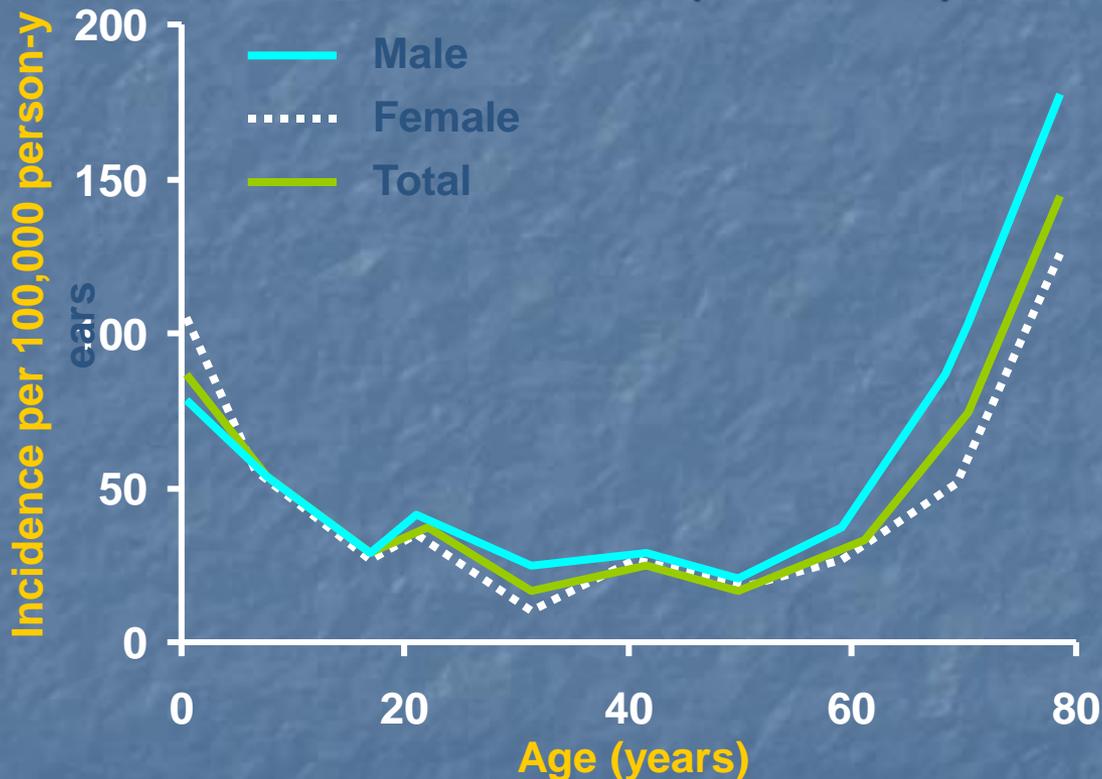


Emerging Trends in Epilepsy Medications: Choosing the Most Appropriate AED

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Incidence and Prevalence of Epilepsy in the United States

**Community incidence¹:
Rochester, Minn (1935–1984)**



- Epilepsy affects more than 3 million people²
- 200,000 new cases of epilepsy diagnosed annually²

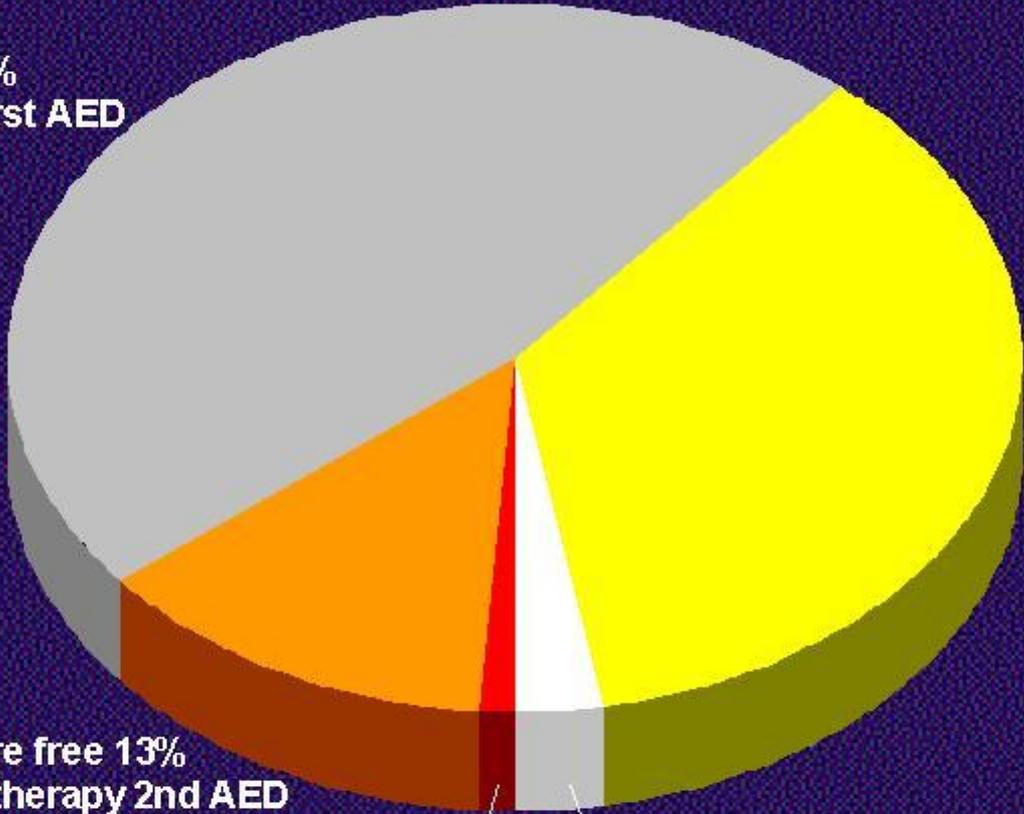
1. Hauser WA et al. *Epilepsia*. 1993;34:453–468. Adapted with permission of *Epilepsia*.

2. Epilepsy Foundation. Epilepsy Fact Sheet. <http://www.epilepsyfoundation.org/about/factsfigures.cfm>. Accessed June 2, 2009.

Choosing an Antiepileptic Drug (AED)

- Seizure type
- Epilepsy syndrome
- Pharmacokinetics
 - Drug interactions
 - formulation
- Concomitant medical/psychiatric conditions
- Adverse effects
- Cost

Success in AED regimens



Seizure free 47%
Monotherapy first AED

Not seizure free 36%
All regimens attempted

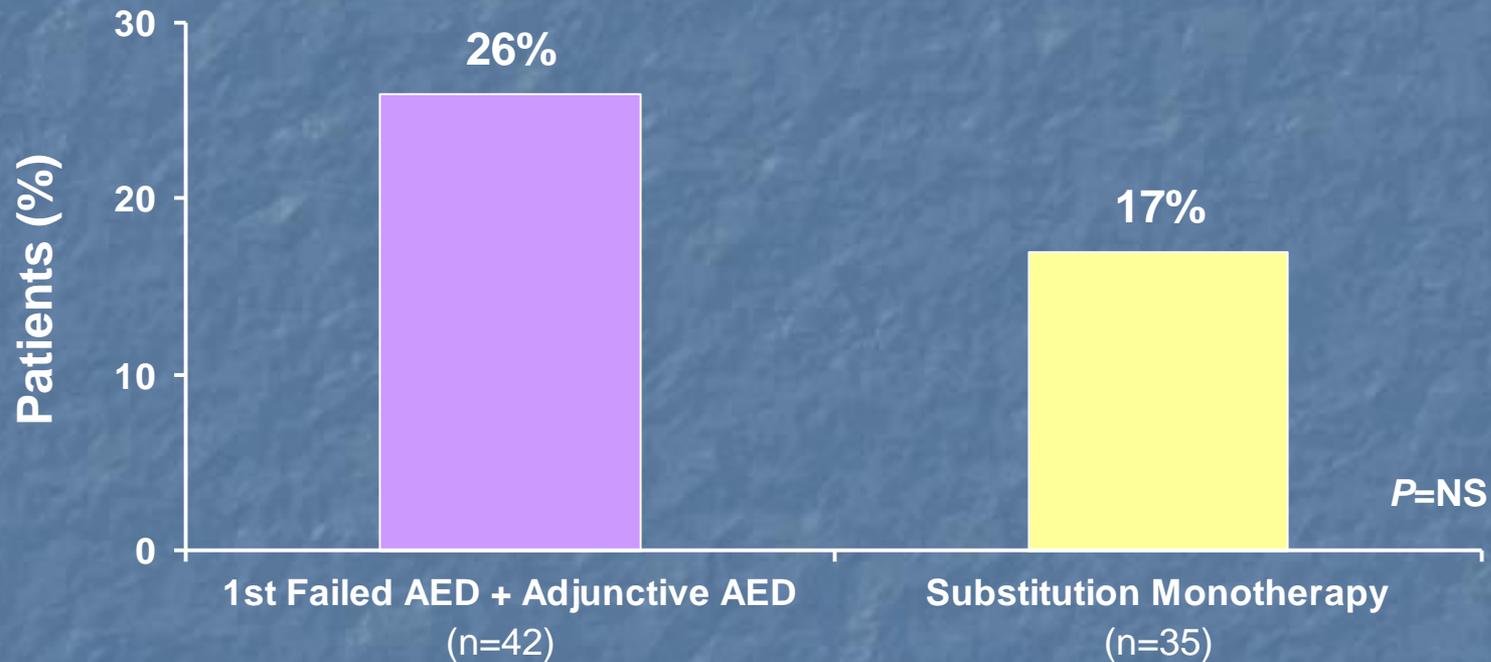
Seizure free 13%
Monotherapy 2nd AED

Seizure free 1%
Monotherapy 3rd AED

Seizure free 3%
Polytherapy

When Monotherapy Fails.....

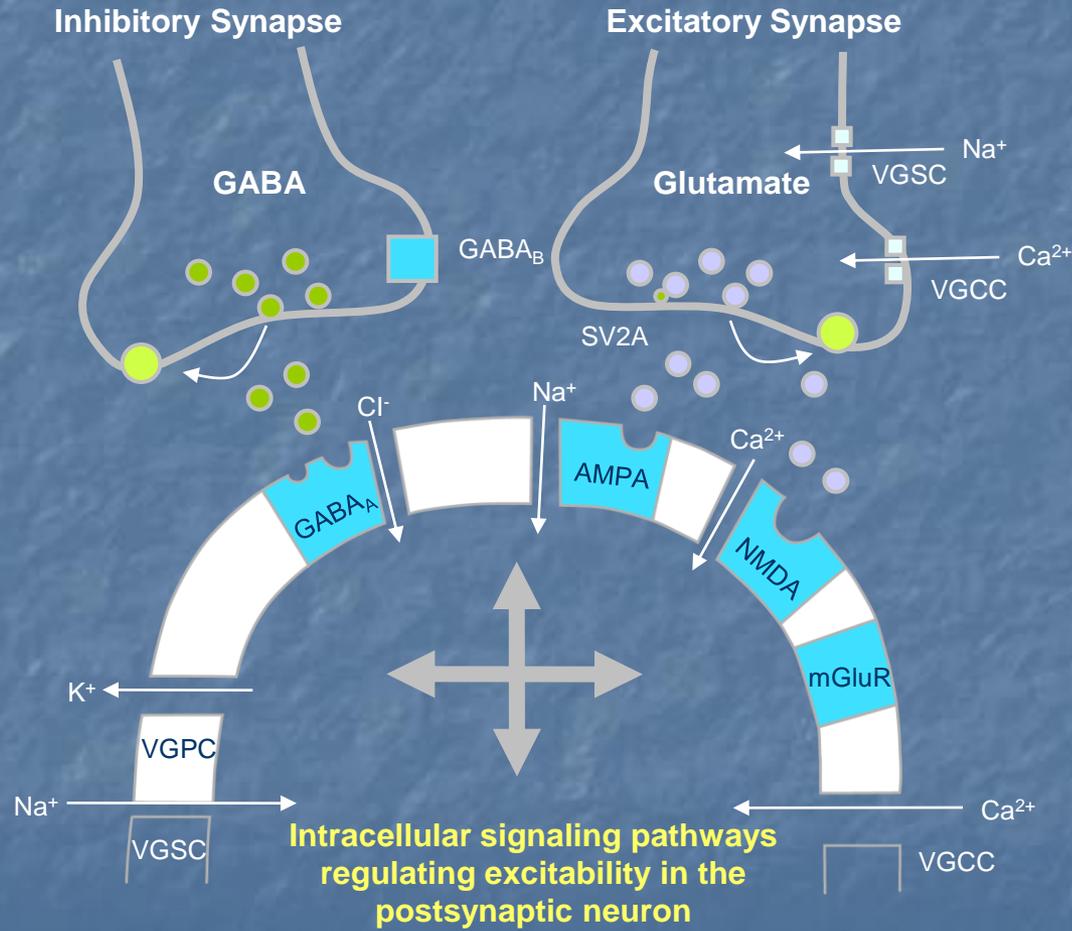
Seizure Freedom with Adjunctive Therapy or Substitution Monotherapy in Patients with Inadequate Seizure Control on First Well-Tolerated AED



Factors Governing Neuronal Excitability

- Enhanced excitation (e.g., glutamate)
- Na^+ and Ca^{2+} -mediated currents (APs, PDS)
- Reduced inhibition (e.g., GABA)
- K^+ currents (membrane hyperpolarization)
- Changes in extracellular ionic fields ($\uparrow\text{K}^+$, $\downarrow\text{Ca}^{2+}$, change in extracellular space, etc.)
- Changes in pH (acidosis/alkalosis)

AED Mechanisms of Action

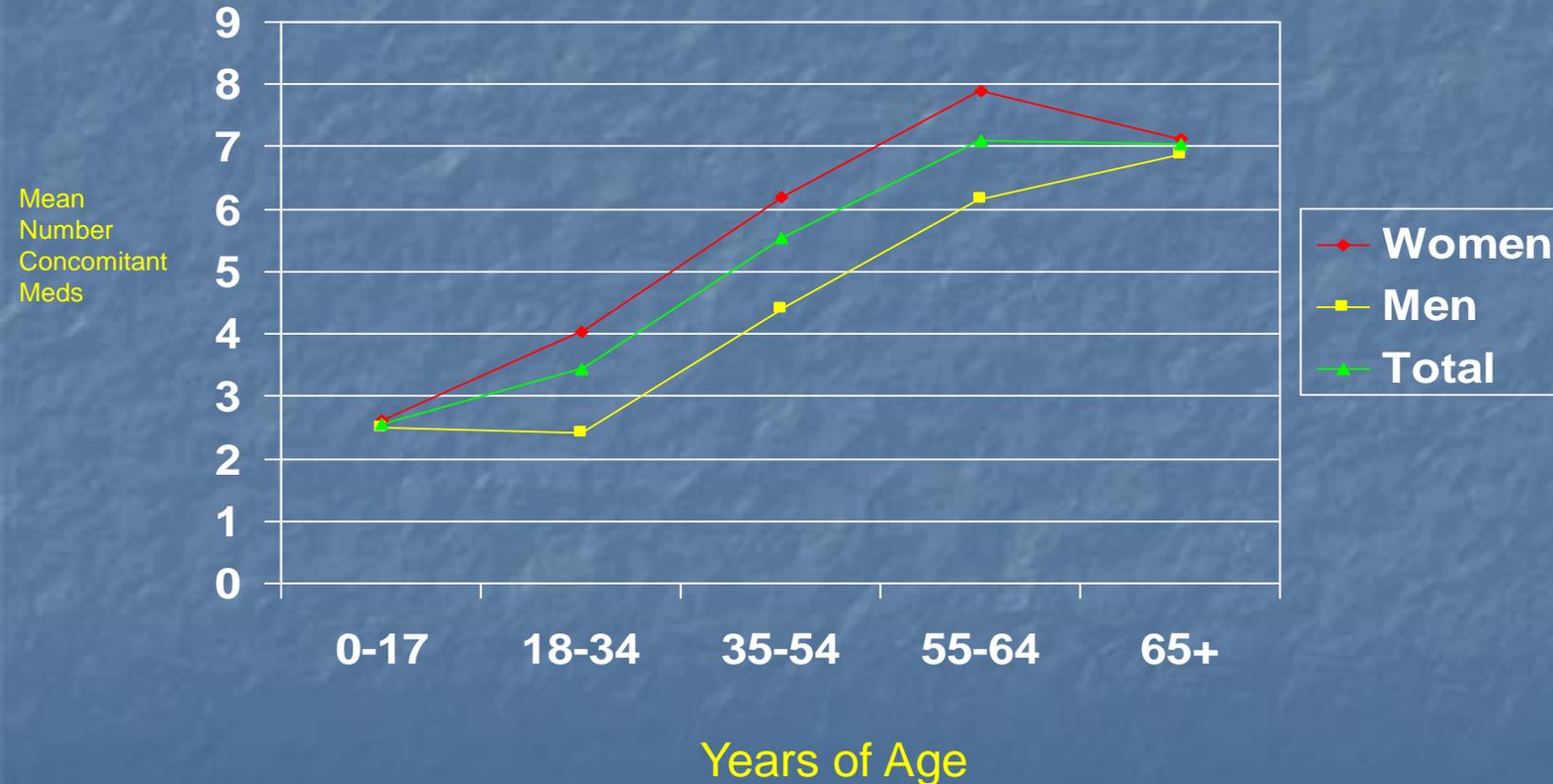


VGSC=voltage-gated sodium channel; SV2A=synaptic vesicle protein; VGCC=voltage-gated calcium channel; VGPC=voltage-gated potassium channel; AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA=N-methyl-D-aspartate receptor; mGluR=metabotropic glutamate receptor.

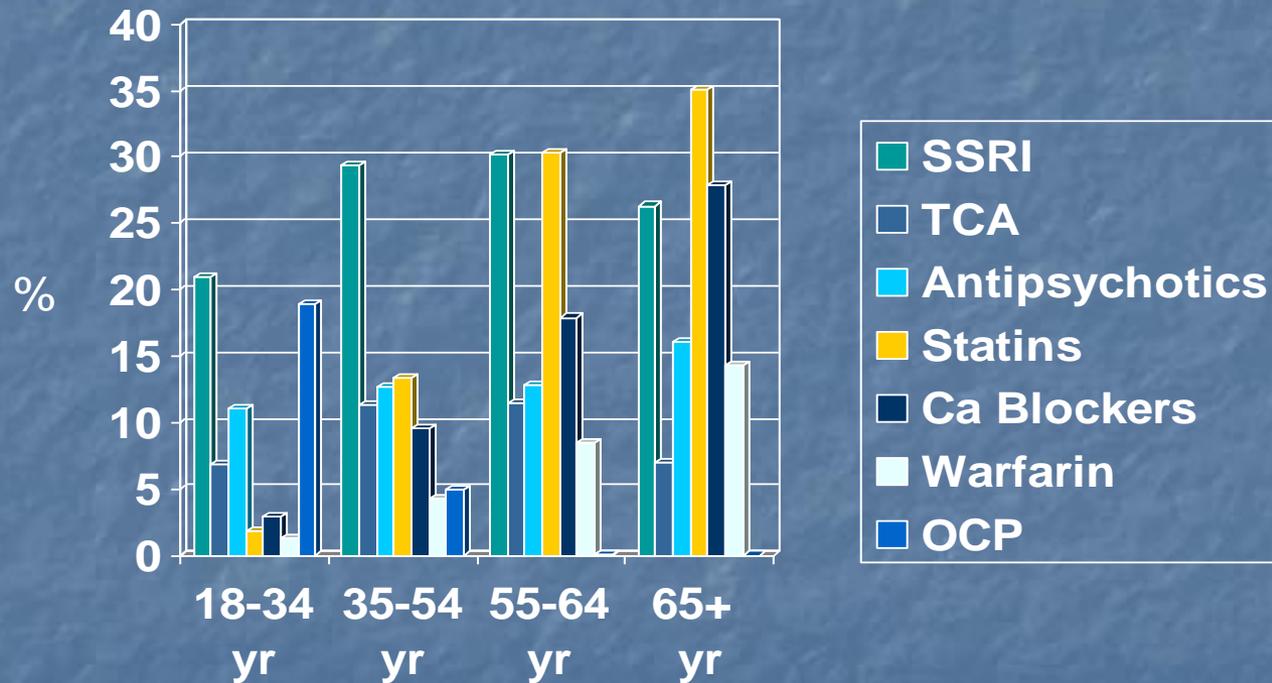
Comorbid Disorders in Older Veterans with Epilepsy

■ Dyslipidemia	80%
■ Hypertension	53.8%
■ Stroke	52.7%
■ Cardiac disease	48.1%
■ Diabetes	28.3%
■ Cancer	23.8%
■ Psychiatric disease	21.6%
■ Renal disease	12.3%
■ Liver disease	2.7%
■ Parkinson's disease	2.7%

Polypharmacy in Patients with Epilepsy: Age & Gender Effects

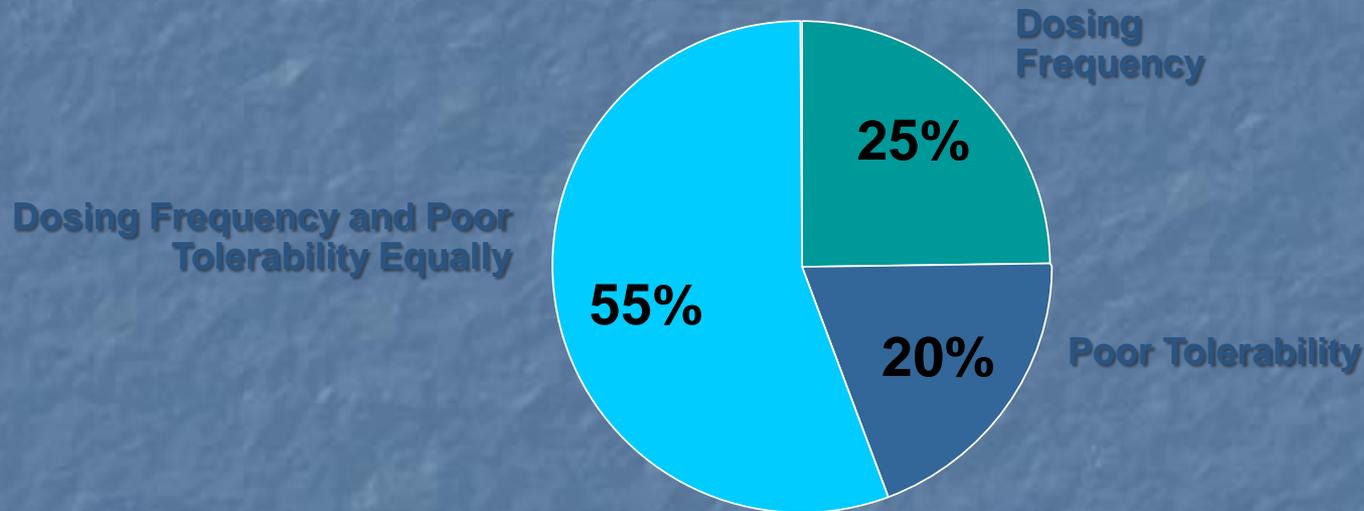


Concomitant Medication use by Age

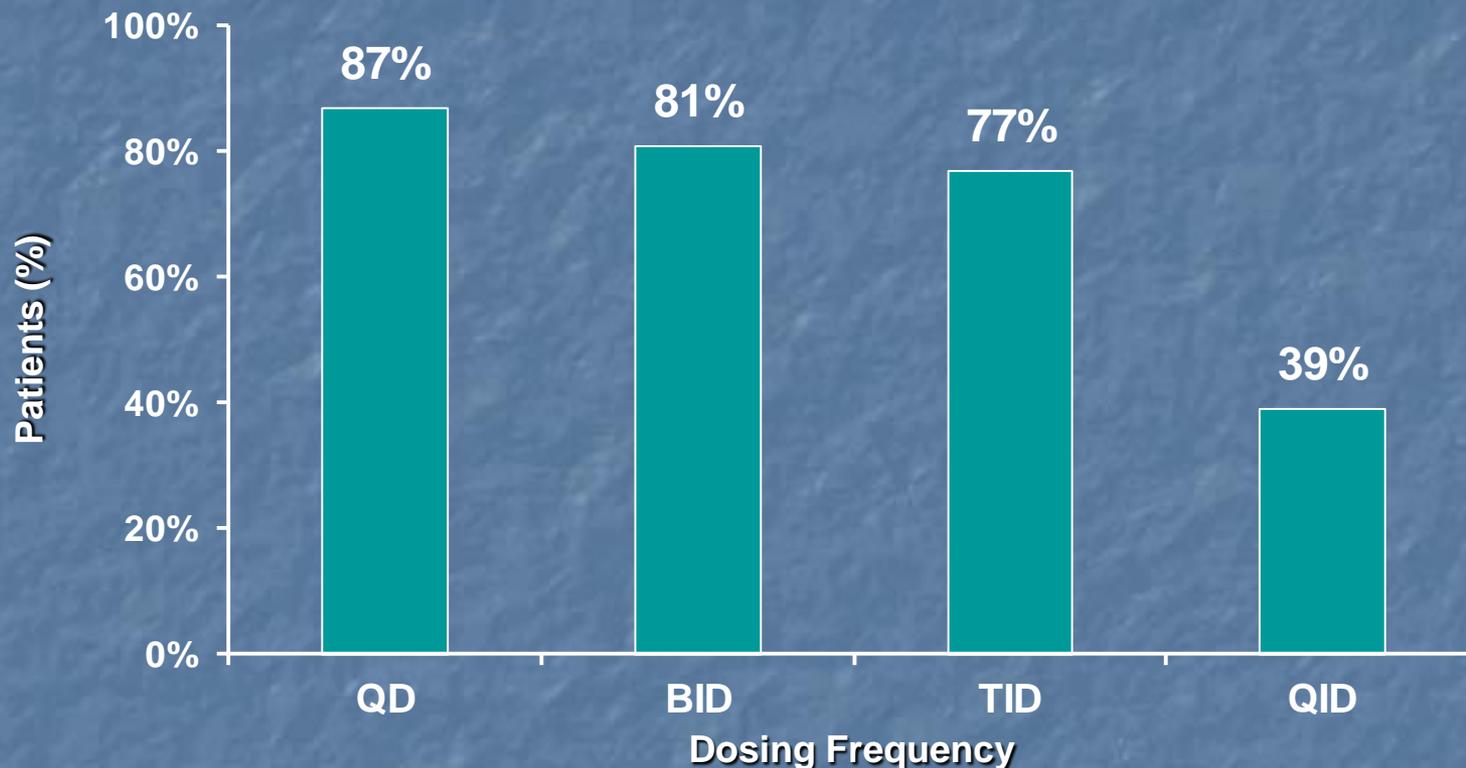


Favorable Tolerability and Convenient Dosing Are Essential for Compliance

Leading Cause of Noncompliance in Epilepsy Patients (n=102)



Less Frequent Dosing Encourages Compliance



- Noncompliance with AEDs is a major factor in breakthrough seizures and recurrence of seizures
- Higher compliance rates are associated with QD dosing

N = 24 patients followed for 2 to 37 weeks.

1. Adapted from Cramer JA, et al. *JAMA*. 1989;261:3273-3277. Used with permission. 2. Montouris GD, et al. *Curr Med Res Opin*. 2007;23:1583-1592.

Dosing Frequency & Medication Adherence in Chronic Disease

TABLE 3 Traditional Meta-Analysis of Dosing Frequency Analyses of Taking, Regimen, and Timing Adherence^a

Frequency of Dosing	N (%) Groups [N of Patients] in Taking Adherence Analysis	Taking Adherence ^b (95% CI)	N (%) Groups [N of Patients] in Regimen Adherence Analysis	Regimen Adherence ^c (95% CI)	N (%) Groups [N of Patients] in Timing Adherence Analysis	Timing Adherence ^d (95% CI)
Once daily	33 (50.8) [n=2,006]	93.0 (91.2-94.7)	35 (46.1) [n=2,118]	81.8 (77.9-85.7)	20 (42.6) [n=936]	76.9 (72.5-81.3)
Twice daily	22 (33.8) [n=1,259]	85.6 (82.5-88.8)	24 (31.6) [n=826]	74.2 (70.0-78.5)	16 (34.0) [n=650]	59.3 (40.6-58.0)
Three times daily	9 (13.8) [n=362]	80.1 (72.0-88.2)	13 (17.1) [n=321]	62.8 (55.4-70.1)	8 (17.0) [n=343]	35.9 (21.8-50.1)
Four times daily	1 (1.5) [n=57]	84.4 (78.5-90.3)	4 (5.3) [n=86]	68.2 (48.9-87.4)	3 (6.4) [n=109]	18.8 (10.1-27.5)

AED Nonadherence Is Associated with Serious Clinical Events and Increased Medical Costs

Nonadherent (32,365 patient-yr) Adherent (91,678 patient-yr)

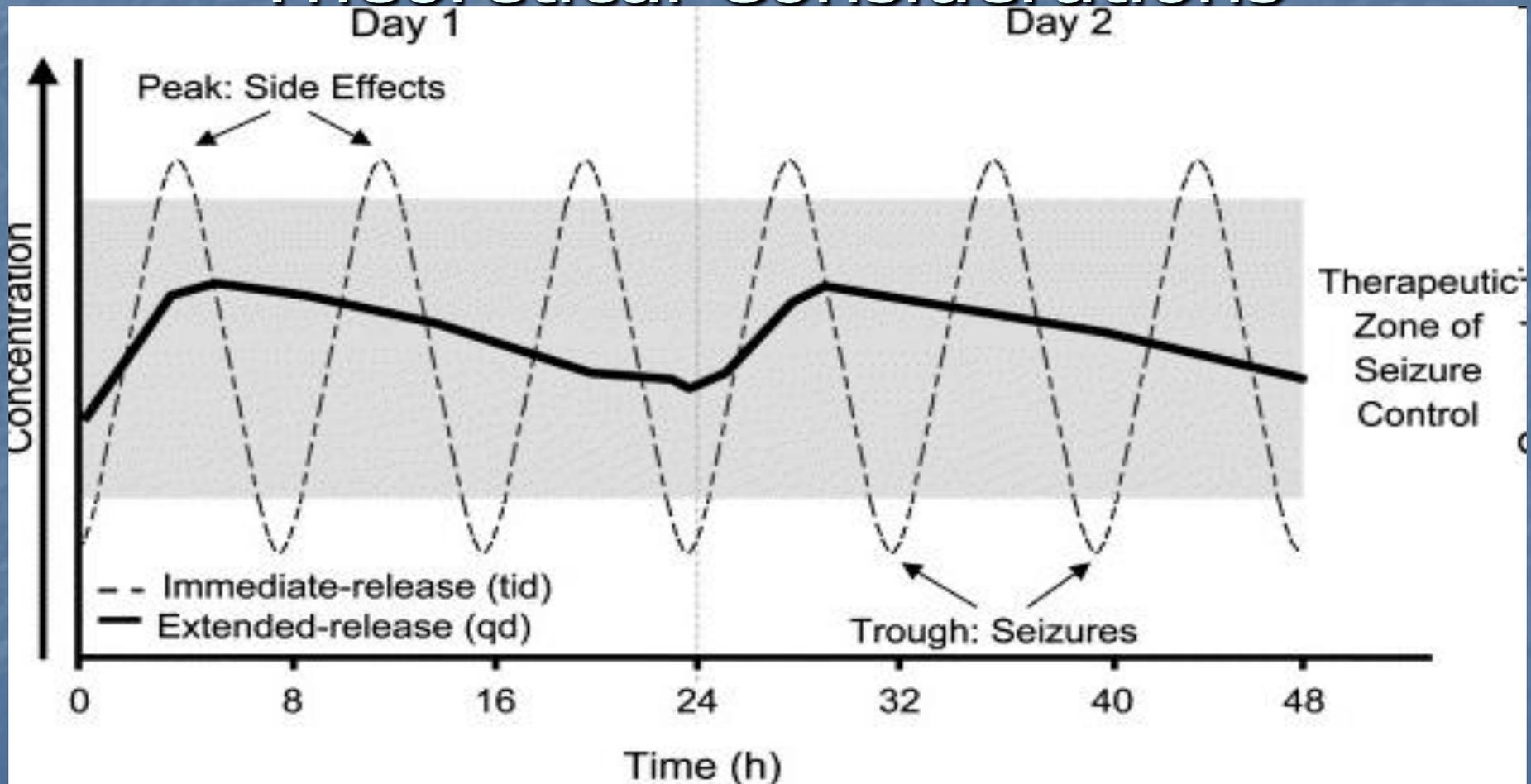
Event ¹	Incidence Rate	Incidence Rate	Ratio of Nonadherence to Adherence (95% CI)
ED visits	1.48	0.99	1.50 (1.49-1.52)
Hospitalization	1.34	0.72	1.86 (1.84-1.88)
MVA injuries	0.011	0.005	2.08 (1.81-2.39)
Fractures	0.54	0.45	1.21 (1.18-1.23)
Head injuries	0.37	0.50	0.73 (0.72-0.75)

Compared with adherent behavior, nonadherence is associated with:

- Threefold increased risk of death (HR, 3.32; 95% CI, 3.11-3.54; $P < 0.001$)¹
- Annual increase of over \$2000 per patient in emergency department and inpatient costs ($P = 0.001$)²

ER vs IR

Theoretical Considerations



New AED Options

Ezogabine: Overview

- International non-proprietary name is retigabine
- FDA requested US non-proprietary name changed to ezogabine due to similarity to another product
 - Brand name filed with FDA is Potiga™ (Trobalt™ rest of world)
- Co-development between Valeant and GSK
- Submitted to FDA and EMA in October, 2009 for partial onset seizures
 - EMA granted approval on March 28, 2011 as adjunctive therapy for POS in adults aged 18 and older with epilepsy
 - GSK and Valeant submitted response to FDA “complete response letter” on April 15, 2011
- Extended release formulation is in development

Ezogabine: Mechanism of Action

■ First-in-class MOA:

- Ezogabine acts primarily through opening of neural voltage-gated potassium channels KCNQ2 and KCNQ3 (aka Kv7.2 and Kv7.3)
 - Genetic studies have found mutations in KCNQ2 and KCNQ3 that lead to benign familial neonatal seizures
- Kv7 channel family consists of five members that regulate the M current that opposes other depolarizing input to control neuron excitability
 - Ezogabine stabilizes Kv7 channels in open conformation, enhancing M current and hyperpolarizing the neuron

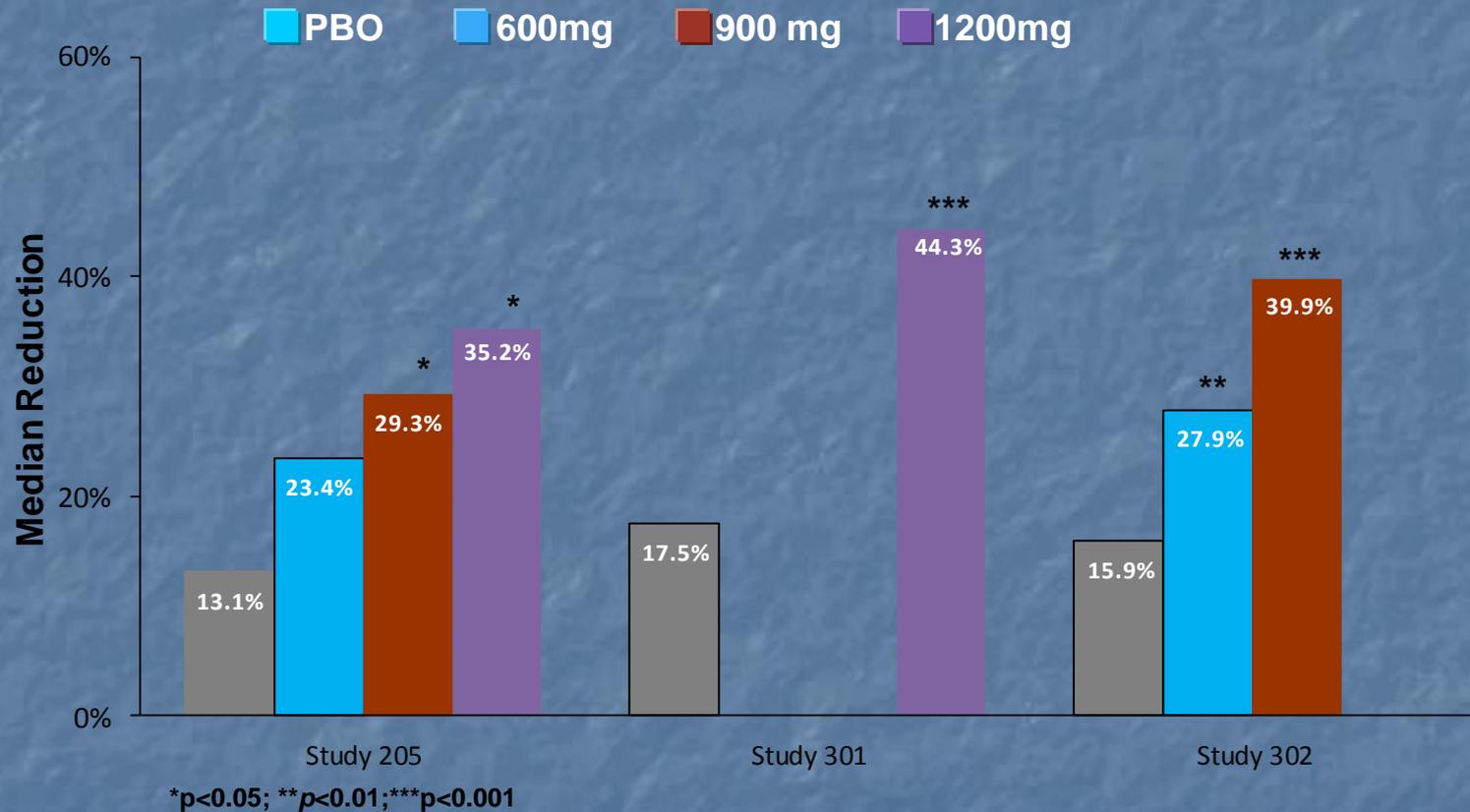
- Ezogabine binds Kv7.2 through Kv7.5 potassium channels

Brodie S, Lerche H, Gil-Nagel A, Elger C, Hall S, Shin P, Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy *Neurology*® 2010; 75:1817-1824.

Bialer M, Johannessen S, Levy R, Perucca E, Tomson T, White S, Progress report on new antiepileptic drugs: A summary of the Tenth Eilat Conference (Eilat X). *Epilepsy Research* 2010; 92:89-124.

- Troponin and T-tropomyosin: Functional characteristics. www.embnet.org/embnet
- Expression of the Kv7 channels in heart tissue and smooth muscle may be reasons for QT prolongation and urinary bladder issues

Ezogabine Pivotal Trials Primary Efficacy Endpoints: Median Percent Reduction in Seizure Frequency



FDA EZG backgrounder: Food and Drug Administration, Center for Drug Evaluation and Research (CDER), *Peripheral and Central Nervous System Drugs Advisory Committee Meeting , Potiga (ezogabine) Tablets Background Package*, August 11, 2010.

Ezogabine Pivotal Trials: Common Adverse Events $\geq 10\%$

Incidence of AEs Across Controlled Epilepsy Trials

	Percent of Patients				
	Placebo (n=427)	EZG 600 mg/day (n=281)	EZG 900 mg/day (n=273)	EZG 1200 mg/day (n=259)	EZG TOTAL (n=813)
Dizziness	9	14.6	23	32	23.2
Somnolence	12	15	24.5	26.6	22.0
Confusional State	2.6	4	7.7	16	9.2
Fatigue	6	16	15	13	14.7
Tremor	3	2.5	9.5	12.4	8.1
Coordination Abnormal	3	5	5	11.6	7.5
Blurred Vision	2	2	4.4	10.4	5.6

Ezogabine Pivotal Trials: Urinary/Bladder Adverse Events

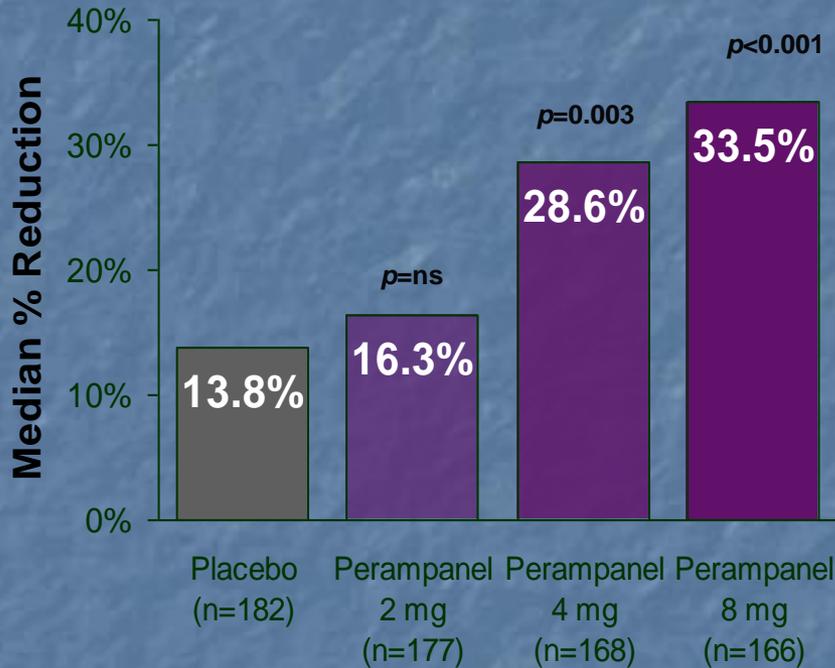
- ◆ Preclinical studies with EZG demonstrated distended bladders and some with renal lesions believed to be secondary to voiding dysfunction and urinary retention
 - Led to close monitoring of urinary function (including post-residual voiding) in trials
- ◆ Renal and urinary disorder AEs were reported for greater proportions of patient in the EZG group than PBO group (17% vs. 12.9%) and may be dose-related
- ◆ There were 5 SAE in 4 EZG-treated patients related to the urinary system (vs. 1 PBO)
 - SAE included renal colic, urinary retention, and atonic bladder (patients continued treatment), and renal failure and urinary incontinence (discontinued treatment)
 - One patient developed permanent sequelae from urinary retention and now has an apparent need for permanent need for self- catheterization

Perampanel (Fycompa): Mechanism of Action

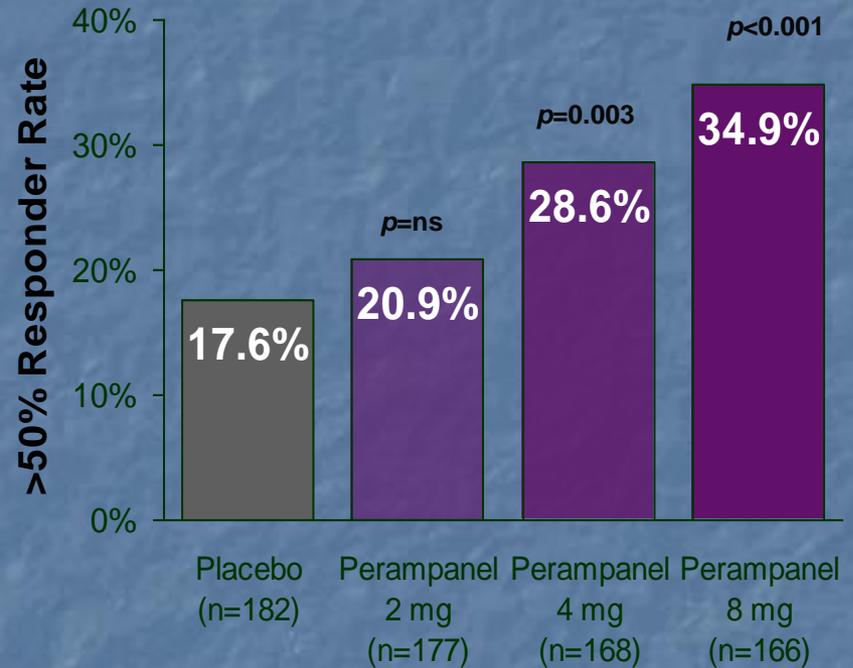
■ **MOA:**

- Highly selective noncompetitive AMPA glutamate receptor antagonist
- Low affinity for kainate and NMDA receptors
- No competition with radio-labeled AMPA for binding to AMPA-type glutamate receptor
- Inhibits AMPA-induced increase in intracellular Ca^+ in rat cortical neurons

Perampanel (306): Primary Efficacy Endpoints: Percent Median Reduction & Response Rate



ITT Population, Maintenance



ITT Population, Maintenance

Perampanel (306) Adverse Events

Incidence of treatment-emergent adverse events (TEAEs) (safety population)

	Placebo (n = 185)	Perampanel 2 mg (n = 180)	Perampane 14 mg (n = 172)	Perampanel 8 mg (n = 169)
TEAEs in >5% of patients in any treatment group				
Dizziness	18 (9.7)	18 (10.0)	28 (16.3)	45 (26.6)
Somnolence	12 (6.5)	22 (12.2)	16 (9.3)	27 (16.0)
Headache	16 (8.6)	16 (8.9)	19 (11.0)	18 (10.7)
Fatigue	5 (2.7)	8 (4.4)	13 (7.6)	9 (5.3)
Upper respiratory tract infection	5 (2.7)	11 (6.1)	6 (3.5)	3 (1.8)
Nasopharyngitis	3 (1.6)	7 (3.9)	9 (5.2)	3 (1.8)
Gait disturbance	2 (1.1)	1 (<1)	2 (1.2)	9 (5.3)

Krauss GL, Serratosa JM, Villanueva VE, Endziniene M, Hong Z, French J, Yang H, et al. Efficacy and safety of perampanel, an AMPA receptor antagonist, as a adjunctive therapy in a phase III study of patients with refractory partial-onset seizures. [abstract] AAN 2011

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA

These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression

Closely monitor patients particularly during the titration period and at higher doses

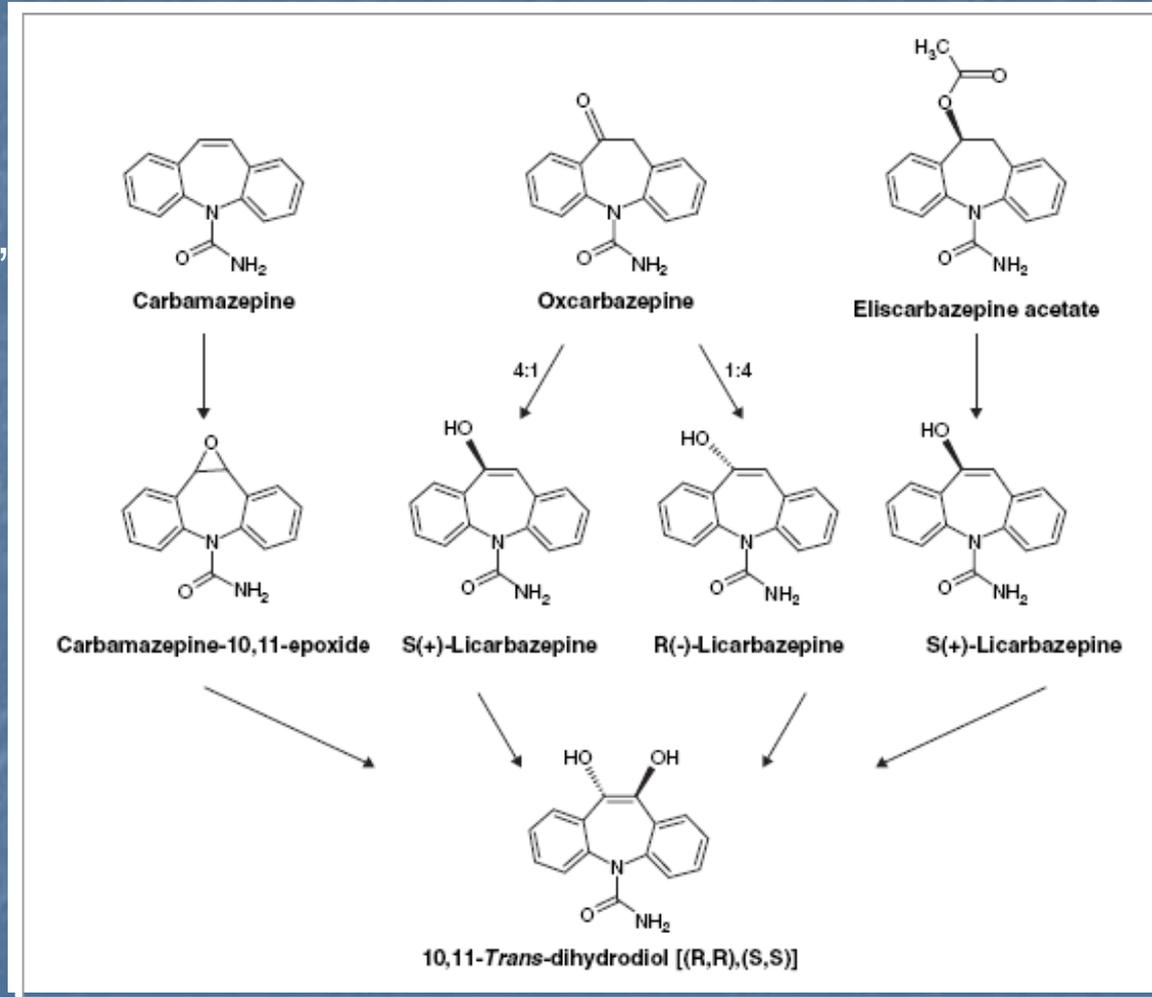
Eslicarbazepine Acetate Under Review: FDA

Eslicarbazepine: Overview

- Development and marketing by Sunovion
- NDA submitted to FDA in March 2009 based on 3 ex-US studies
 - FDA issued a Complete Response Letter in May 2010, reportedly requesting further studies that include US patients
 - US Phase III study recently initiated to support its NDA
 - Brand name filed with FDA is Stedesa™

Eslicarbazepine: Chemical Structure

- ◆ Shares dibenzazepine nucleus with CBZ and OXC, but with 5-carboxamide substitute
- ◆ ESL is structurally different at the 10,11 position
 - Carbamazepine-10,11-epoxide believed partly responsible for adverse effects of CBZ



Eslicarbazepine: Mechanism of Action

■ MOA:

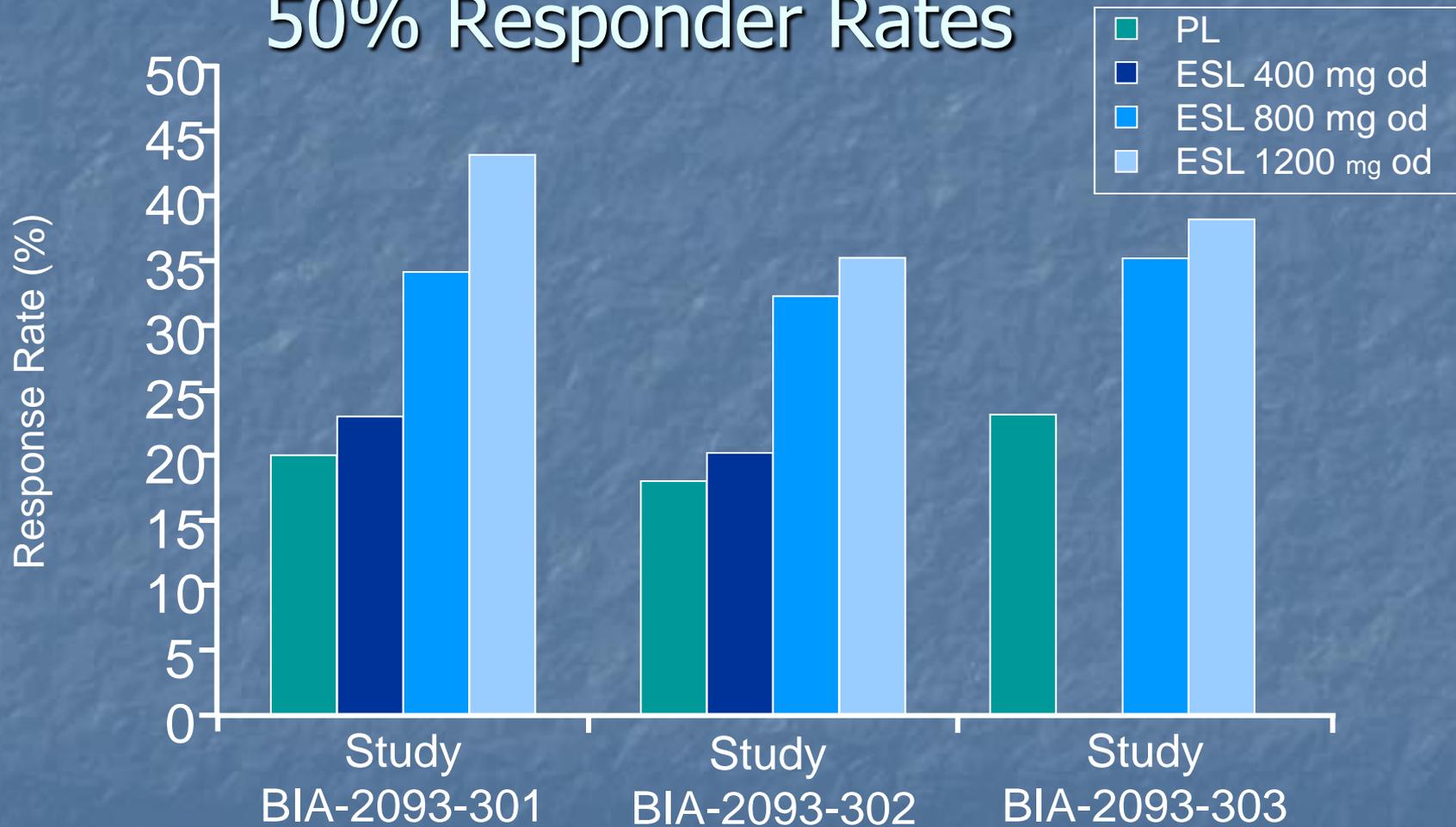
- Binds and blocks voltage-gated Na⁺ channels
 - Same drug class as carbamazepine and oxcarbazepine
 - Compared with carbamazepine, oxcarbazepine, and R-licarbazepine, the S-enantiomer of licarbazepine (eslicarbazepine) demonstrated greater binding selectivity for the inactive state of the sodium channel over the resting state

Stephen LJ, Brodie MJ. Pharmacotherapy of Epilepsy, Newly approved and developmental agents. *CNS Drugs*, 2011;25(2):89-107

Elger C, Bialer M, Cramer JA, Maia J, Almeida L, Soares-da-Silva P. Eslicarbazepine Acetate: A double-blind, add-on, placebo-controlled exploratory trial in adult patients with partial-onset seizures. *Epilepsia* 2007;48(3):497-504.

Results from 3 Eslicarbazepine Pivotal Trials:

50% Responder Rates



Eslicarbazepine Pivotal Study #1 (BIA-2093-301): Safety Results

Summary of Treatment-Emergent Adverse Events

Number (%) of Patients				
Preferred Term	Placebo (n=102)	ESL 400 mg (n=100)	ESL 800 mg (n=98)	ESL 1200 mg (n=102)
Any TEAE	32 (31.4)	44 (44.0)	49 (50.0)	62 (60.8)
Dizziness	2 (2.0)	4 (4.0)	14 (14.3)	14 (13.7)
Headache	6 (5.9)	5 (5.0)	9 (9.2)	11 (10.8)
Diplopia	0	2 (2.0)	7 (7.1)	11 (10.8)
Somnolence	2 (2.0)	6 (6.0)	9 (9.2)	10 (9.8)
Vertigo	1 (1.0)	2 (2.0)	2 (2.0)	6 (5.9)

Treatment-emergent adverse events affecting >5% of patients and leading to discontinuation in >2% of patients in any treatment group.