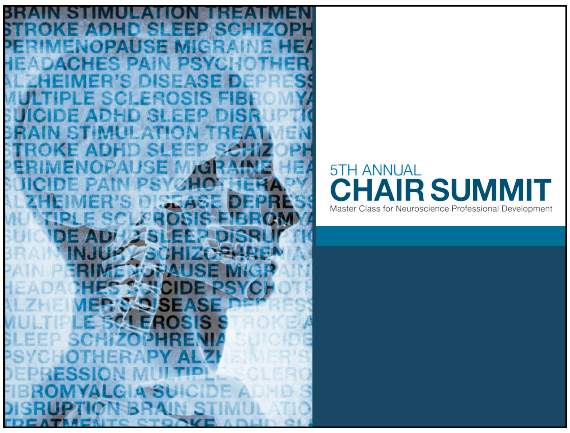

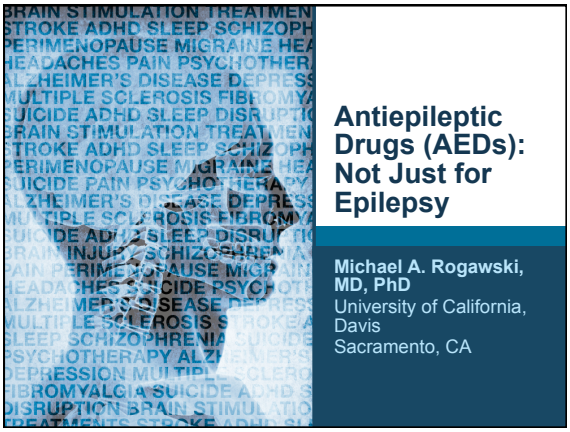

Michael A. Rogawski, MD, PhD

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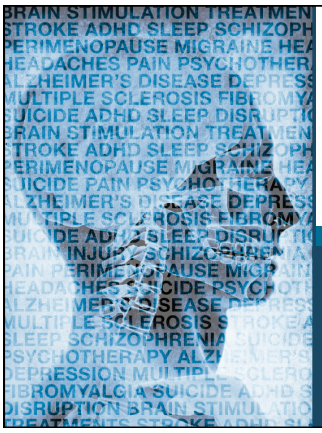
- ***Consultant:*** Eli Lilly and Company; ONO Pharma USA, Inc.; Sepracor, Inc.; SK Life Science, Inc.; Upsher-Smith Laboratories, Inc.



Learning Objective

Identify the mechanisms responsible for the efficacy of antiepileptic drugs in non-epileptic conditions

Antiepileptic Drugs (AEDs)

FDA-Approved Agents

- Chronic treatment of epilepsy (26 agents):
  - acetazolamide, carbamazepine, clobazam, clonazepam, clorazepate, ethosuximide, ethotoin, ezogabine/retigabine, felbamate, gabapentin, lamotrigine, lacosamide, levetiracetam, mephenytoin, methsuximide, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, trimethadione, valproate, vigabatrin, zonisamide
- Acute therapy of status epilepticus (5 agents):
  - diazepam, fosphenytoin, lorazepam, midazolam, propofol

Prescribing information available from Drugs@FDA.gov.

Antiepileptic Drugs

In Late-Stage Development in the U.S.

- Eslicarbazepine acetate*¥
- Brivaracetam*
- Ganaxolone*
- Perampanel*§
- BGG 492*

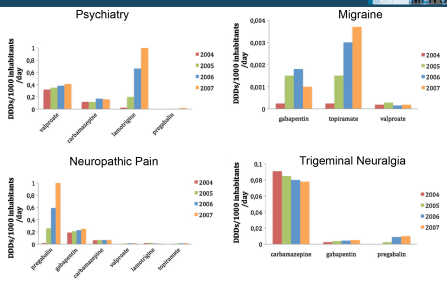
Investigational agent; not FDA-approved

¥ Approved by the European Medicines Agency in April 2000

§ Approved by the European Medicines Agency in July 2012

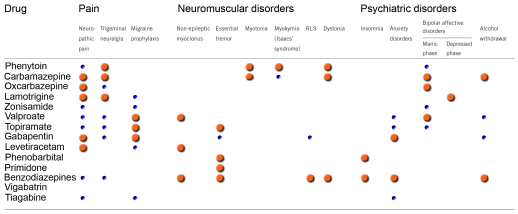
Prescription Patterns of AEDs in Patients With Epilepsy

Norwegian Prescription Database



Landmark CJ, et al. *Epilepsy Res*. 2011;95(1-2):51-59. PMID: 21435840.

AEDs for the Treatment of Non-Epileptic Conditions



Rogawski MA, Loscher W. *Nat Med*. 2004;10(7):685-692. PMID: 15229516.

Phenytoin
partial, GTC

Carbamazepine
Oxcarbazepine
partial, GTC, bipolar mania*

Felbamate
partial
Lennox-Gastaut

Zonisamide
partial, GTC
myoclonus,* absence, infantile spasms,* Lennox-Gastaut

Lamotrigine
partial, GTC
absence*, myoclonus*
Lennox-Gastaut
bipolar disorder*

Valproate
partial, GTC
myoclonus, absence, migraine, bipolar mania

Topiramate
partial, GTC
myoclonus,* absence,* migraine, tremor*

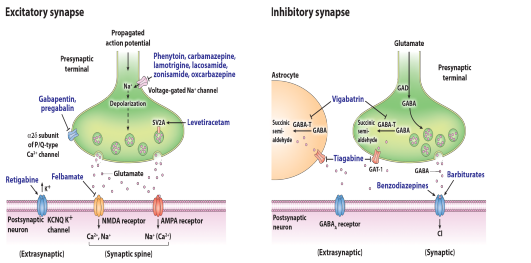
Gabapentin
partial, GTC, neuropathic pain, anxiety*, migraine*

Levetiracetam
partial, myoclonus*, absence*

* Off label use
GTC = generalized tonic clonic; Partial = partial-onset seizures

Levy RJ, et al. Antiepileptic Drugs. 5th ed. 2002.

Mechanisms of Action for Common AEDs



Levy RJ, et al. *Antiepileptic Drugs*. 5th ed. 2002.

AEDs Are Effective in Bipolar Disorder

Drug	Efficacy in Bipolar Disorder		Putative Mechanism
	Manic Phase	Depressive Phase	
Carbamazepine*	○		Na^+ channel
Oxcarbazepine*	○		Na^+ channel
Valproate	○		↑↑ GABA turnover, Na^+ channel
Lamotrigine		○	Na^+ channel, Ca^{2+} channel

* Not FDA-approved for the treatment of bipolar disorder.
GABA = gamma-aminobutyric acid

Rogawski MA, Loscher W. *Nat Med*. 2004;10(7):685-692. PMID: 15229516.

AEDs Are Effective in Bipolar Disorder (cont'd)

Drug	Efficacy in Bipolar Disorder		Putative Mechanism
	Manic Phase	Depressive Phase	
Phenytoin*	○		Na^+ channel
Zonisamide*	○		Na^+ channel
Levetiracetam*	○		SV2A, Ca^{2+} channel
Gabapentin*	Not effective (adjunct anxiety)		α2δ Ca^{2+} channel

* Not FDA-approved for the treatment of bipolar disorder.
SVA2 = synaptic vesicle glycoprotein 2A

Rogawski MA, Loscher W. *Nat Med*. 2004;10(7):685-692. PMID: 15229516.

Pipeline Drugs With Promise: Bipolar Disorder

- Valnoctamide
  - Available in France, Holland, Switzerland, and Italy from 1964 to as recently as 2005
  - Active in mouse models of bipolar disorder[1]
  - 2010 study by Bersudsky and colleagues[2]
    - Add-on to risperidone (beginning with 2 mg/day)
    - Five weeks valnoctamide
    - Results suggest valnoctamide could be substitute for valproate as mood stabilizer
- Retigabine
  - 2010 study by Dencker and Husum[3]
    - Active in mouse model of bipolar disorder

1. Kristensen LV. *J Neurochem*. 2012;121(3):373-382. PMID: 22356228.
2. Bersudsky Y, et al. *Bipolar Disord*. 2010;12(4):376-382. PMID: 20636634.
3. Dencker D, et al. *Behav Brain Res*. 2010;207(1):78-83. PMID: 19815032.

Molecular Targets of AEDs

Na^+ Channels
- Phenytoin 1938
- Carbamazepine 1974
- Lamotrigine 1994
- Fosphenytoin 1996
- Oxcarbazepine 2000
- Eslicarbazepine lacetate

Na^+ Channel Slow Inactivation
- Lacosamide 2008

$GABA_A$ Receptors
- Phenobarbital 1912
- Primidone 1954
- Clonazepam 1975

GABA Transporter
- Tiagabine 2007

GABA Transaminase
- Vigabatrin 2009

Ca^{2+} Channels
- Ethosuximide 1960

Years denote timing of FDA approval.
Drugs@FDA.gov.

Molecular Targets of AEDs

- $\alpha 2\delta$
  - Gabapentin 1993
  - Pregabalin 2004
- SVA2
  - Levetiracetam 1999
  - Brivaracetam* ----
- *KCNQ* K+ Channel
  - Retigabine* -----
- Mixed
  - Valproate 1978
  - Felbamate 1993
  - Topiramate 1996
  - Zonisamide 2000
  - Rufinamide 2009

* Investigational agent; not FDA-approved.
Years denote timing of FDA approval.
Drugs@FDA.gov.

Episodic Disorders Represent a Unique Type of Medical Syndrome

- Symptoms: cardiac arrhythmia, myotonia, periodic paralysis, seizure, migraine headache
- Dramatic events occur paroxysmally, often in otherwise normal individuals
- Often nonprogressive; full recovery between attacks
- Often have inciting factor, but may not be obvious
- Even neuropathic pain can be considered episodic: innocuous stimulation in allodynia triggers pain
- ? Depression, bipolar disorder

Episodic Disorders Are Commonly Channelopathies

- Cardiac muscle
  - Long QT syndrome: K+, Na+
- Skeletal muscle
  - Hyperkalemic periodic paralysis, paramyotonia congenita, potassium-aggravated myotonia, myotonia congenita, hypokalemic periodic paralysis: Na+, Cl-, Ca^{2+}
- Cerebellum/neuromuscular junction
  - Episodic ataxia, type 1 and myokymia: K+
  - Episodic ataxia, type 2/Familial hemiplegic migraine/ Spinocerebellar ataxia type 6: Ca^{2+}

Rose MR. *Brit Med J.* 1998;316(7138):1104-1105. PMID: 9552942.

Episodic Disorders Are Commonly Channelopathies

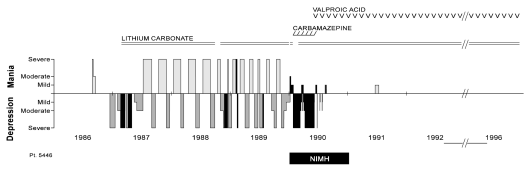
- Spinal cord
  - Hyperekplexia: glycine receptor
- Brain/cranium
  - Familial hemiplegic migraine, type 1/episodic ataxia, type 2: Ca^{2+}
- Dorsal root ganglion/spinal cord
  - Neuropathic pain: acquired Na^{+}/Ca^{2+}
- [? Brain region ?]
  - Depression, bipolar disorder (?channel?)

Rose MR. *Brit Med J.* 1998;316(7138):1104-1105. PMID: 9552942.

Bipolar Disorder. . .

- Has characteristics of an episodic disorder
- Antiepileptic drugs are often effective

Life Chart Showing Continuous Cycling in a Woman With Bipolar I Disorder



Post RM, et al. *Neuropsychobiology*. 1998;38(3):152-166. PMID: 9778604.

Clinical Connections

- Anti-manic effect of antiepileptic drugs resides in their ability to selectively inhibit synaptic transmission, especially with high frequency firing (Na^+ channels, SV2A)
- Antidepressant effect of antiepileptic drugs must represent a distinct action
  - 5-hydroxytryptamine (5-HT) reuptake (unlikely)
  - Inhibition of GABA release
  - Selective block of high-voltage activation of Ca^{2+} channels (?)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