Update on the Medical Management of Epilepsy

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Disclosures

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- Speakers Bureau
  - SK Pharmaceuticals
  - Neuralis
  - UCB
  - Eisai

Layout of Presentation

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- Define Epilepsy
- Compare old and new AEDs
- CBD
- Options for medically refractory patients

Epilepsy

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- 4th most common neurological disorder
- 2.5-3 million people are estimated to have epilepsy in the US
- Approximately 1% of the US population
- About 5% of epilepsy patients have acute repetetive seizures
- Still associated with fear of disclosing diagnosis

Risks of Seizures

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- Socioeconomic Costs
  - School performance
    - 56% finish high school and 15% finish college
  - Intellectual functioning (seizures vs. drugs)
  - Social adjustment
  - Employment
    - 40%-60% are employed (although these jobs are often below their potential)
    - 15%-20% are unemployed
    - 20% retire early
  - Driving
- Costs to Society

Driving

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- Physician reporting is not required
- Honor system but patient required to report
- No driving for 3 months from last seizure
- Paperwork needs to be completed and DPS medical safety board then reviews
- Do not recommend writing letters saying its ok for patients to drive

Risks of Seizures

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- Co-Morbidities
  - Depression and psychiatric disorders
  - Sleep Apnea, weight gain etc.
- Morbidity
  - Accidents, Injuries
- Mortality
  - Sudden unexpected death in epilepsy
  - Status epilepticus, Suicide, Accidents, Cancer, Infections etc.

Diagnosis

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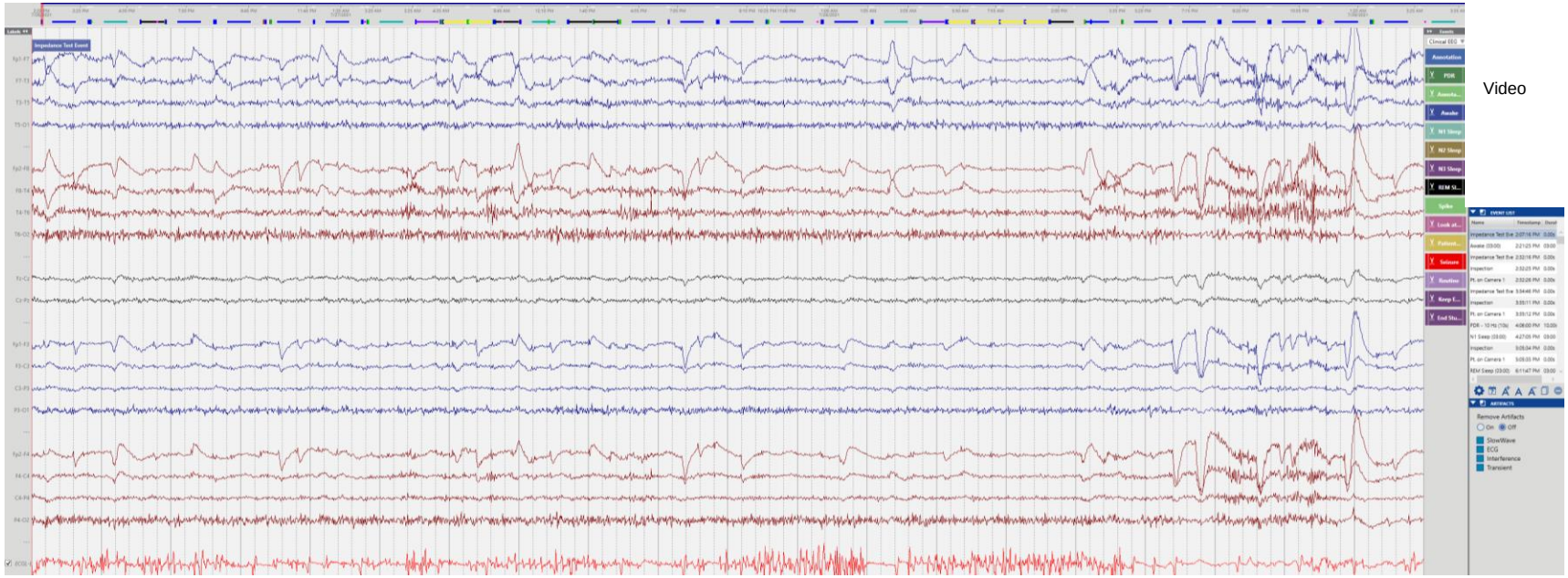
- There has been a growing trend towards ordering extended ambulatory VEEG studies
- Coding changes related to VEEG



Diagnosis

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- History
- EEG
  - Routine – for initiating and withdrawing treatment
  - Extended recordings
- MRI
  - 7T MRI at HMH

Assessment of Seizures

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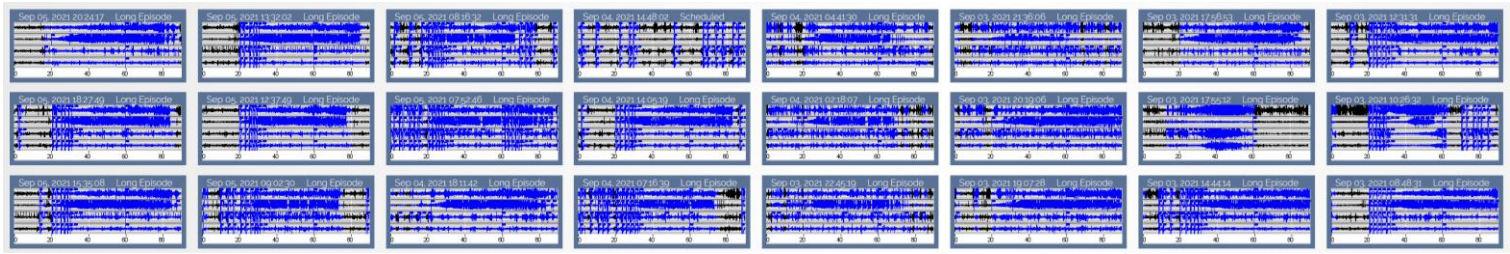
- Mostly by patient reports
- Devices such as Neuropace are changing that paradigm



Patient and Caregiver Assessment

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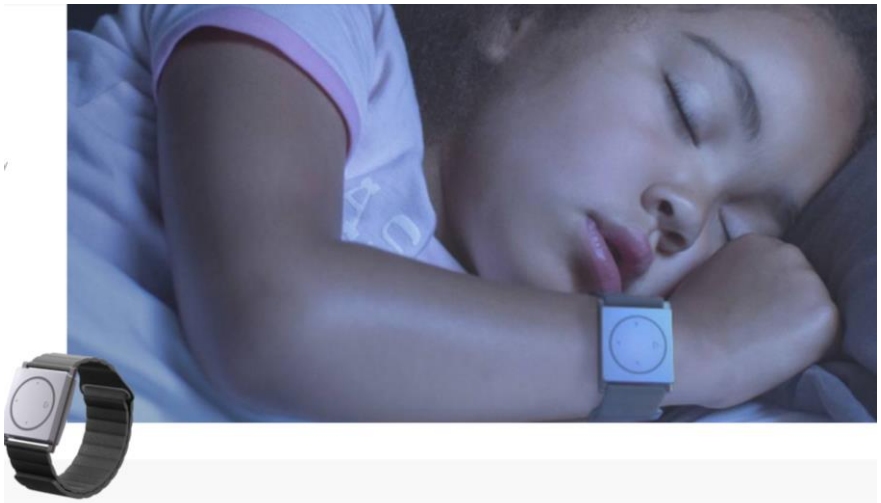
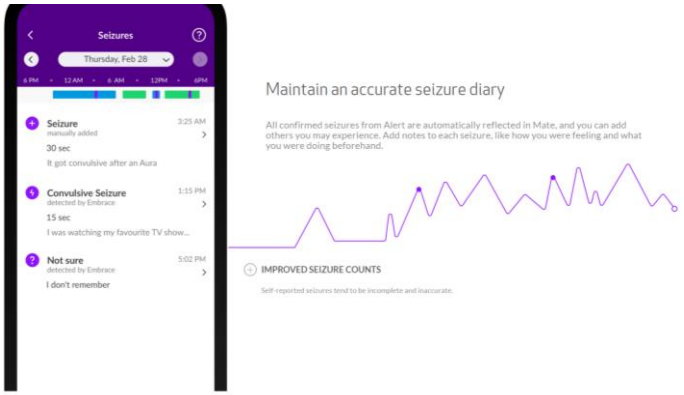
- Movement detection devices
- We typically prescribe the Embrace 2 watch





Typical Treatment Algorithm

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- Diagnosis made of unprovoked seizures
- Pick appropriate medication
  - Seizure type
  - Comorbidities
  - Short and long term side effects/risks
- Switch/add medications based on tolerability/efficacy
- Define when patient is refractory

AED Effectiveness

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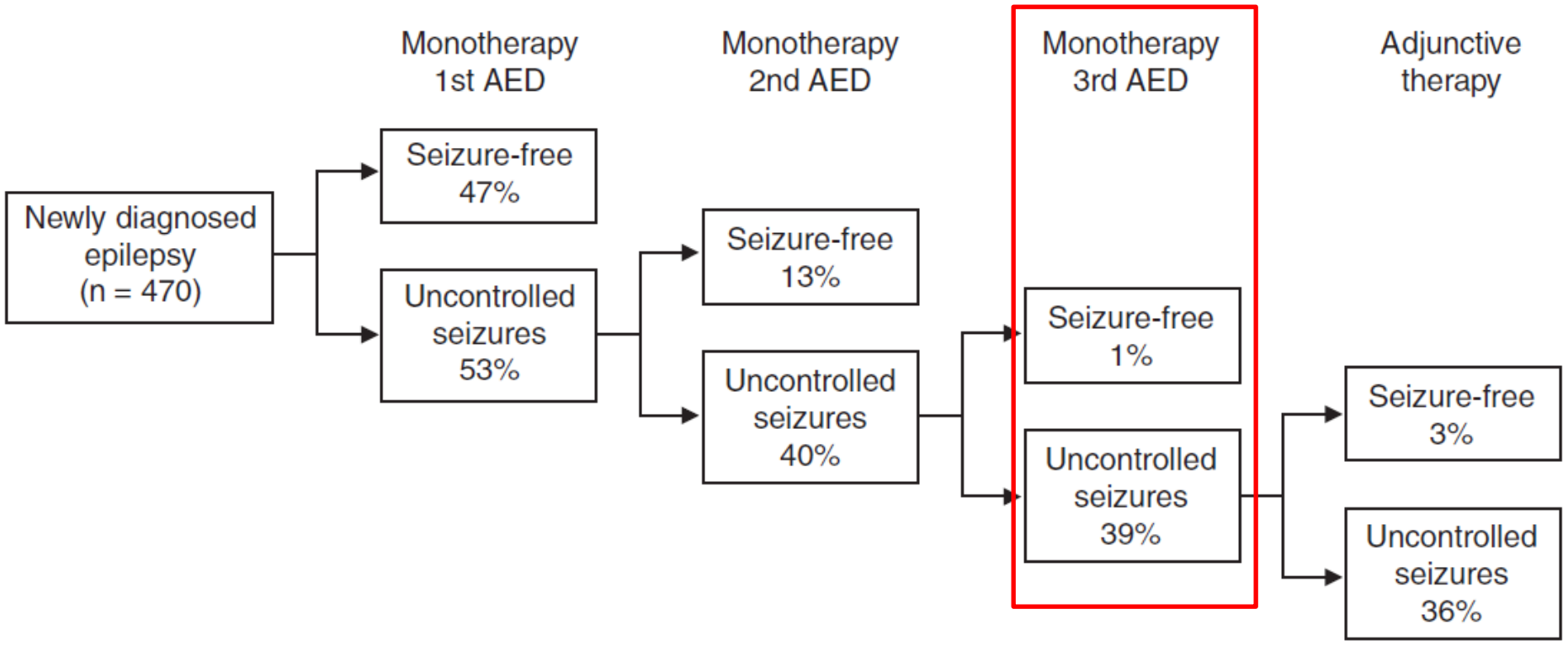

Stein MA and Kanner AM. "Management of Newly Diagnosed Epilepsy". *Drugs* 2009

Relationship of Adverse Events to QOL Scores

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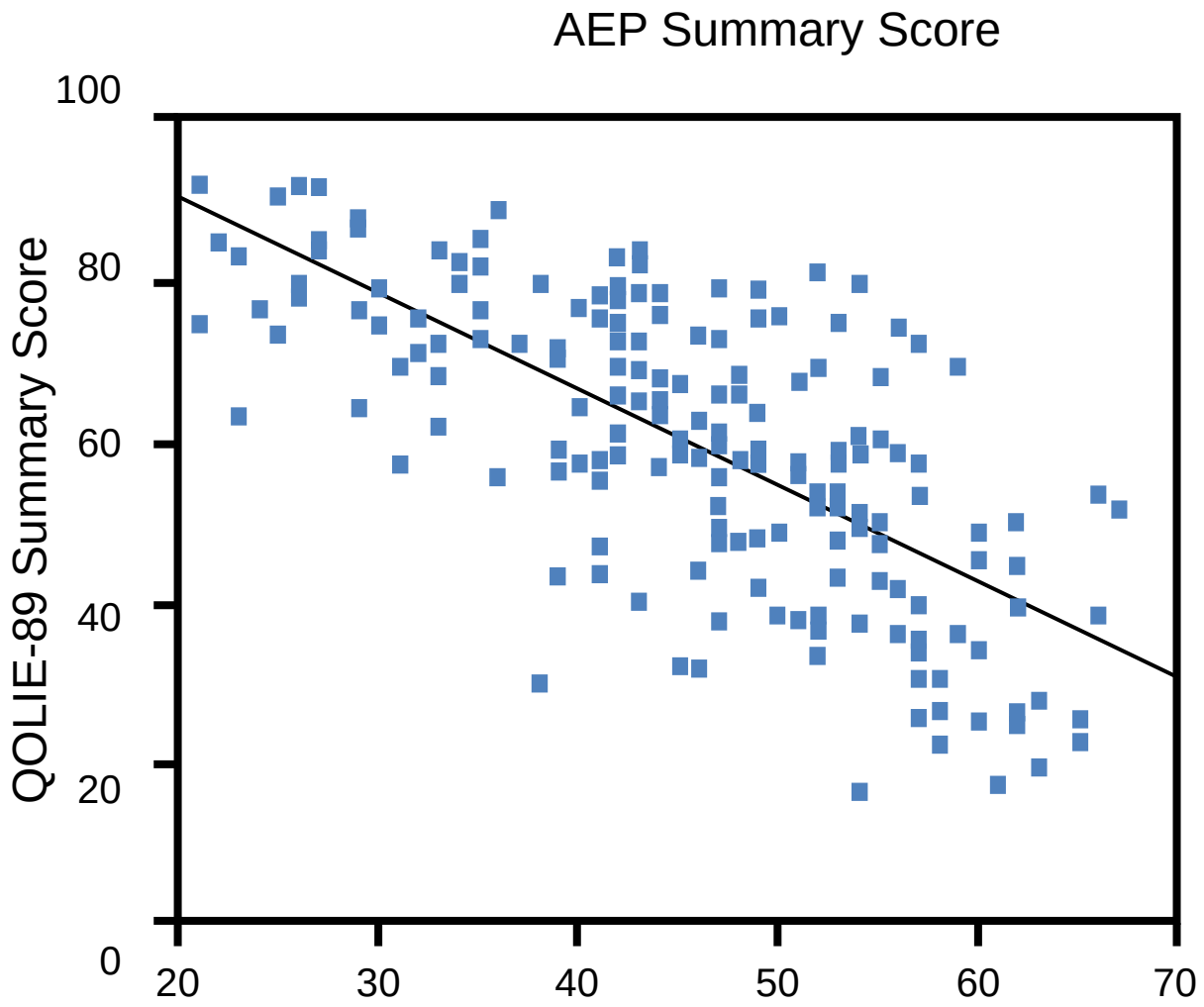

N = 194
(r = -0.71,
P<.0001)

Gilliam F, et al. 2000.

Important Characteristics of an Anti Epileptic Medication

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- **Needs to be effective**
- **Minimal side effects**
- Convenient –once daily dosing is best
- Rapid-acting
- Broad spectrum of activity
  - Effective for both partial onset and generalized seizures
- Not associated with exacerbation of seizures
- Multiple mechanisms of action/multiple formulations
- Linear pharmacokinetics
- No drug interactions
- Ability to monitor levels

Cenobamate, Nasal Diazepam, Midazolam, Fintepla

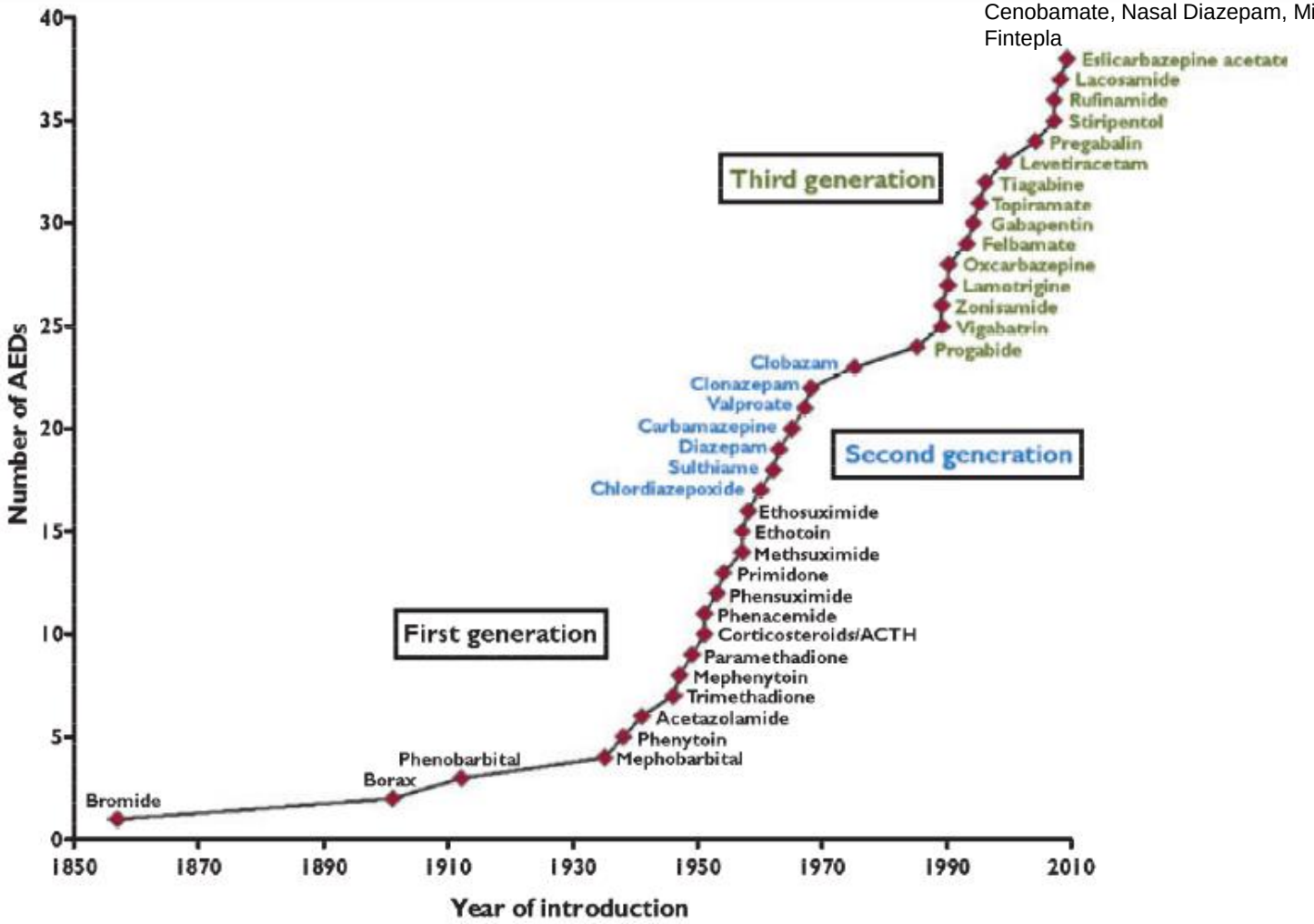
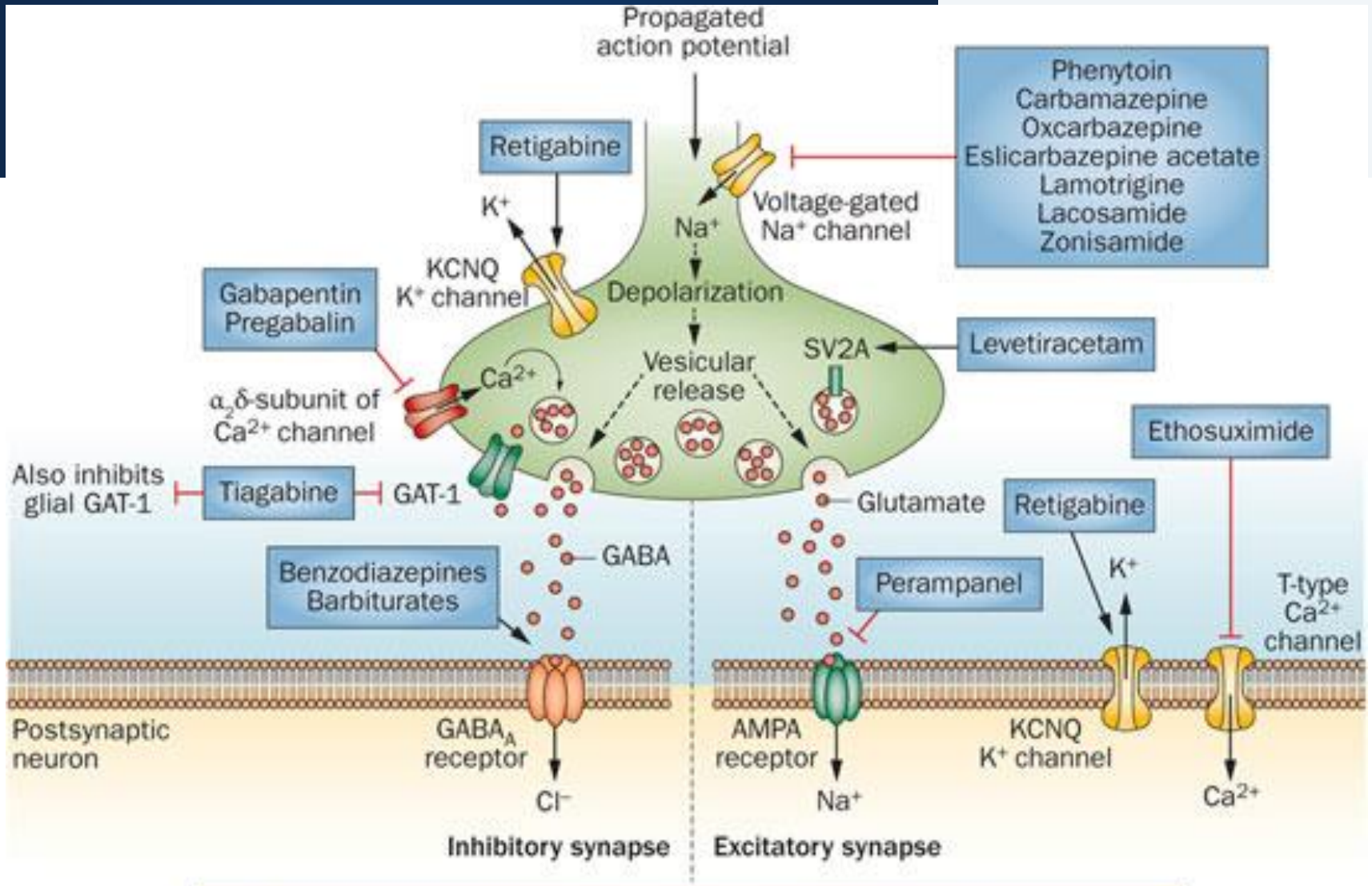


Figure 1.
Introduction of AEDs to the market from 1853 to 2009 (adapted from data by Shorvon, 2009a,b). Licensing varied from country to country. We give here the year of first licensing or the first mention of clinical use in a country of Europe, the United States, or Japan (see Shorvon, 2009a,b, for further details). We have not included all derivatives of listed AEDs or AEDs used solely for treatment of status epilepticus.



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

Cenobamate

- Na channel
- Gaba

Highlights of the "Newer AEDs"

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Brivaracetam	-Targets Synaptic Vesicle Protein 2A -Medication can be started at effective dose
Clobazam	-1,5 Benzodiazepine -Broad spectrum of activity in all seizure types associated with LGS -Tolerance does not appear to be an issue as demonstrated by their pivotal trial and long term data
Eslicarbazepine Acetate	-Unique molecule as recognized by the FDA -Inhibition of voltage gated sodium channels -Main Aes are dizziness and somnolence and can be limited by starting at 400 mg per day

Highlights of the "Newer AEDs"

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Lacosamide	-Proposed mechanism is that it enhances slow inactivation of voltage gated sodium channels -Twice daily dosing -PO and IV formulation available -Well tolerated (dizziness, headache, nausea, diplopia are most common AEs)
Perampanel	-AMPA receptor antagonist -Black box warning for behavioral side effects including hostility, aggression and homicidal ideation - Risk of Homicidal ideation less than 0.1% -Once daily dosing -Indication for both partial and generalized seizures
Cenobamate	-Inhibits voltage gated Na currents and is a positive allosteric modulator of GABA -Studies also showed high efficacy and seizure free rates - Efficacy sustained in open label extension data -Risk of DRESS Syndrome with rapid titration -Efficacy seen at 100 mg/day

Major Side Effects of AEDs

Phenobarbital	Sedation, Hyperactivity, Rash, Osteomalacia
Phenytoin	Gingival hyperplasia, Hirsutism, Peripheral Neuropathy, Bone marrow suppression, Osteomalacia
Primidone	Sedation, Hyperactivity, Rash, Osteomalacia
Ethosuximide	GI Upset, Mood changes, Lethargy, Hiccups, Headache
Carbamazepine	Hyponatremia, Leucopoenia, Hepatitis, Rash
Valproate	Thrombocytopenia, Tremor, Hair loss, Weight gain, Hepatitis, Pancreatitis
Felbamate	Hepatic Failure, Aplastic Anemia
Gabapentin	Sleepiness, Weight gain
Lamotrigine	Rash (increased risk with VPA)
Topiramate	Cognitive slowing, Renal stones, Acute Glaucoma, Weight Loss
Tiagibine	Dizziness, Somnolence, Spike Wave Stupor
Oxcarbazepine	Hyponatremia, Rash (No Leucopoenia)
Zonisamide	Rash, Renal stones

Major Side Effects of New AEDs

Leviteracetam	Sedation, Irritability
Lacosamide	Dizziness, Headaches, Nausea, Diplopia
Eslicarbazepine Acetate	Dizziness and somnolence, Hyponatremia
Clobazam	Sleepiness, Irritability in some patients
Perampanel	Aggression, Hostility, Homicidal Ideation, Sedation
Brivaracetam	Somnolence, fatigue, dizziness, gait disturbance,
Cenobamate	Somnolence, Dizziness, Risk of DRESS (no patients with slow titration)

Risks Associated With Enzyme Inducing AEDs

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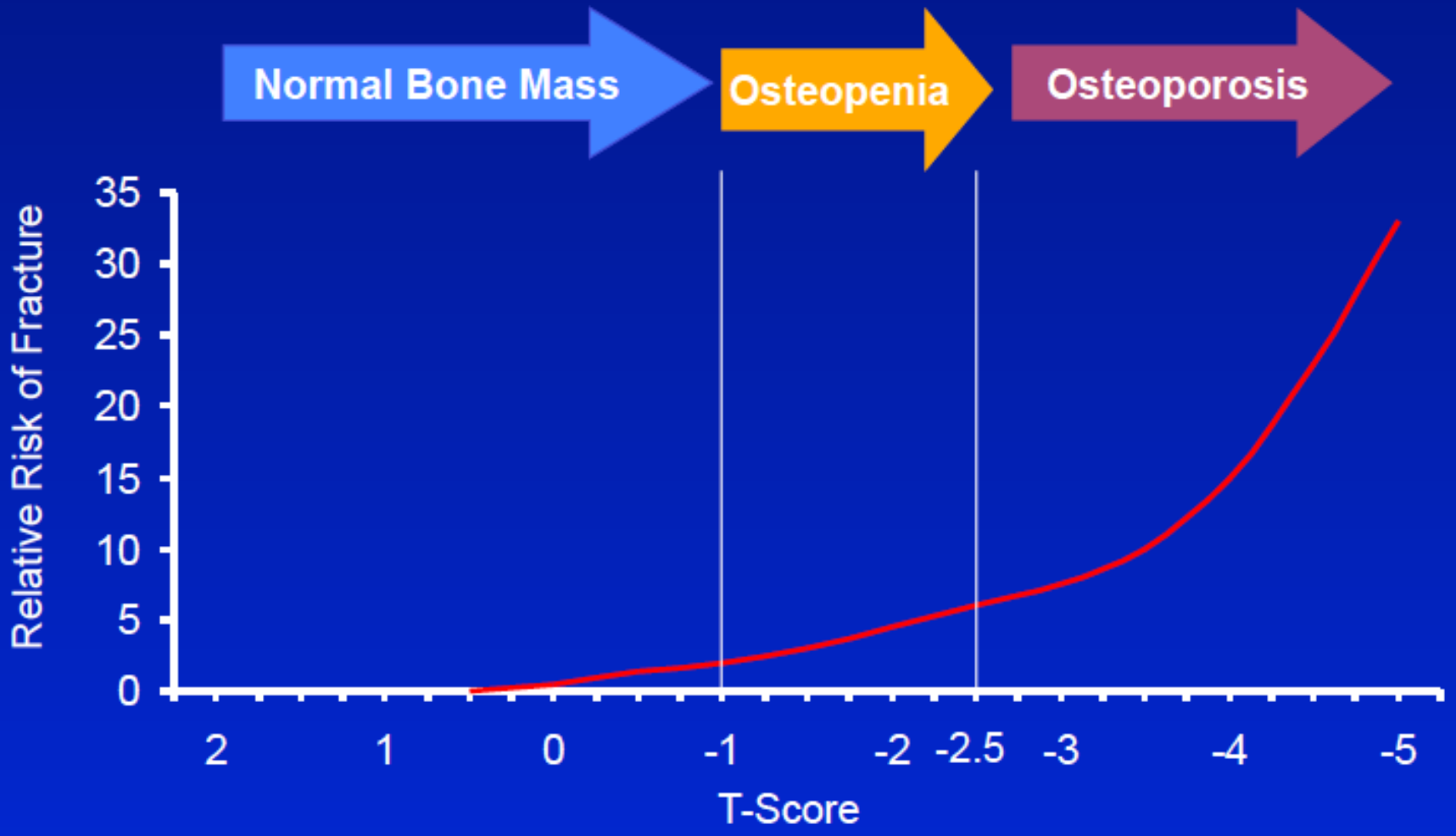
- Bone Mineral Density
- Sexual function
- Effects on levels of antidepressant and antipsychotic medications
- Increased clearance of chemotherapeutic agents
- Abnormal lipid profiles
- Higher risk of statin use
- Higher cardiovascular morbidity and mortality

BMD: Radiographic Definitions



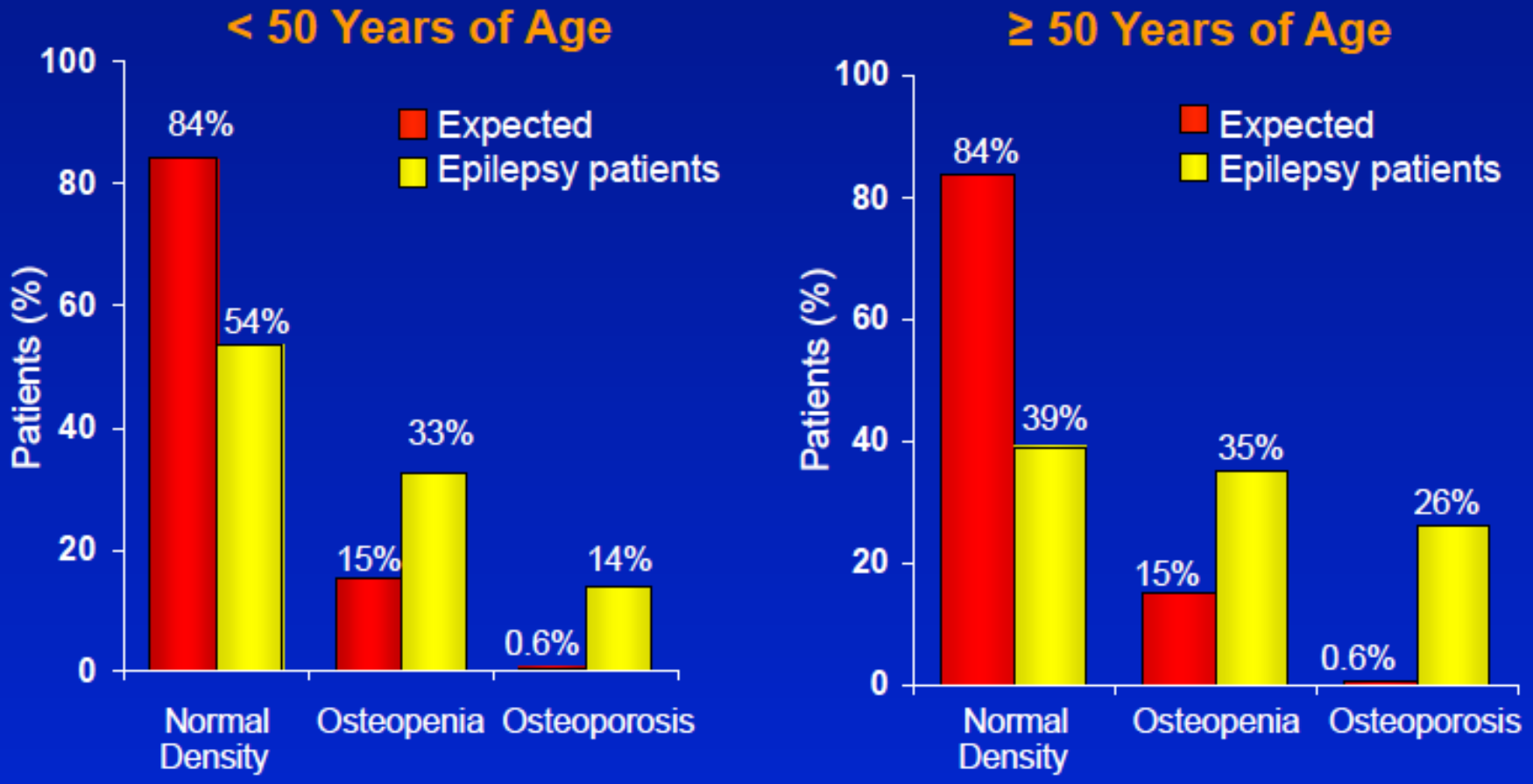
WHO; Meunier PG, et al. *Clin Ther*. 1999;21:1025-1044.

Bone Health

- Increased incidence of osteopenia, osteomalacia, and fracture with some AEDs
  - No prospective trials have been performed to define the frequency of fractures in epilepsy
- Most tested AEDs have been shown to reduce BMD
  - Primarily associated with enzyme-inducing AEDs, including phenytoin
- Factors associated with reduced BMD
  - Polypharmacy
  - Generalized seizures

Ensrud KE, et al. *Neurology.* 2004;62:2051-2057.

Spine BMD in Patients Receiving Enzyme-Inducing AEDs



Men and women on enzyme-inducing AEDs.

Pack AM, et al. *Epilepsy Behav.* 2003;4:169-174.

Table 3. Effect of enzyme-inducing antiepileptic drugs on the pharmacokinetics of chemotherapeutic, antiretroviral, and immunosuppressive drugs

Concomitant drug	EIAED(s)	Effect of EIAED on concomitant drug	Number of subjects: Total	Number of subjects: EIAED	Number of subjects: No EIAED[a,b,c]	References
Chemotherapeutic drugs						
Busulphan	PHT	↓ AUC	n = 17	n = 9	n = 8[a]	Hassan et al. (1993)
Methotrexate/teniposide	CBZ, PHT, PB	↑ Clearance	n = 182[d]	n = 12	n = 170[b]	Relling et al. (2000)
Paclitaxel	EIAEDs	↑ MTD	n = 24[d]	n = 18	n = 6[a]	Fetell et al. (1997)
Paclitaxel	EIAEDs	↑ MTD	n = 34[d]	n = 27	n = 7[b]	Chang et al. (1998)
Irinotecan	CBZ	↓ AUC	n = 64[d]	n = 52	n = 12[b]	Santisteban et al. (2009)
	PHT	↓ AUC				
Etoposide	PHT, PB	↑ Clearance	n = 29[d]	n = 7	n = 22[b]	Rodman et al. (1994)
Vincristine	CBZ, PHT	↓ AUC	n = 15	n = 9	n = 6[a,b,e]	Villikka et al. (1999)
Tipifarnib	EIAEDs	↓ AUC	n = 47[d]	n = 23	n = 24[c]	Cloughesy et al. (2005)
Erlotinib	PB	↑ MTD ↓ AUC	n = 83[d]	n = 53	n = 30[c]	Prados et al. (2006)
Erlotinib	EIAED	↑ Clearance ↓ AUC	n = 32[d]	n = 32		Raizer et al. (2010)
Gefitinib/sirolimus	EIAEDs	↓ AUC ↑ MTD	n = 34[d]	n = 19	n = 15[c]	Reardon et al. (2006)
Imatinib	EIAEDs	↓ MTL	n = 224[d]	n = 85	n = 28[a] n = 111[b]	Pursche et al. (2008)
Temsirolimus	PHT	↓ AUC	n = 36	n = 17	n = 19[a]	Kuhn et al. (2007)
Antiretroviral drugs						
Lopinavir/ritonavir	PHT	↓ AUC	n = 24[f]	n = 24		Lim et al. (2004)
Nevirapine	EIAEDs	↓ $t_{½}$	n = 36[f]	n = 32	n = 4[a]	L'homme et al. (2006)
Efavirenz	CBZ	↓ $t_{½}$	n = 16[f]			Zhu et al. (2009)
Immunosuppressive drugs						
Cyclosporin	CBZ	↓ Steady-state concentration	n = 6	n = 3	n = 3[c]	Cooney et al. (1995)
Cyclosporin	PHT	↑ Clearance	Animals			D'Souza et al. (1988)

AUC, area under the plasma concentration-time curve; CBZ, carbamazepine; EIAED, enzyme-inducing antiepileptic drug; MTD, maximum tolerated dose; MTL, mean through level; PB, phenobarbital; PHT, phenytoin; SN-38, 7-ethyl-10-hydroxy-camptothecin; $t_{½}$, elimination half-life.

↑ = increased; ↓ = decreased.

[a] Non-EIAED.

[b] No anticonvulsants.

[c] Not specified.

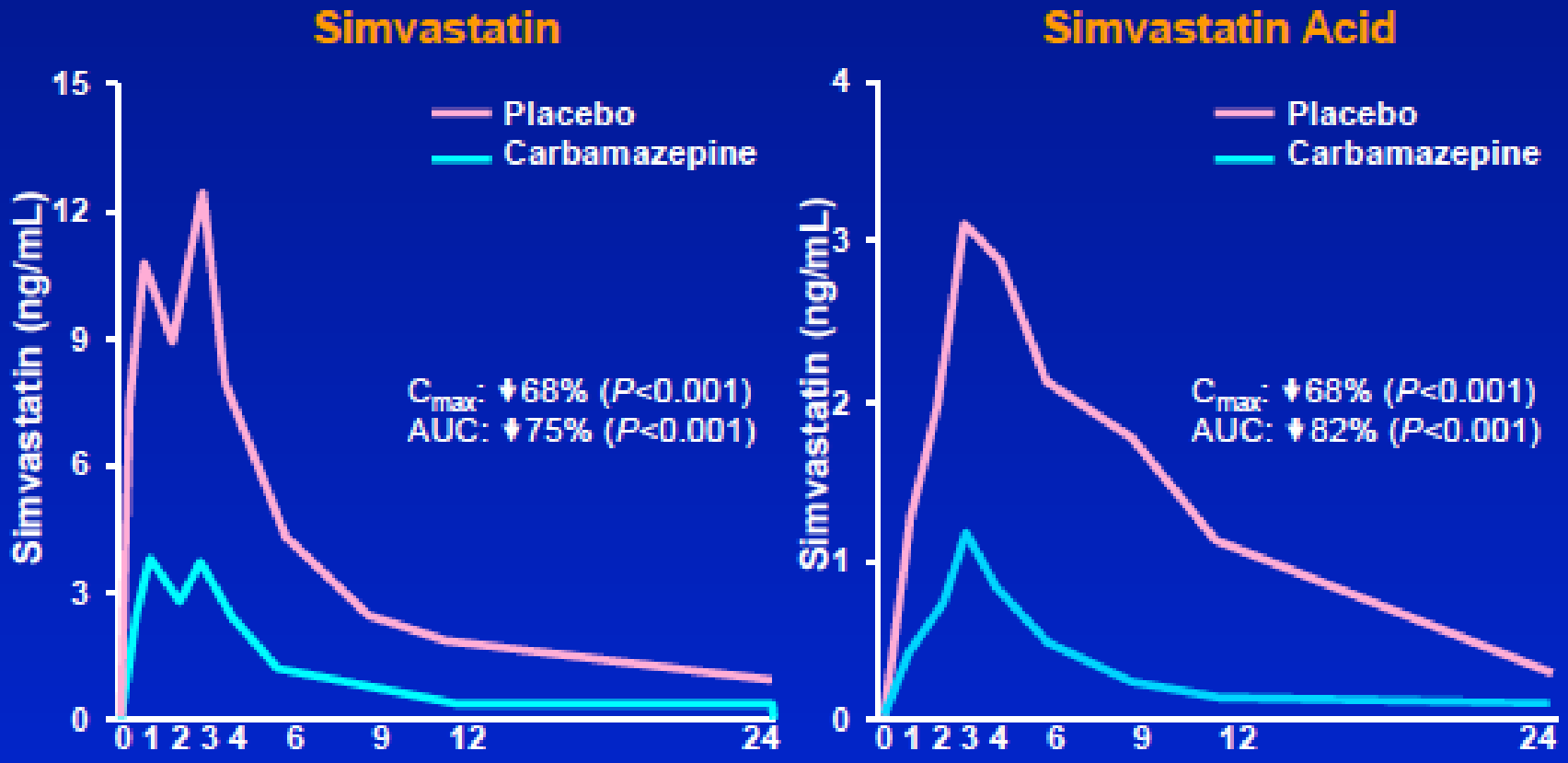
[d] Prospective series.

[e] Includes oxcarbazepine.

[f] Healthy volunteers.

Brodie et al., 2013

Reduced Statin Levels: Drug Interaction With Enzyme-Inducing AED



Ucar M, et al. *Eur J Clin Pharmacol*. 2004;59:879-882.

Table 4. Vascular mortality and morbidity in patients with epilepsy

Study	Study size	Standardized ratio	95% CI
Neligan et al. (2011)	19,114 person-years	IHD mortality: **1.5***	1.1–2.0
		CBVD mortality: **2.9***	2.1–3.9
Olesen et al. (2011)	~213,000 person-years[a] (epilepsy patients without prior history of stroke)	CVD mortality: **1.6***	1.6–1.7
		MI morbidity: **1.1***	1.0–1.2
		Stroke morbidity: **2.2***	2.1–2.4
Mu et al. (2011)	~7,000 person-years[a]	Cardiac disease mortality: 1.6	0.5–5.2
		CBVD mortality: 1.1	0.4–3.6
Ding et al. (2006)	~5,000 person-years[a]	MI mortality: **10.7***	5.6–95.3
Gaitatzis et al. (2004)	~23,000 person-years[a]	IHD morbidity: **1.3***	1.2–1.5
		IHD morbidity, age 16–64: **1.6***	1.3–2.0
		CVA morbidity: **7.0***	6.4–7.6
		CVA morbidity, age 16–64: **14.2***	12.0–16.7
Nilsson et al. (1997)	53,250 person-years	IHD mortality: **2.5***	2.3–2.7
		CBVD mortality: **5.3***	4.9–5.8
Annegers et al. (1984)	"Approached 10,000 person-years"	IHD mortality: 1.2	0.9–1.5
		IHD mortality, age 25–44: **5.7***	1.8–13.3
		IHD mortality, age 45–64: **2.5***	1.4–4.1
		IHD morbidity: **1.6***	1.2–2.2
		IHD morbidity, idiopathic epilepsy only: **1.5***	1.0–2.2

CI, confidence interval; IHD, ischemic heart disease; CBVD, cerebrovascular disease; CVD, cardiovascular disease; MI, myocardial infarction; CVA, cerebrovascular accident.

Data marked with an asterisk* are statistically significant (i.e., the lower limit of the 95% CI is ≥1).

[a]Person-years calculated by author of this section of the review (SM), not directly given in study.

Take Home Message

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- Avoid Using “Older” agents – especially enzyme inducing AEDs
- “Newer” agents have less complicated pharmacokinetics and seem to be better tolerated
- Cognitive profile appears to be better with newer AEDs

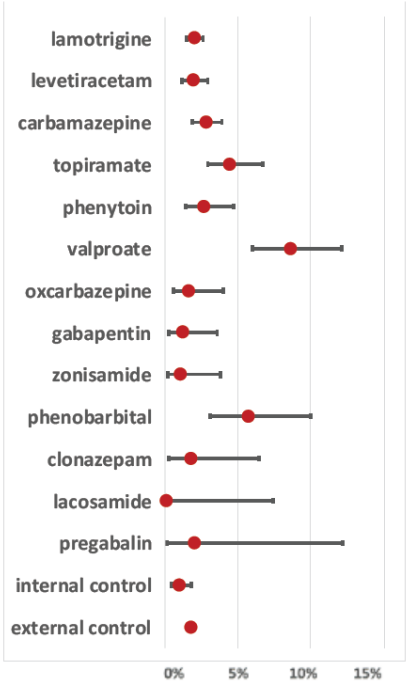
Special Considerations in Treating Women With Antiepileptic Drugs

- Menstrual cycle regularity
- Hormonal contraception
- Fertility and ovulatory function
- Sexuality
- Bone health
- Pregnancy/breastfeeding

Morrell MJ. *Epilepsia*. 1996;37(suppl 6):S34-S44.
Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 1998;51:944-948.

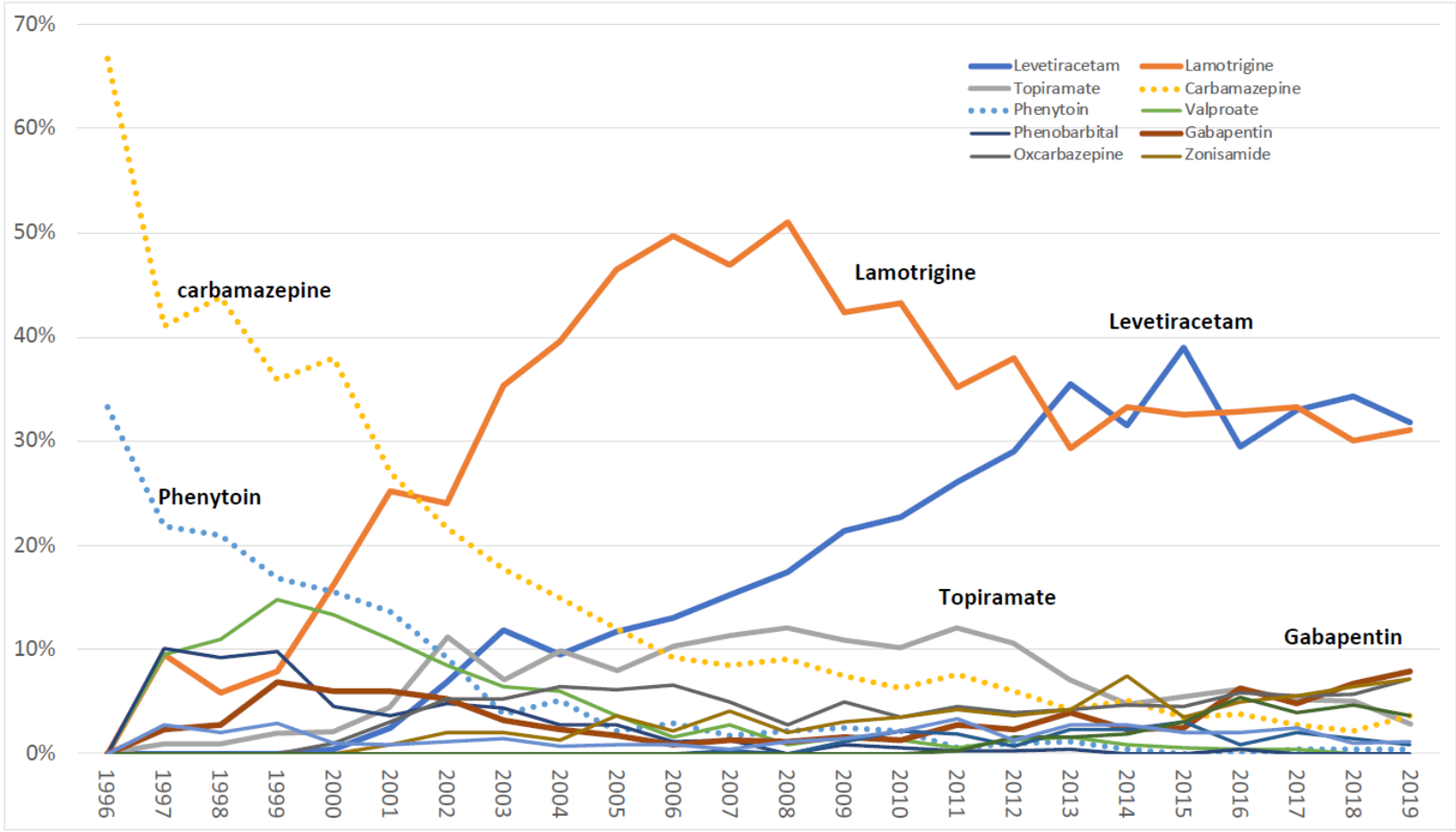
AED Pregnancy Registry – 2020
aedpregnancyregistry.org

Risk of malformations for specific AED in monotherapy and the control groups

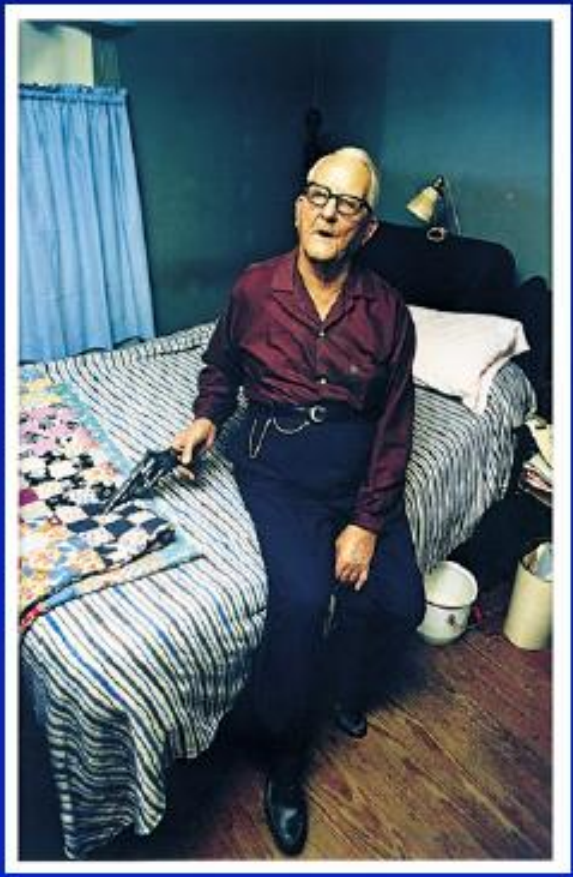


N	%	95% CI
2484	1.9%	(1.5 to 2.6%)
1253	1.8%	(1.2 to 2.7%)
1210	2.7%	(1.9 to 3.8%)
544	4.4%	(2.9 to 6.3%)
462	2.6%	(1.5 to 4.5%)
360	8.6%	(6.0 to 12.1%)
312	1.6%	(0.7 to 3.8%)
263	1.1%	(0.37 to 3.5%)
218	0.9%	(0.23 to 3.7%)
212	5.5%	(3.1 to 9.6%)
122	1.6%	(0.41 to 6.5%)
65	0.0%	(0 to 7.4%)
51	1.9%	(.28 to 13.6%)
1023	0.9%	(0.46 to 1.8%)
289,365	1.7%	(1.6 to 1.7%)

Time Trends of Enrollment for Specific AEDs:



Epilepsy in the Elderly
adverse effects (AE) of medications



- *dose-dependent* side effects are common: dizziness, somnolence, ataxia, diplopia
- *drug-specific* side effects are common hyponatremia, tremor, cardiac effects, encephalopathy, cognitive suppression
- AE's occur at lower serum concentrations
- AE's more likely to result in non-compliance

What to use????

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- Limited high class evidence
- Registration designed trials not conforming to clinical use
- Fixed dose and titration of medication
- Varying outcomes measures among studies
- Do not factor in special needs of the individual patient

Rescue Medications

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- 5% of all epilepsy patients have acute repetitive seizures
- 3-4 X increased risk of SUDEP in patients
- Only 20% of those patients have a rescue plan
- 2 Medications became available in 2020 for treatment of acute repetitive seizures
- Diazepam (Valtoco)
- Midazolam (Nayzilam)
- “Fire extinguisher” analogy

What to use?

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- Avoid using enzyme inducing AEDs
- Use medications with simplified regimens
  - Extended release
  - Once daily dosing
  - Cleaner pharmacokinetic profiles
- Need to rapid onset of action
- AEs can sometimes be used in certain comorbidities or should be avoided when certain comorbities present
- Focal Epilepsy – All approved meds are indicated
- Generalized Epilepsy
  - VPA, TPM, LTG, LEV, FYC, ZNS

Cannibas in History

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- Cannibas sativa – ? ~8,000 bce in China - rope
- Cultivated, used for garments, bowstrings, paper and medicine in China
- 2700 bce – cannibas (ma) for menstruation, gout, rheumatism, malaria, constipation, and absentmindedness (Abel, 1980)
- 1st Century AD in China > 100 ailments
- Medicinal use in ancient Egypt, India, Africa, Greece, Rome and Arab world

Exogenous Cannabinoids

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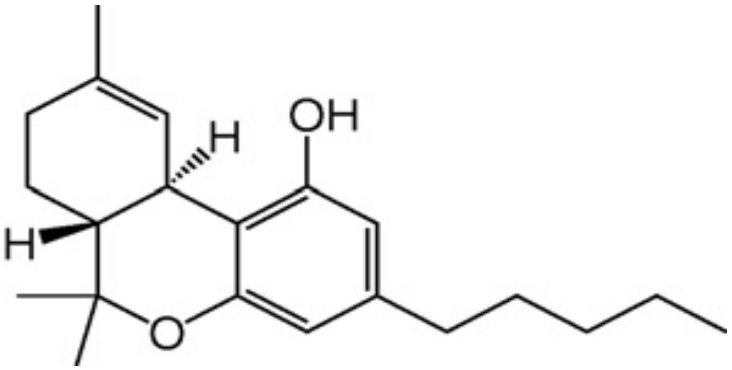
Δ^9 Tetrahydrocannabinol (THC)

Psychoactive

CB1 agonist

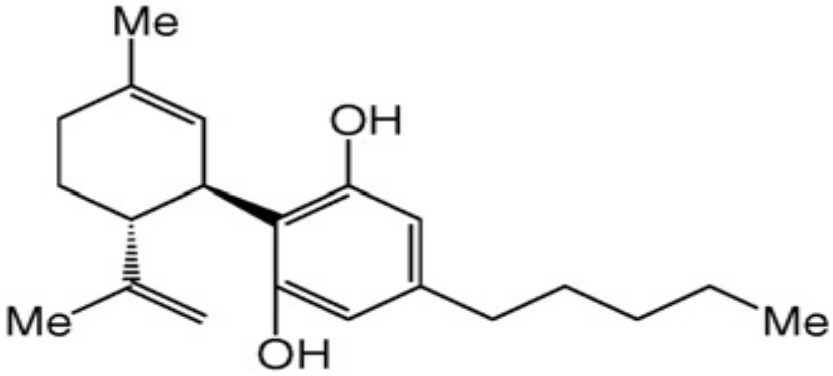


Cannabidiol (CBD)

Non-psychoactive

Very slight CB1/CB2 indirect antagonist; opposes some CNS effects of THC

Antagonist at GPR55 receptor, ? CBD receptor



CBD: Anti-seizure & Anti-epileptic effects

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- CBD has anticonvulsant effects in > 6 seizure models in rats and mice; independently of CNS CB1 receptors (Jones et al, Seizure 2012; Hill et al, Endocannabinoids 2013:164-204; Hill et al, *Brit J of Pharm* 2013; *Karler & Turkanis, J Clin Pharm 2013*)
- CBD reduces epileptiform activity *in vitro* (Jones et al. 2010, *J Pharm Exp Ther)*
- CBD reduces mortality in pentylenetetrazol (PTZ) induced seizures (Jones et al. 2010, *J Pharm Exp Ther)*

From Whalley with permission

Marijuana Use Among Epilepsy Patients (Gross et al, 2004)

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- Tertiary care center: 136 patients
  - 48% lifetime use
  - 21% active users, 15% in last month

Effects	Seizure severity, n = 28	Seizure frequency, n = 28	Medication side effects, n = 28
Improved (%)	19 (68)	15 (54)	3 (11)
Worsened (%)	0 (0)	0 (0)	1 (4)
No effect (%)	9 (32)	13 (46)	24 (85)

CBD: Potential Clinical Uses

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- Epilepsy
- Neuropsychiatric disorders
  - Anxiety
  - Psychosis/Schizophrenia
  - Addiction
- Neonatal hypoxic-ischemic encephalopathy

Conclusions

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- Treatment of patients requires a great deal of awareness regarding AE profiles of different medications
- AEs can sometimes be leveraged to treat comorbidities
- Goal is always seizure freedom
- Be aware of issues treating women especially during pregnancy

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