

# **Old vs New Medicines in Epilepsy**

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# “Old” Medicines for Epilepsy

- ❖ Phenobarbital (Luminal) - 1912
- ❖ Phenytoin (Dilantin) - 1938
- ❖ Primidone (Mysoline) - 1952
- ❖ Benzodiazepines - 1965
- ❖ Ethosuximide (Tegretol) - 1958
- ❖ Carbamazepine (Tegretol) - 1963
- ❖ Valproic acid (Depakine) - 1967

# **“New” Medicines for Epilepsy (1989-2004)**

- ❖ **Felbamate (Felbatol)**
- ❖ **Fosphenytoin (Cerebix)**
- ❖ **Gabapentin (Neurontin)**
- ❖ **Lamotrigine (Lamictal)**
- ❖ **Levetiracetam (Keppra)**
- ❖ **Oxcarbazepine (Trileptal)**
- ❖ **Pregabalin (Lyrica)**
- ❖ **Tiagabine (Gabitril)**
- ❖ **Topiramate (Topamax)**
- ❖ **Vigabatrin (Sabril)**
- ❖ **Zonisamide (Zonegran)**

# Critical Properties Differentiating Antiepileptic Drugs

- ❖ Mechanisms of action
- ❖ Spectrum of activity (seizure types and syndromes)
- ❖ Efficacy
- ❖ Adverse effect profile
- ❖ Drug interactions
- ❖ Ease of use
- ❖ Cost

# Mechanisms of Action of AEDs

	Na channel blockade	↑ GABA levels	↑ GABA-A responses	↑ Cl influx	Ca channel blockade	Other
BZD	-	-	●	-	-	-
CBZ	●	?	-	-	● (L)	●
VPA	●	●	?	?	● (T)	●
PB	-	●	●	●	-	●
PHT	●	?	-	-	?	●
ETS	-	-	-	-	● (T)	-
GBP	?	●	-	-	● (N,P/Q)	-
LTG	●	●	-	-	● (N,P/Q,R,T)	●
LEV	-	-	●	-	● (N)	●
OXC	●	?	-	-	● (N,P)	●
TGB	-	●	-	-	-	-
TPM	●	●	●	-	● (L)	●
VGB	-	●	-	-	-	-

● Major action      ● Minor action or relevance unclear

# Efficacy Spectrum of Available AEDs

<b>All seizures &amp; syndromes</b>	<b>All seizures except absence</b>	<b>Partial and tonic-clonic</b>	<b>Absence only</b>
<b>Valproic acid</b>	<b>Phenobarbital</b>	<b>Carbamazepine*</b>	<b>Ethosuximide</b>
<b>Benzodiazepines</b>	<b>Primidone</b>	<b>Phenytoin*</b>	
<b>Lamotrigine§</b>		<b>Oxcarbazepine*</b>	
<b>Topiramate§</b>		<b>Vigabatrin*</b>	
<b>Zonisamide (?)</b>		<b>Gabapentin*</b>	
<b>Levetiracetam (?)</b>		<b>Tiagabine*</b>	
<b>Felbamate (?)</b>			

\* May exacerbate myoclonic and absence seizures.

Vigabatrin is also effective in infantile spasms.

§Lamotrigine may aggravate severe myoclonic epilepsy

Topiramate efficacy in absence seizures has not been established

# Some Important Side Effects of Newer AEDs

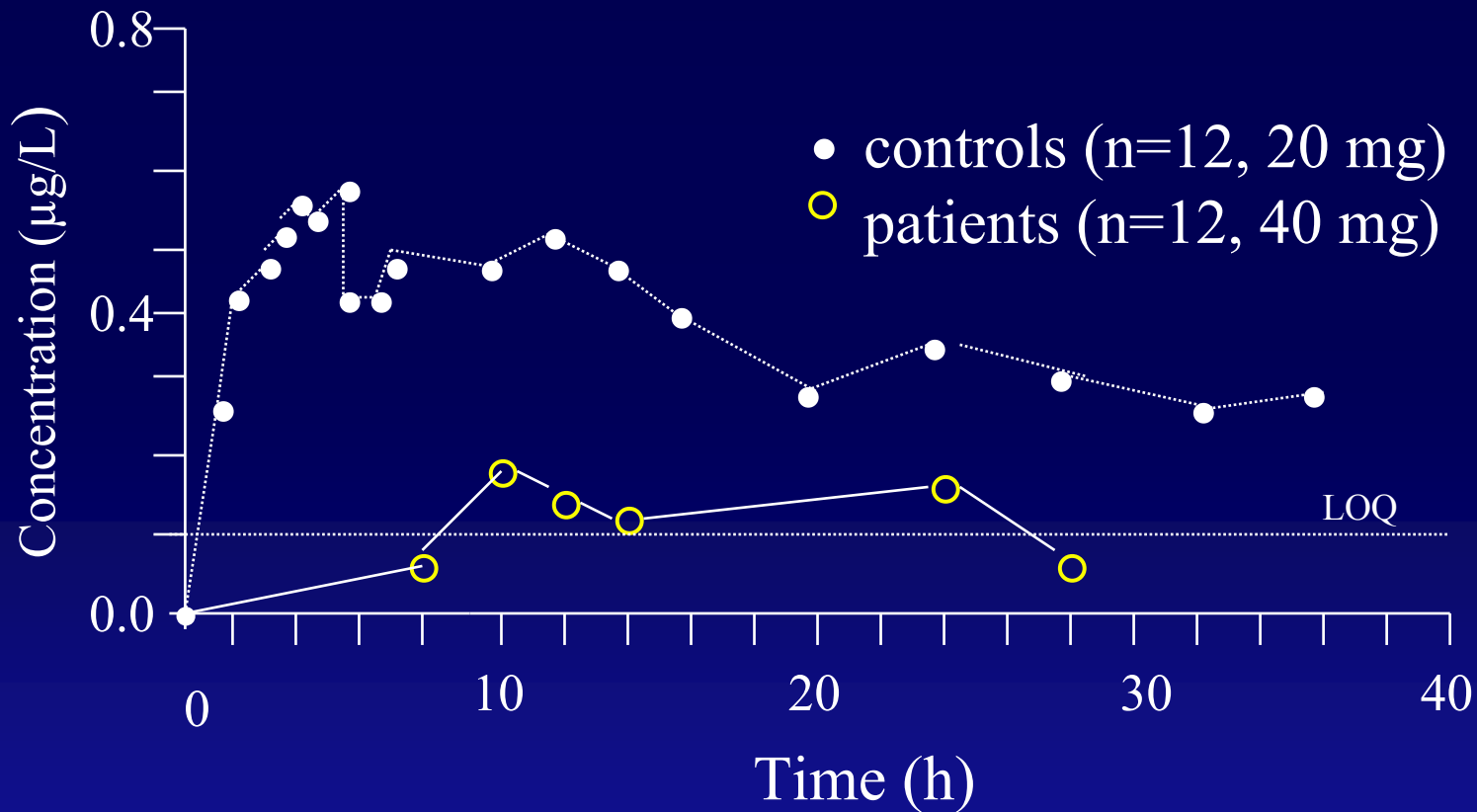
<b>FBM</b>	<b>G.i. problems, aplastic anemia, liver toxicity</b>
<b>GBP</b>	<b>Sedation, weight gain, behavioral changes</b>
<b>LEV</b>	<b>Sedation, fatigue, behavioral changes</b>
<b>LTG</b>	<b>Skin rashes, dizziness, insomnia</b>
<b>OXC</b>	<b>Skin rashes, dizziness, ataxia</b>
<b>TGB</b>	<b>Dizziness, tremor, mood changes</b>
<b>TPM</b>	<b>Mental slowing, weight loss, nephrolithiasis</b>
<b>VGB</b>	<b>Visual field defects, weight gain, behavioral changes</b>
<b>ZNS</b>	<b>Mental slowing, weight loss, nephrolithiasis</b>

# AEDs-Oral Contraceptives Interactions

Benzodiazepines	No interaction	Mattson et al, 1986
Carbamazepine	↓ contraceptive efficacy	Crawford et al, 1990
Phenytoin	↓ contraceptive efficacy	Back et al, 1980
Phenobarbital	↓ contraceptive efficacy	Crawford et al, 1990
Primidone	↓ contraceptive efficacy	Coulam et al, 1979
Valproate	No interaction	Crawford et al, 1986
Felbamate	↓ contraceptive efficacy	Saano et al, 1995
Gabapentin	No interaction	Eldon et al, 1993
Lamotrigine	↓ serum LTG levels	Holdich 91/Sabers 03
Levetiracetam	No interaction	Raguenau-M, 2002
Oxcarbazepine	↓ contraceptive efficacy*	Jensen et al, 1992
Tiagabine	No interaction	Mengel et al, 1994
Topiramate	↓ contraceptive efficacy*	Rosenfeld et al, 1997
Vigabatrin	No interaction	Bartoli et al, 1995
Zonisamide	No interaction	Mather et al, 2002

\* At dosages > 200 mg/day

# Effect of Enzyme Inducing AEDs on Plasma Nisoldipine Levels after a Single Nisoldipine Dose



# Clinical Reports of “Synergistic” AED Combinations

<b>Combination</b>	<b>Seizure type</b>	<b>Ref.</b>
<b>VPA + ETS</b>	<b>Absence</b>	<b>Rowan et al, 1983</b>
<b>VPA + CBZ</b>	<b>Partial</b>	<b>Gupta and Jeavons, 1985 Panayiotopoulos et al, 1993</b>
<b>VPA + LTG</b>	<b>Various</b>	<b>Pisani et al, 1999 Brodie et al, 1997</b>
<b>LTG + TGB</b>	<b>Partial</b>	<b>Schapel et al, 1996</b>
<b>VGB + TGB</b>	<b>Partial</b>	<b>Leach and Brodie, 1994</b>
<b>TPM + LTG</b>	<b>Partial</b>	<b>Stephens et al, 1996</b>

# Factors Favoring Ease of Use

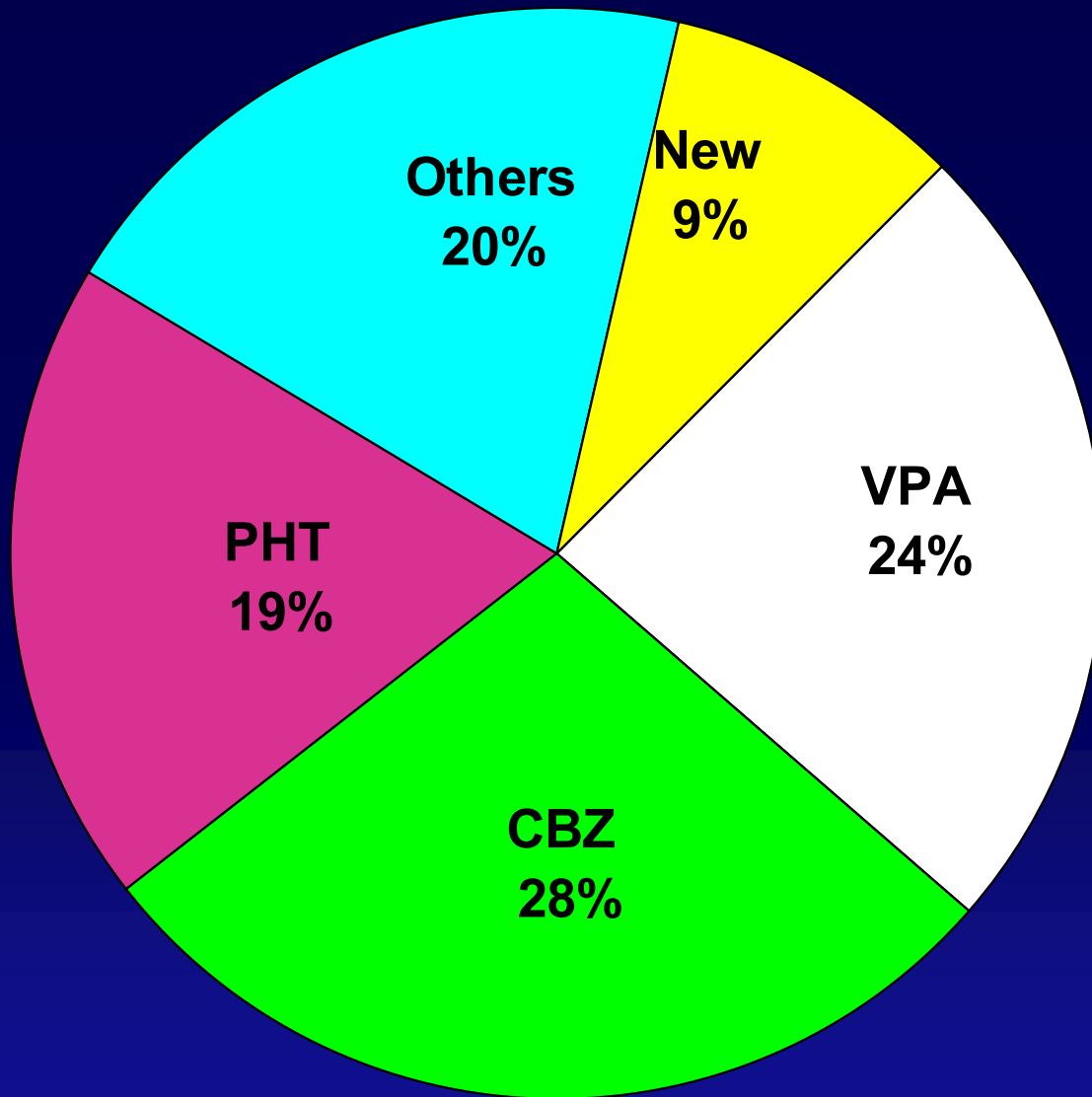
- ❖ Broad spectrum – no seizure aggravation
- ❖ High efficacy, good tolerability
- ❖ No contraindications
- ❖ No adverse drug interactions
- ❖ Friendly pharmacokinetics / once daily dosing
- ❖ Fast titration
- ❖ Availability of a friendly pediatric formulation
- ❖ Availability of parenteral formulation

# Acquisition Costs of AEDs

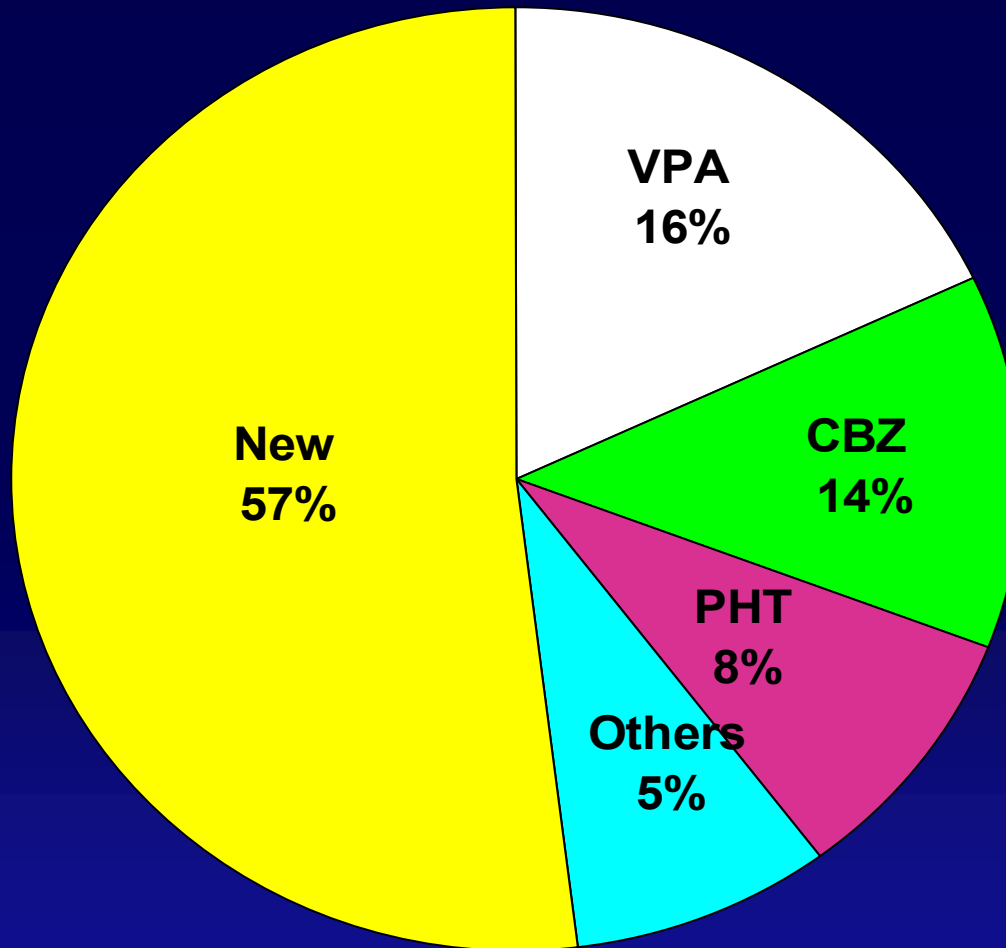
## 1-year treatment, Italy, 2002

	<u>mg/day</u>	<u>Euro</u>		<u>mg/day</u>	<u>Euro</u>
Phenobarbital	150	41	Oxcarbazepine	1200	513
Phenytoin	300	68	Vigabatrin	2500	1425
Clobazam	20	126	Tiagabine	30	1519
Carbamazepine	800	128	Lamotrigine	300	1623
Ethosuximide	750	133	Gabapentin	2400	2179
Valproate	1000	172	Topiramate	300	2264
			Levetiracetam	2000	2697
			Felbamate	2400	3864

# Worldwide Prescriptions (2002)



# Worldwide Market Value (2002)



# Conclusions

- ❖ New AEDs are NOT more efficacious than older agents
- ❖ Some new AEDs offer advantages because of broad spectrum and improved tolerability
- ❖ Most new AEDs are not enzyme inducers, and are less likely to cause drug interactions
- ❖ How to match these properties with patient's characteristics ....?

# Special – Risk Groups

- ❖ Embryos
- ❖ Infants, children
- ❖ The elderly
- ❖ Multiple handicaps (e.g. brain damage)
- ❖ Hepatic and renal disease
- ❖ Autoimmune disease
- ❖ Other comorbidities
- ❖ Associated therapies

Thank you for your attention!

