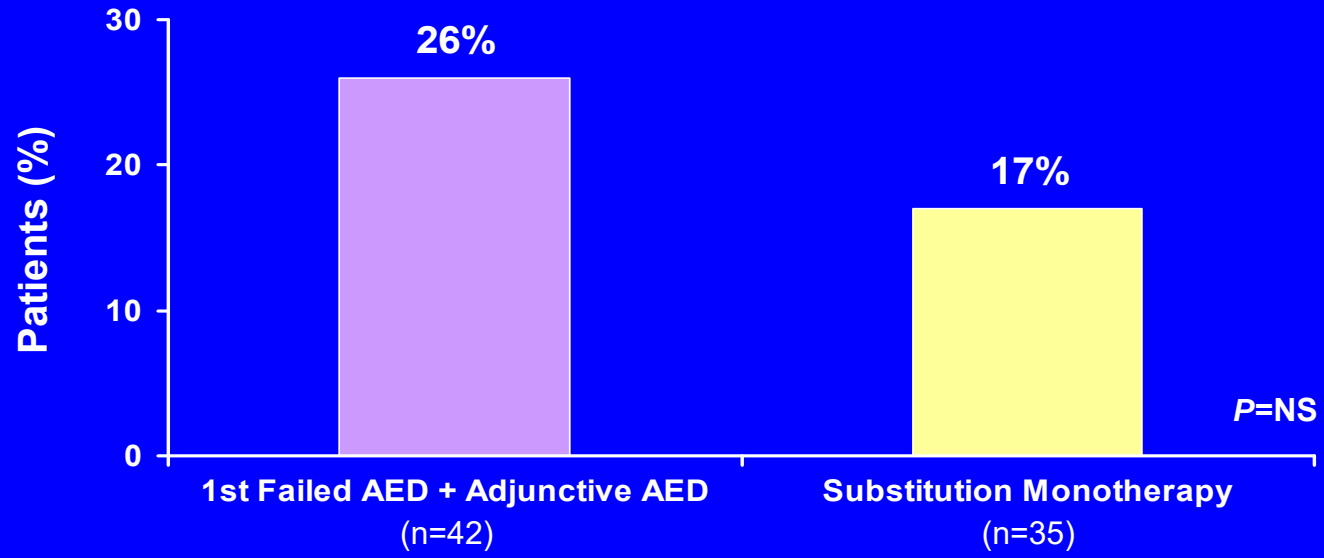
Success in AED regimens



Kwan and Brodie. *N Engl J Med*. 2000.

When Monotherapy Fails……

Seizure Freedom* with Adjunctive Therapy or Substitution Monotherapy in Patients with Inadequate Seizure Control on First Well-Tolerated AED



- Adjunctive AED therapy may be more effective when initiated immediately after failure of first AED vs after failure of second AED

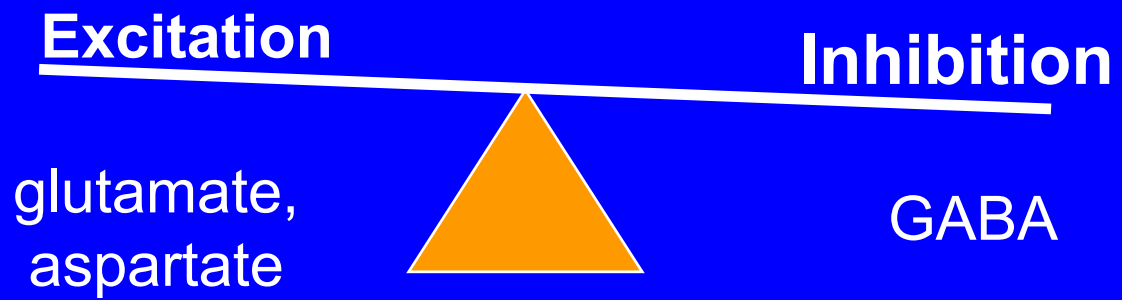
*Seizure freedom=no seizures of any type for ≥1 year.

Graph adapted from: Kwan P, et al. *Seizure*. 2000;9:464-468. Used with permission.

Mechanism of Action – Importance

- Understanding mechanisms of seizure generation leads to development of AEDs
- Understanding AED MOA leads to better understanding of mechanisms of seizure generation
- MOA understanding may help in appropriate AED selection
- MOA considered in combination therapy
- Adverse effects of AEDs may be dependent on MOA

Normal CNS Function

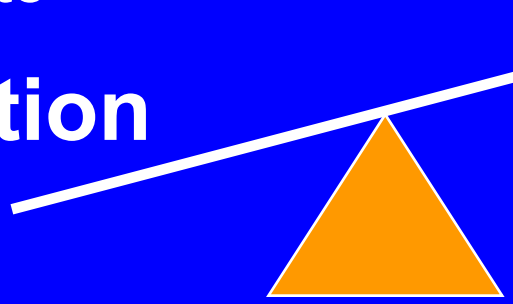


Abnormal Excitation

glutamate,
aspartate

Inhibition

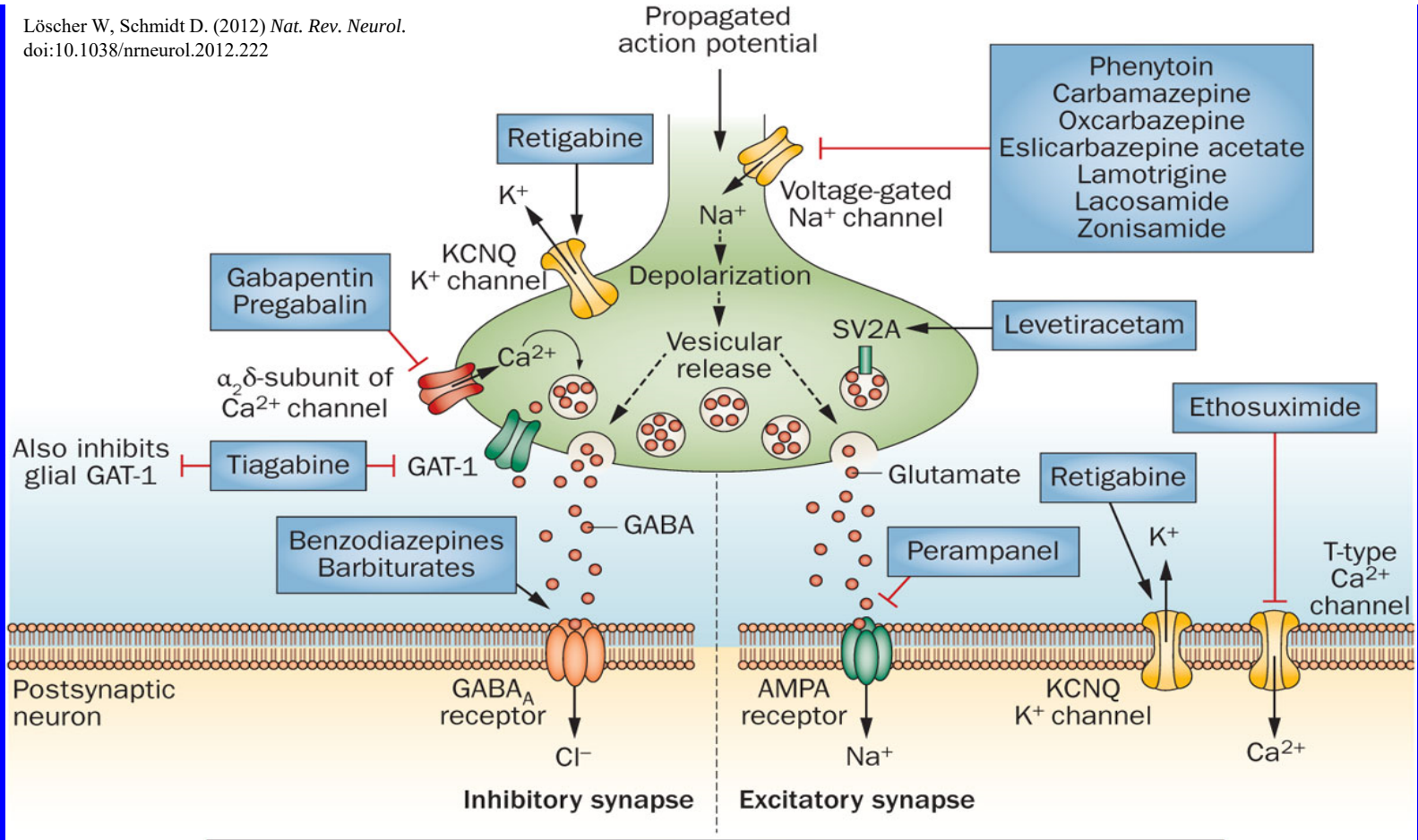
Excitation



GABA

Membrane depolarization leads to enhanced excitatory receptor function and reduced GABA receptor function. This pattern of 'voltage-dependence' leads to an even greater level of excitation

Löscher W, Schmidt D. (2012) *Nat. Rev. Neurol.*
doi:10.1038/nrneurol.2012.222



Not illustrated:

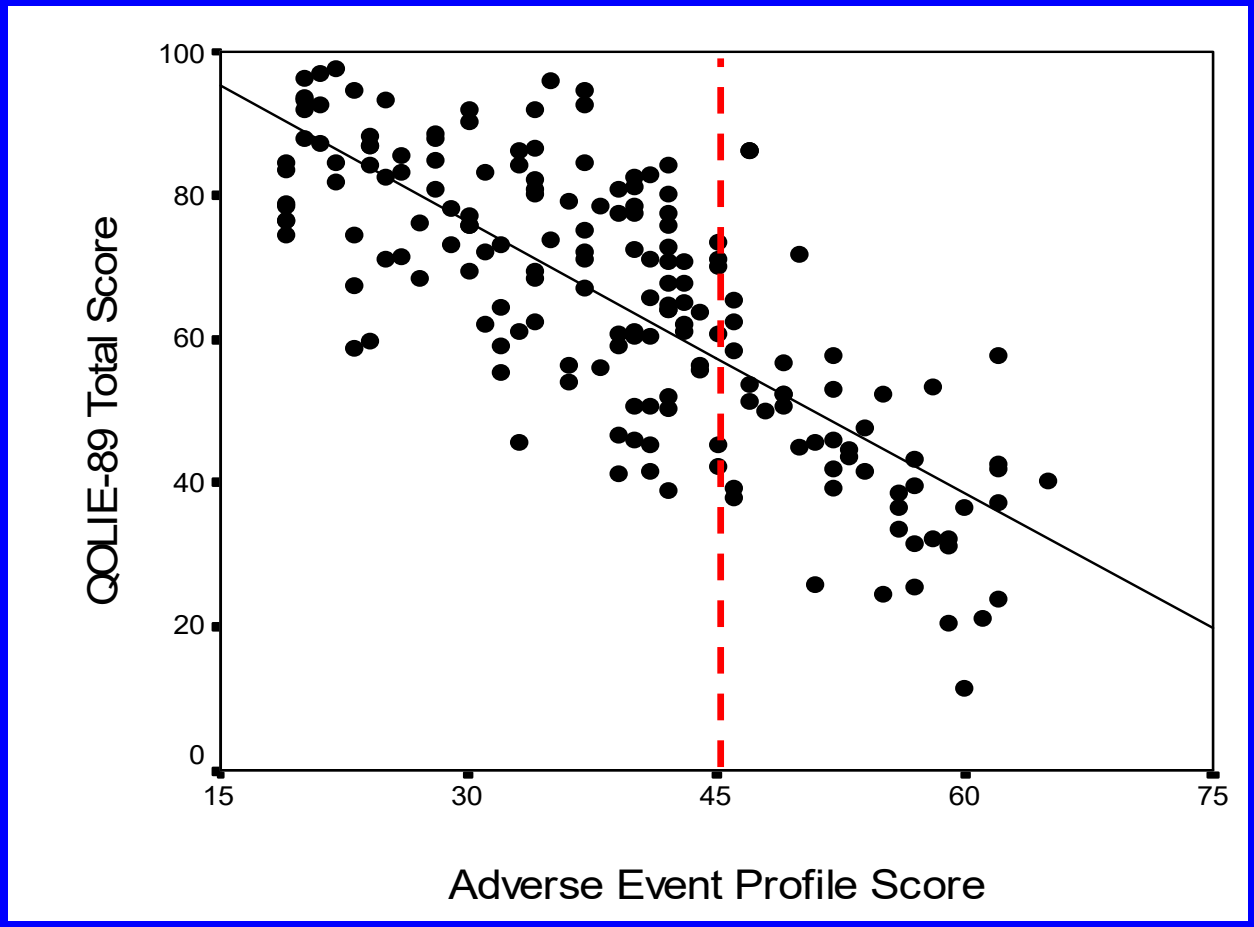
- Vigabatrin → ↓ GABA degradation

and drugs with multiple mechanisms:

- Valproate → ↑ GABA turnover, ↓ Na^+ channels, ↓ NMDA receptors
- Topiramate → ↓ Na^+ channels, ↓ AMPA/kainate receptors, ↑ $GABA_A$ receptors
- Felbamate → ↓ Na^+ channels, ↑ $GABA_A$ receptors, ↓ NMDA receptors

Adverse Effects:
When the Treatment is Perceived as Worse than the Disease

AED Toxicity and Quality of Life



(n=200, r = -0.78, p< 0.0001) Gilliam et al, *Neurology* 58 (suppl5): S9-19, 2002

VA Cooperative Trial I:

Reason for AED Failure

	CBZ	PB	PHT	PRM	All Patients
	N=101	N=101	N=110	N=109	N=421
Toxicity alone	12	19	18	36	85
Toxicity plus seizures	30	33	29	35	127
Seizures alone	3	4	1	3	11
Total Failures	45	56	48	74	233

Mattson et al, *NEJM*, 1985

Spectrum of Psychiatric Diagnoses in People with CNS Diseases with Focus on Epilepsy

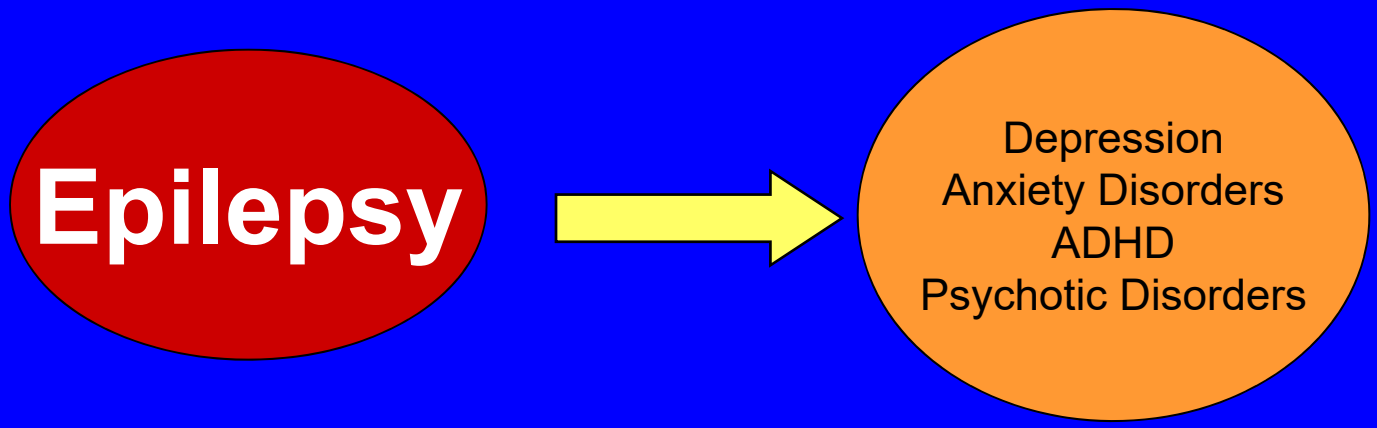
- Affective Disorders:
  - Depressive Disorders
  - Bipolar Affective Disorders (BAD)
- Psychotic Disorders
- Anxiety Disorders
- Personality Disorders
- Cognitive Disorders
- Delirium

Prevalence Rates of Psychiatric Disorders in Epilepsy

	In Epilepsy (Range)	In the General Population (Range)
Depression	11-60%	12-15%[1]
Anxiety	19-45%	2.5-6.5%[2]
Psychosis	2-8%	0.5-0.7%[3]
ADHD	25-30% ?	2-10%[4,5]

1. Anthony JC, et al. *Epidemiol Rev*. 1995;17(1):240-242.
2. Weissman MM, Merikangas KR. *J Clin Psychiatry*. 1986;47(suppl):11-17.
3. Kessler RC, et al. *Arch Gen Psychiatry*. 1994;51(1):8-19.
4. Costello EJ. *J Am Acad Child Adolesc Psychiatry*. 1989;28(6):836-841.
5. Rutter M. *J Child Psychol Psychiatry*. 1970;11(1):49-62.

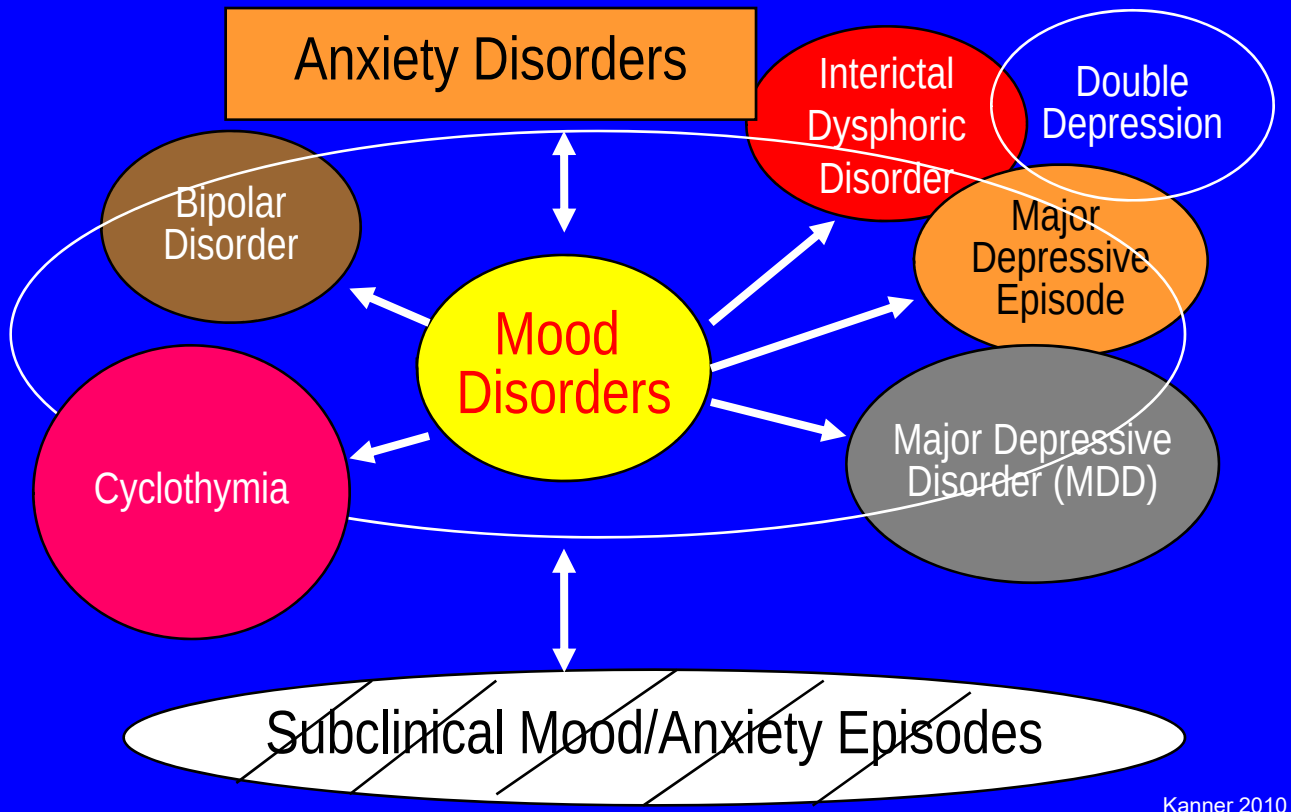
Long Held Assumptions…



Not A New Concept: Hippocrates' Writings

- "…*melancholics ordinarily become epileptics, and epileptics melancholics*: of these two states, what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy."

The "Pleomorphic" Expressions of Depression in Epilepsy



Kanner 2010

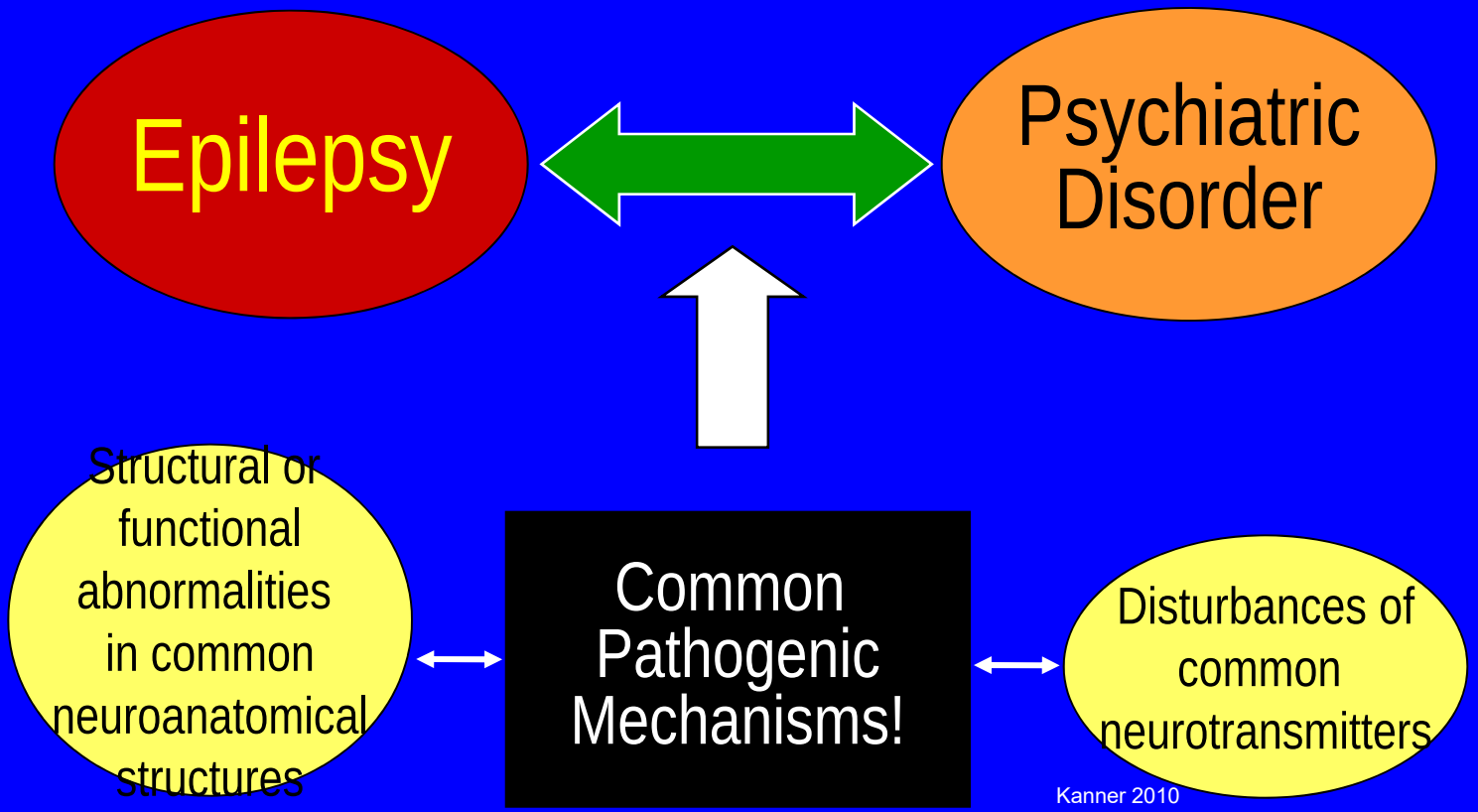
Postictal Symptoms of Depression

Postictal Symptom	Frequency (N=100)	Duration (Range, Hours)
Poor frustration	36	24 (0.5-108)
Anhedonia	33	24 (0.1-148)
Hopelessness	25	24 (1.0-108)
Helplessness	31	24 (1.0-108)
Crying bouts	26	6 (0.1-108)
Suicidal ideation	*13*	*24 (1.0-240)*
Irritability	30	24 (0.5-108)
Guilt	23	24 (0.1-240)
Self deprecation	27	24 (1.0-120)

Any postictal symptom of depression, n=43 patients
Median number of symptoms: 5 (range: 2-9)

Kanner AM, et al. Neurology. 2004;62(5):708-713.

These data possibly result from a bidirectional relation between depression and epilepsy



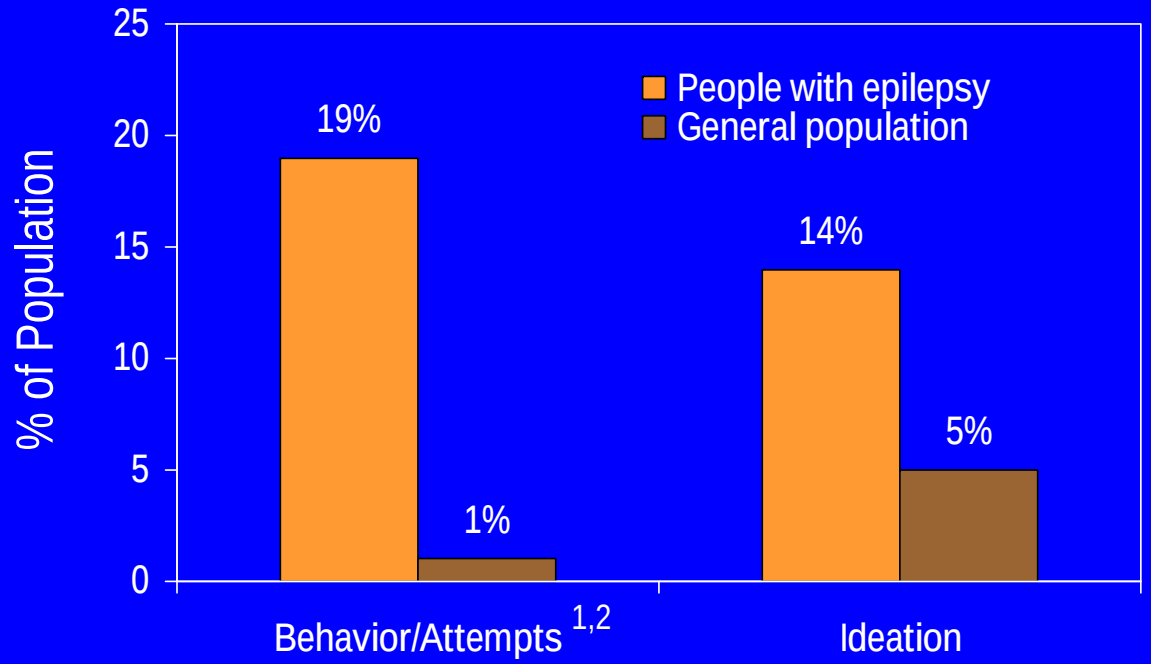
Kanner 2010

Epilepsy, Psychiatric Disorders and Suicide

	Rate Ratio	P value
No Epilepsy	1	
Epilepsy	2.4 (2.0-2.8)	<0.0001
Epilepsy +		<0.0001
Affective Disorder	32.0 (20.8-49.4)	<0.0001
Anxiety Disorder	11.4 (4.16-31.4)	<0.0001
Schizophrenia	12.5 (8.05-22.7)	<0.0001

Christensen et al. Lancet Neurology 6: 693–98, 2007

Risk of Suicidal Ideation and Attempt in People with Epilepsy



1. Boylan LS, et al. *Neurology.* 2004;62(2):258-261.
2. Jones JE, et al. *Epilepsy Behav.* 2003;4(suppl 3):S31-S38.

What about AEDs and Suicidality?

FDA Alert of suicidality associated with AEDs:

- **80% *increased* risk for suicidality for AED vs placebo (OR=1.80; 95% CI=1.24-2.66)**
- **2.1 more suicidality events per 1,000 people exposed to AEDs (95% CI=0.7-4.2)**
  - **4.3/1,000 in the drug treated group**
  - **2.2/1,000 in the placebo group**
- **"The increased risk of suicidality was:**
  - **Generally consistent for the 11 AEDs**
  - **Consistently increased risk across indications"**

Epilepsy & Reproductive Health a Consensus Statement

1. Reproductive endocrine disorders common among women with epilepsy and probably contribute to decreased fertility
2. Should be screened regularly for menstrual disorder, infertility, obesity, hirsutism and galactorrhea
3. May require further endocrine testing
4. Reproductive endocrine disorder should be considered in terms of etiology and potential contributory factors, including epilepsy and AEDs (in particular valproic acid)
5. Potential benefits of a change of AEDs must be balanced against seizure control and the side effects of alternative

Bauer et al J Neurol Neurosurg Psychiat 2002;73:121-12

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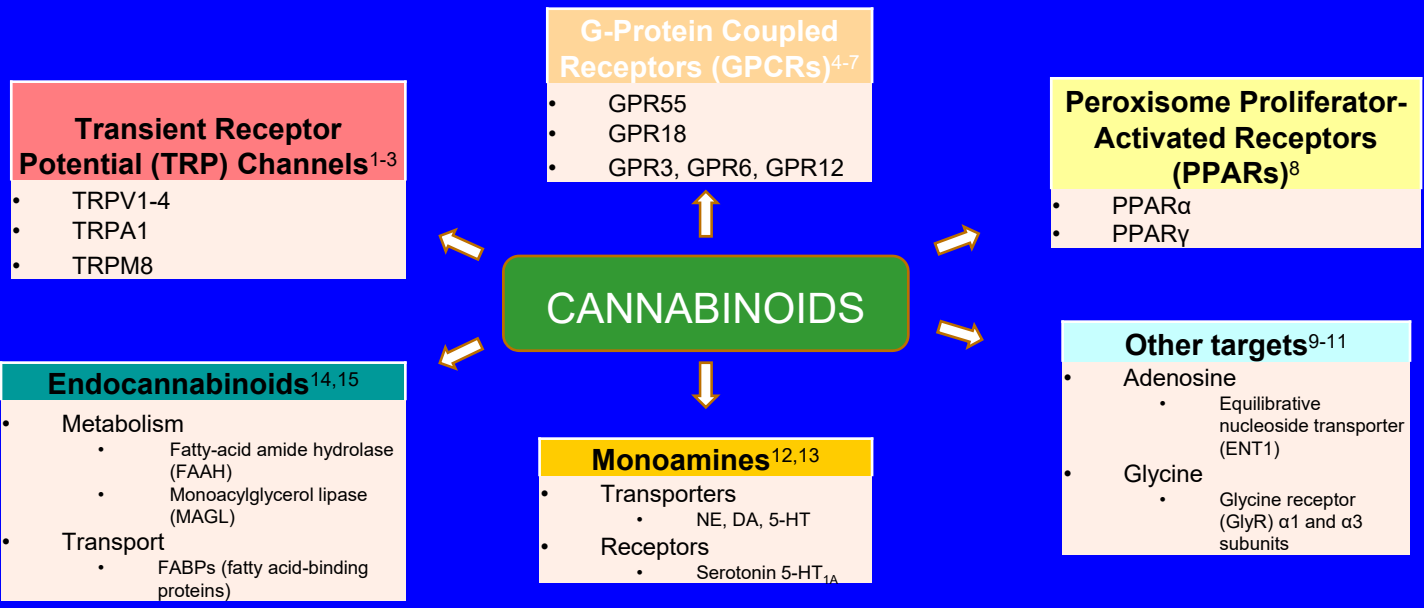
Pregnancy and Epilepsy

- 96% of pregnancies in mothers with epilepsy produce normal children
- Spontaneous abortions and pre-term birth are more common in women with epilepsy
- There is an increased rate of fetal malformations associated with antiepileptic drug exposure
- Seizures during pregnancy may be harmful
  - Tonic-clonic seizures associated with intracranial hemorrhage, fetal bradycardia and lower IQ in children
  - Status associated with increased fetal and maternal mortality in some studies
  - Insufficient data on non-convulsive seizures

Harden CL et al. Neurology. 2009 Jul 14;73(2):133-41. [PubMed]

Cannabinoid Targets Beyond CB_1 and CB_2



1. Iannotti FA et al. *ACS Chem Neurosci.* 2014; 5, 1131-1141. 2. De Petrocellis L et al. *Br J Pharmacol.* 2011; 163(7):1479-94. 3. De Petrocellis L et al. *Acta Physiol.* 2012; 204(2):255-66. 4. Sylantyev S et al. Proc Natl Acad Sci USA. 2013; 110, 5193-5198. 5. McHugh D et al. BMC Neurosci. 2010; 11:44. 6. Laun AS et al. Biochem Biophys Res Commun. 2017; 490(1):17-21. 7. Brown KJ et al. Biochem Biophys Res Commun. 2017; 493(1):451-454. 8. O'Sullivan SE. Br J Pharmacol. 2016; 173(12):1899-910. 9. Hejazi N et al. Mol. Pharmacol. 2006; 69:991–997. 10. Xiong W et al. J Exp Med. 2012; 209(6):1121-34. 11. Liou GI et al. Invest Ophthalmol Vis Sci. 2008; 49 (12):5526-31. 12. Banerjee SP et al. J Pharmacol Exp Ther, 1975; 194 (1) 74-81. 13. Russo EB et al. Neurochem Res. 2005; 30(8):1037–1043. 14. Longa JZ et al. Proc Natl Acad Sci USA. 2009; 106(48):20270-5. 15. Elmes MW et al. J Biol Chem; 2015 290(14):8711-21