ASMs: When to Start, How to Select, Mix and Stop

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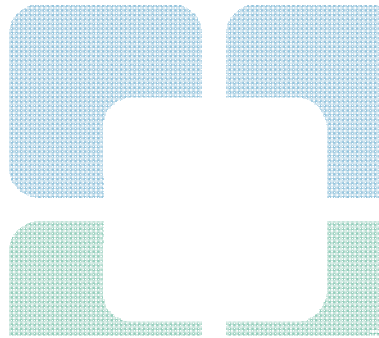
Objectives

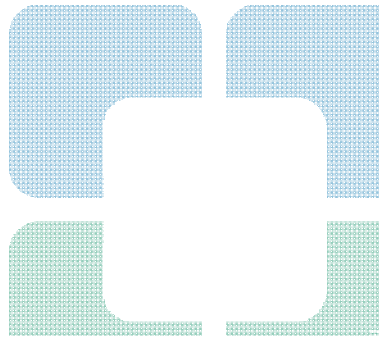
Faced with a concern about potential for epileptic seizures-

1. When do we Start ASM (Anti Seizure Medication)?
2. How do we navigate among the choices of ASMs?
3. When do we Stop ASM?



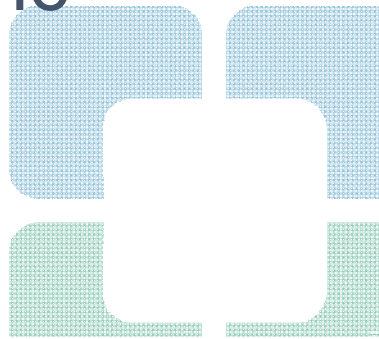
Disclosures

None



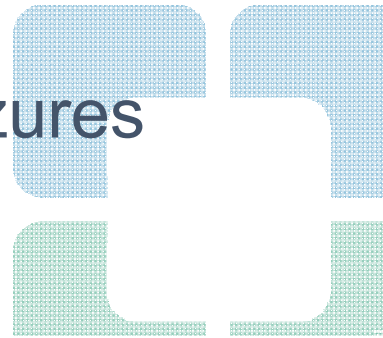
The sentinel paroxysmal event

- Is it an epileptic seizure?
  - 17% of patients presenting to a dedicated first seizure clinic had “seizure mimickers”
  - Commonest mimickers were Reflex syncope and Psychogenic non epileptic seizures
  - Complex Migraines, TIA, Other psychiatric disorders (Dissociative episodes, Panic attacks), Sleep disorders



The sentinel paroxysmal event

- Epileptic seizure (ILAE 2005)
  - “transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”
- Epilepsy
  - “refers to the tendency to have recurrent spontaneous epileptic seizures”
  - 1991 report defined it as two unprovoked seizures occurring 24 hours apart

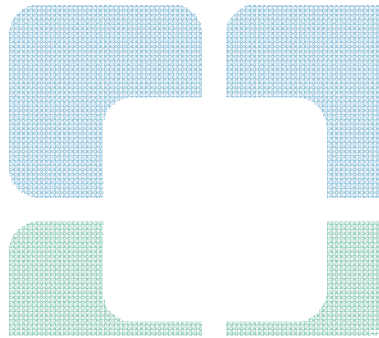


Epilepsy

- ILAE (2013) defines epilepsy as:
  a) At least two unprovoked (or reflex) seizures occurring 24 hours apart
  b) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures or
  c) Diagnosis of an epilepsy syndrome

OK.. It was an Epileptic seizure, what next

- >170,000 individuals in United States alone will have a first seizure each year
- >50% will not have additional seizures
- Distinguishing those with risk of additional seizures is key for ASM treatment consideration



ASM: To Start or To Defer

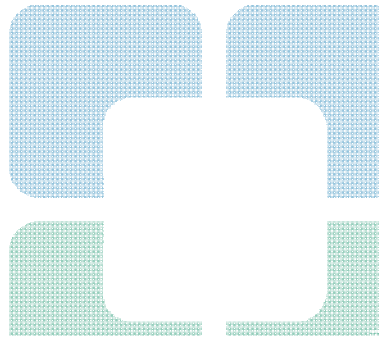
The main overarching considerations:

- The probability of further Seizure Recurrence as determined by clinical presentation, EEG and Neuroimaging
- The Effectiveness of ASM therapy in preventing seizure recurrence
- Probability and Degree of harm if seizures were to recur
- Probability and Degree of harm expected from ASM related adverse effects

The Evaluation of Risk

Up to 10% of the population will have a seizure by age 80, 2-3% will have a diagnosis of epilepsy

- Classification: Etiology and Contributing factors
  - Provoked Sz: events within 24 hours
  - Acute Symptomatic Sz: insult within preceding week, high mortality for 30 days
  - Remote Symptomatic Sz and
  - Unprovoked Sz

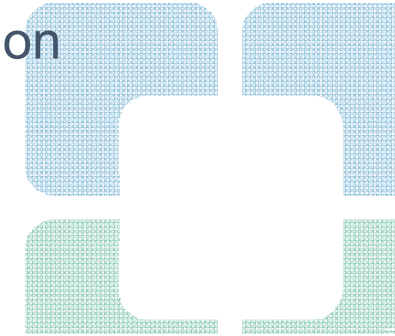


	Recurrence risk (acute symptomatic)	Recurrence risk (remote symptomatic)
Ischemic Stroke	33%	71.5%
Traumatic brain injury	13.4%	46.6%
Meningitis & Encephalitis	16.6%	63.5%

Hesdorffer, Benn, Cascino et al, Epilepsia 2009; 50(5) 1102-1108

The Evaluation of Risk

- Careful History: 39-52% have history of prior seizures
- AAN guidelines (2007) for Unprovoked seizures
  - Adults:
    - EEG, Neuroimaging (Class B evidence)
    - Standard Lab testing or Spinal Tap – insufficient evidence
  - Pediatric Patients:
    - EEG for all children
    - Lab testing, LP, Neuroimaging are recommended based on individual circumstances



The Evaluation of Risk

- Neuroimaging
  - CT changed management in 9% - 17% adult patients and 3% - 8% of pediatric patients
    - Emergent findings are more likely in the right clinical context
  - MRI is more sensitive and preferred imaging modality
- EEG
  - Average yield of 29%
  - Repeat EEGs increase yield up to 84% by third EEG
  - Sleep deprived EEG preferred (13.3% of those with normal initial study showed abnormal findings on sleep deprived study)

SPECIAL ARTICLE

Evidence-based guideline: Management of an unprovoked first seizure in adults

Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society

Neurology® 2015;84:1705–1713

Table 1 Risk of seizure recurrence after an unprovoked first seizure in adults (Class I and II studies)

				Seizure recurrences at various times, n (%)								
Ref.	Class	Age, y	No.	Treated	1 mo	3 mo	6 mo	1 y	2 y	3 y	5 y	>5 y
10, 11	I	70% >19	238	164 (69)	—	—	—	38 (16)	50 (21)	60 (29)	70 (34)	81 (39)
12, 13	I	72% >16	397	204 (51)	24 (6)	58 (15)	75 (19)	98 (25)	111 (28)	—	—	—
17	II	≥16	147	62 (42)	—	—	39 (27)	50 (34)	60 (41)	61 (41)	—	—
18	II	Mean >20	76	36 (47)	2 (3)	18 (24)	20 (26)	22 (29)	—	—	—	—
16	II	≥16	306	41 (13)		55 (18)	79 (26)	111 (36)	136 (44)	144 (47)	—	—
19	II	75% >15	424	?	38 (9)	89 (21)	127 (30)	153 (36)	191 (45)	204 (48)	237 (56)	244 (58)
20	II	14-91	497	127 (26)	—		—	191 (38)	—	—	—	—
15	II	60% >20	812	404 (50)	—		179 (22)	—	288 (35)	—	378 (46)	398 (49)
21	II	≥16	228	113 (50)	—	—	—	68 (30)	—	—	—	—
22	II	18-50	87	45 (52)	—		—	30 (34)	37 (43)	39 (45)	—	—
Total			3,212	1,196 (43)	64 (7)	220 (18)	519 (24)	761 (32)	873 (36)	508 (42)	685 (46)	723 (49)

Increased Risk of Recurrence (Class A)

An adult with a first unprovoked seizure is at greatest risk of recurrence within First Two years (21-45%) and specially in the First Year

This risk appears to be lower for patients treated with ASMs

Cleveland Clinic

Increased Risk of Recurrence

- Prior brain insult or injury causing a seizure (Level A)
- EEG with epileptiform abnormalities (Level A)
- Significant Brain MRI abnormality (Level B)
- Nocturnal Seizure (Level B)
- Age, Sex, FMH, Seizure type, Presentation with status epilepticus or multiple discrete seizures within 24 hours – Did Not Make A Difference

Managing Risk of Recurrence

Does starting ASM after first unprovoked seizure influence:

Short term recurrence?

Long term remission?

Managing Risk of Recurrence

Short term recurrence?

Immediate Treatment Reduces absolute recurrence by 35% for 2 years; QOL unaffected

Long term remission?

Immediate Treatment unlikely to influence >3 year remission or 20 year mortality risk

AMERICAN ACADEMY OF NEUROLOGY

Special Article

CME

Practice parameter: Treatment of the child with a first unprovoked seizure

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society*

Hirtz, Berg et al NEUROLOGY 2003;60:166–175

- 25,000 to 40,000 children in the US experience first unprovoked seizure each year
- <50% will have recurrent seizure

Pediatrics: First Unprovoked Seizure

- 407 patients, followed for > 14 years
- Natural history of an untreated cohort
- Child's risk of seizure recurrence after first unprovoked seizure
- Subsequent risk of developing Refractory Epilepsy
- Mortality risk after first unprovoked seizure

Cleveland Clinic

Shinnar et al, NEUROLOGY 2005;64:880–882

Pediatrics: First Unprovoked Seizure

- 407 patients, followed for > 14 years
- 83% Cryptogenic/Idiopathic; 17% Remote/Symptomatic etiology
- 86% not treated at all or treated for <2 weeks
- 45% experienced seizure recurrence
- 9 deaths (4 probably/possibly related to seizures; 2 treated after first seizure, 2 after second seizure; all were on ASMs)

Cleveland Clinic

Shinnar et al, NEUROLOGY 2005;64:880–882

Pediatrics: First Unprovoked Seizure

After 10 years, 46% had recurrence;19% had 4 or more, 10% had at least 10 seizures

- Idiopathic/cryptogenic 30-50% by 2 years; Remote Symptomatic >50% by 2 years
- Recurrence risk after prolonged first seizure vs brief first seizure is no different

Shinnar et al, NEUROLOGY 2005;64:880–882

Pediatrics: First Unprovoked Seizure

- Evidence of benefit in treating the first unprovoked seizure is weak
- Prognosis of seizure outcome unchanged if treated after first or second unprovoked seizure
- Risks of treatment are significant (data limited to older AEDs)

Shinnar et al, NEUROLOGY 2005;64:880–882

Pediatrics: First Unprovoked Seizure

- Treatment with AED is not indicated for prevention of development of epilepsy (Level B)
- Tailor treatment when benefits of reducing the risk of second seizure outweigh risks of AED treatment related adverse effects (Level B)

Hirtz, Berg et al NEUROLOGY 2003;60:166–175

To Treat or Not To Treat

Treat:

–Acute or Remote Symptomatic seizure from cerebral lesion or insult

–Seizure related complications are present: fracture, aspiration, major injury

–Prior unrecognized seizures present: i.e. auras, myoclonus

Recommend or consider treatment:

–When the risk of recurrence is high

–When a second seizure may be dangerous

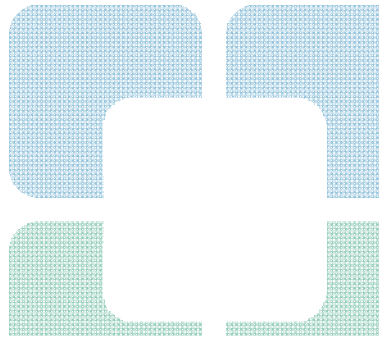
–When it benefits patient's work and function

No treatment with observation:

–Low risk of seizure recurrence

–Patient has good understanding of risks and benefits

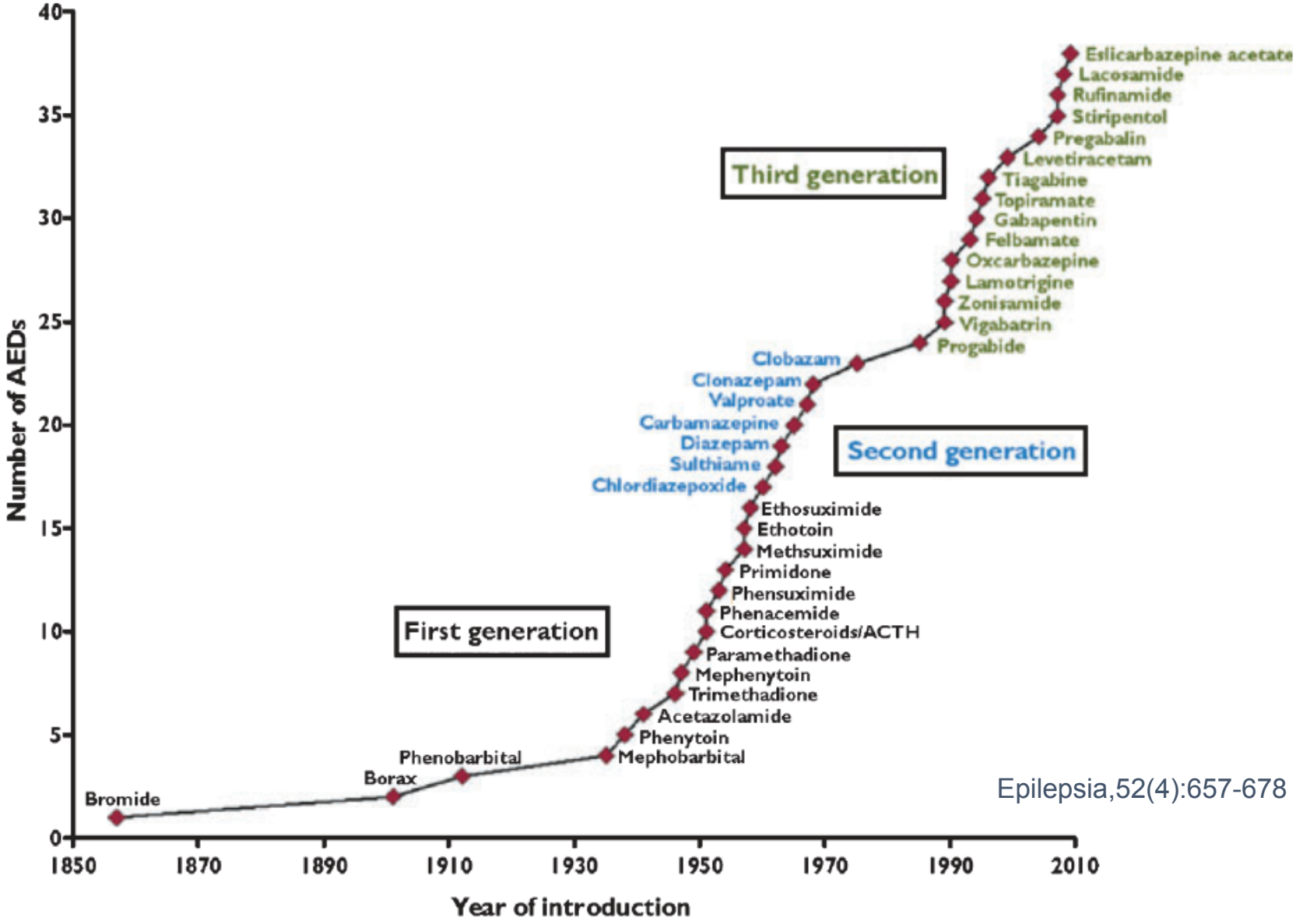
–Patient is agreeable to strategy



ASMs: Many Choices!

FDA approved ASMs

1st Gen	2nd Gen	3rd Gen	Within last 2 years
Carbamazepine	Felbamate	Brivaracetam	Cannabidiol
Clonazepam	Gabapentin	Clobazam	Cenobamate
Chlorazepate	Levetiracetam	Esclicarbazepine	Stiripentol
Diazepam	Lamotrigine	Ezogabine	
Ethosuximide	Oxcarbazepine	Lacosamide	
Lorazepam	Pregabalin	Perampanel	
Phenobarbital	Tiagabinae	Rufinamide	
Phenytoin	Topiramate	Vigabatrin	
Primidone	Zonisamide		
Valproic Acid			



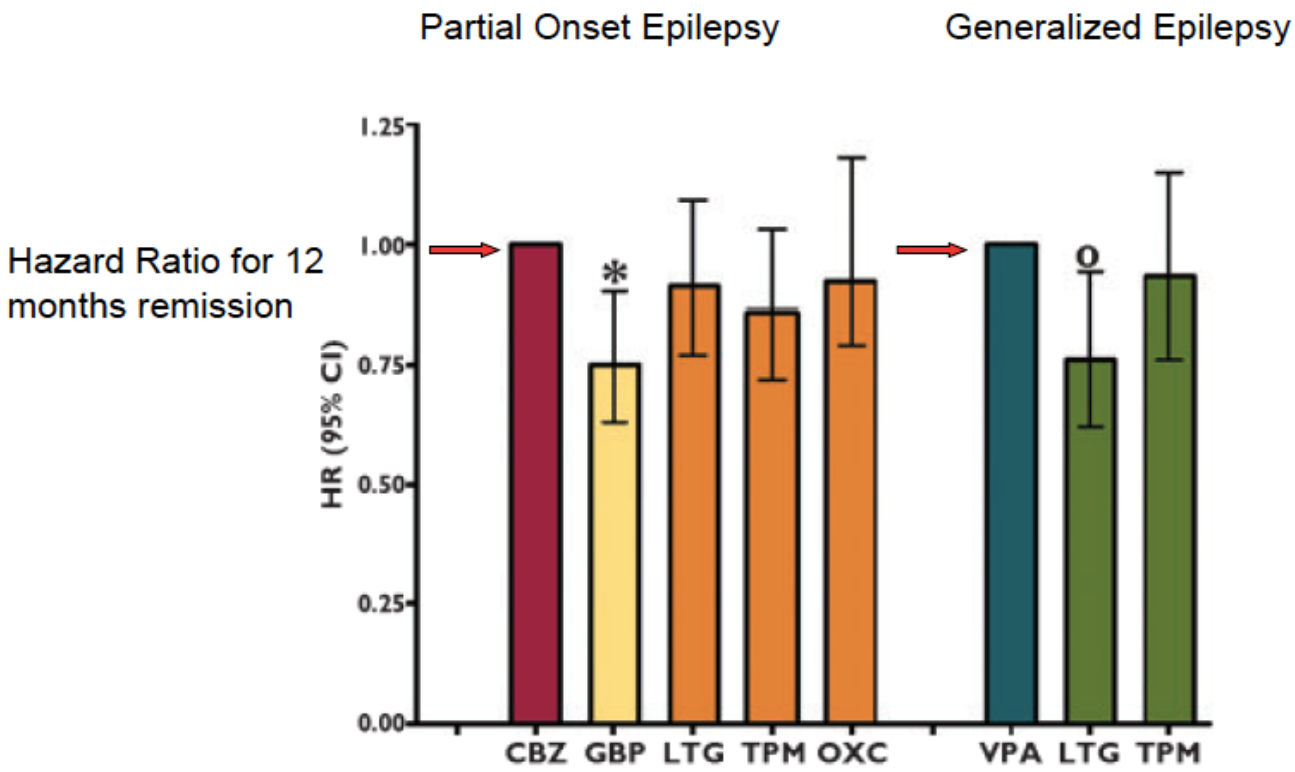
Epilepsia,52(4):657-678

The Old vs The New

- No Class A evidence to show superior efficacy (seizure control rate) of newer drugs compared to the older drugs
- Several studies showed better tolerability and reduced discontinuation rates of newer drugs compared to the older drugs
- When older drugs (like CBZ) are taken in extended delivery formulations, tolerability improved to match newer drugs
- A study showed PGB (pregabalin) to be more effective than LTG (lamotrigine) in refractory partial epilepsy, but another showed LTG better than PGB in newly diagnosed partial epilepsy

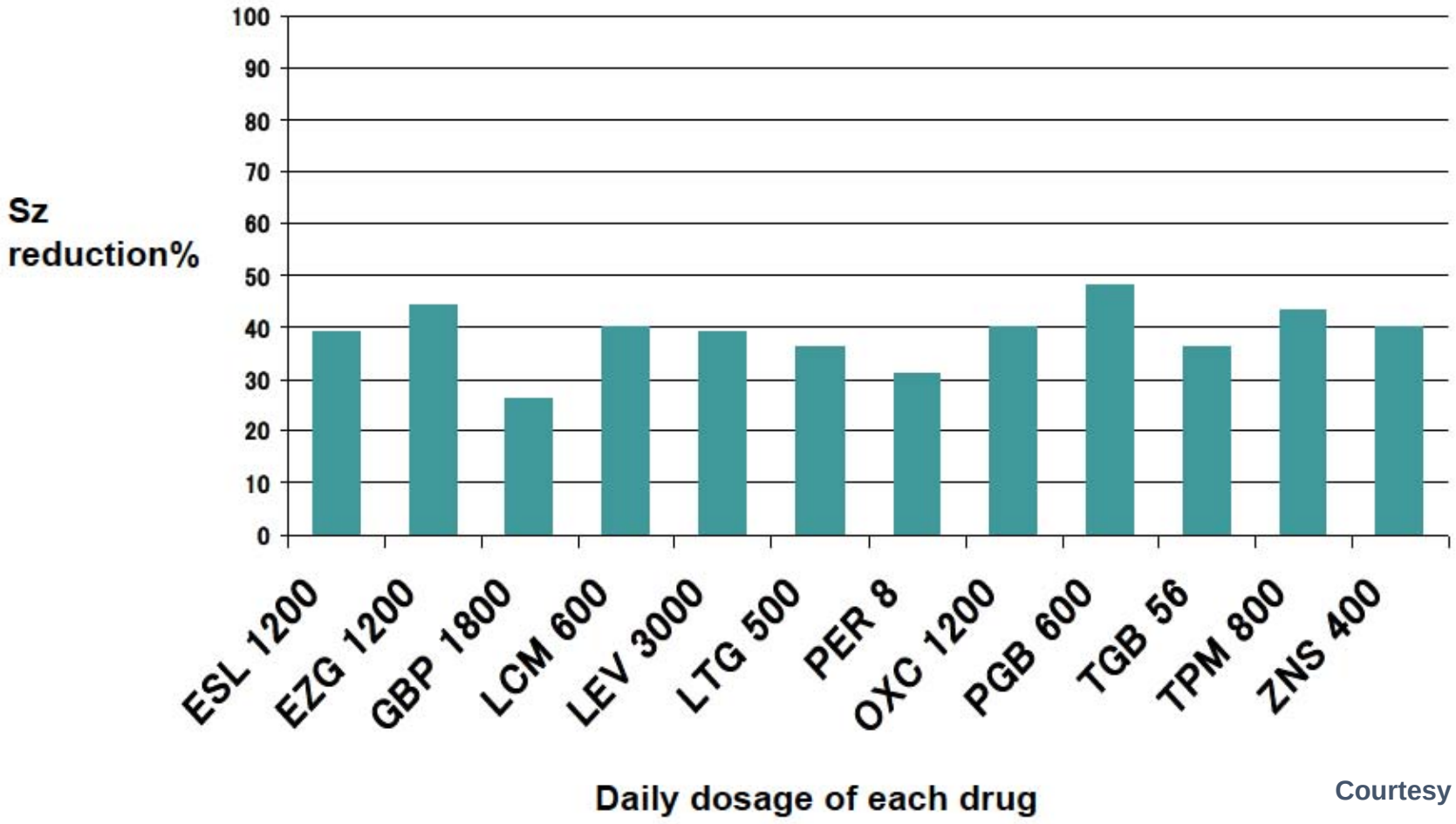
Baulac et al, Epilepsy Research 2010, 91:10
Kwan et al, Lancet Neurology 2011; 10:881

The Old vs The New



Data from: Marson et al, The SANAD Trial 2007, adapted by Löscher & Schmidt 2011

Phase III median Seizure Reduction Rates 1993-2013



Courtesy Dr. NKSo

The New ASMs

- Systematic review of RCTs (62 placebo controlled and 8 RCTs involving >14000 patients) looking at Responder rates (>50% seizure reduction) and Withdrawal (tolerability)
- Small insignificant differences:
  - Responder rates - TPM & LEV >> GBP and TGB
  - Withdrawal OXC and TPM >> GBP and LEV
  - Frequency of adverse effects is comparable
- Deciding factors: Individual patient characteristics and pharmaco-economics

Epilepsia, 52(7):1280–1291, 2011

Choice among ASMs: Focal vs Generalized Seizure

- Individual patient characteristics:
  - Prior allergies
  - Pregnancy, Contraception, Elder age group
  - Side effect profile
  - Co morbid issues like Weight, Hepatic, Renal, Behavioral Health

- Pharmaco-economics
  - Cost
  - State, Insurance, Health System

Epilepsia, 52(7):1280–1291, 2011

Broad-Spectrum Agents

Clonazepam
Phenobarbital
Valproate
Felbamate
Lamotrigine
Topiramate
Zonisamide
Levetiracetam
Rufinamide
Clobazam
Parempanel

Narrow-Spectrum Agents

Partial onset seizures
Phenytoin
Carbamazepine
Oxcarbazepine
Gabapentin
Pregabalin
Tiagabine
Vigabatrin
Lacosamide*
Ezogabine *
Eslicarbazepine*
Brivaracetam*

Generalized Absence
Ethosuximide

Hemodialysis and ASMs

Low Clearance	Intermediate Clearance	High Clearance (supplement post HD)
Phenytoin	Carbamazepine	Ethosuximide
Rufinamide	Felbamate	Esclicarbazepine
Tiagabine	Lamotrigine	Gabapentin
Valproidc Acid	Oxcarbazepine	Lacosamide
		Levetiracetam
		Phenobarbital
		Pregabalin
		Primidone
		Topiramate
		Zonisamide

Asconape JJ in Handbook of Neurology 2014; Vol 119, Chapter 27

Adding ASMs

Combining ASMs

With 25 ASMs n!/r!(n-r)!

2 Drug combinations:

300 possibilities

3 Drug combinations

2300 possibilities

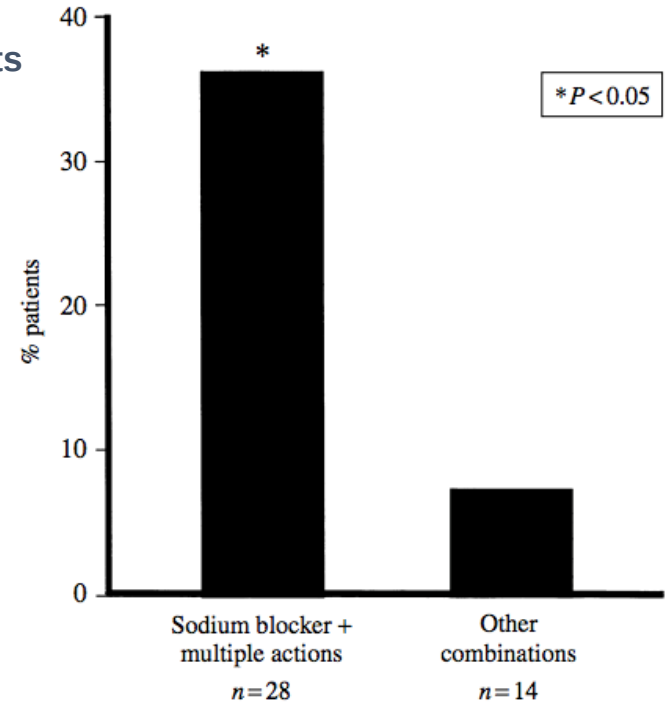
Different mechanism of action

Minimal pharmacokinetic interaction

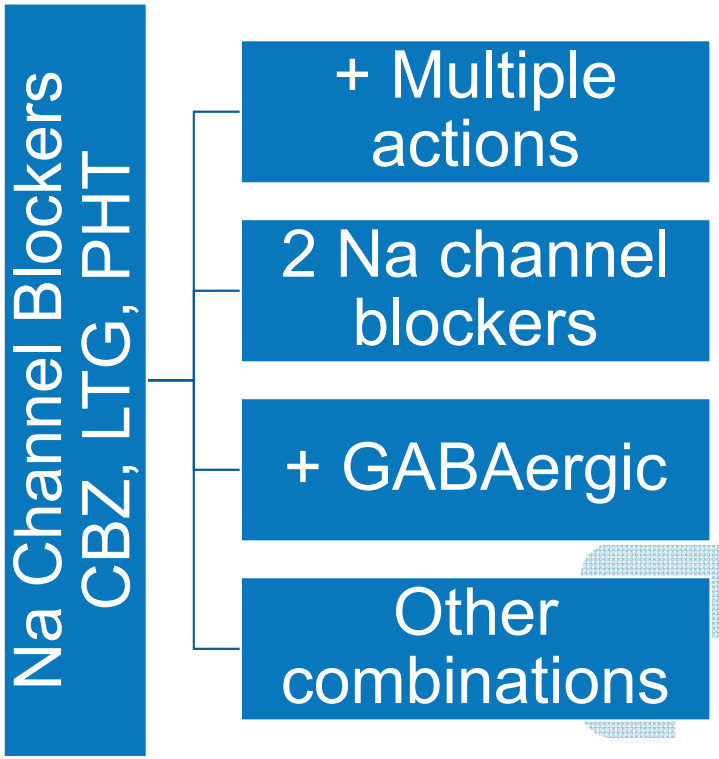
Minimal additive side effects

Potential for synergism

Rationale for selecting multiple mechanism of actions

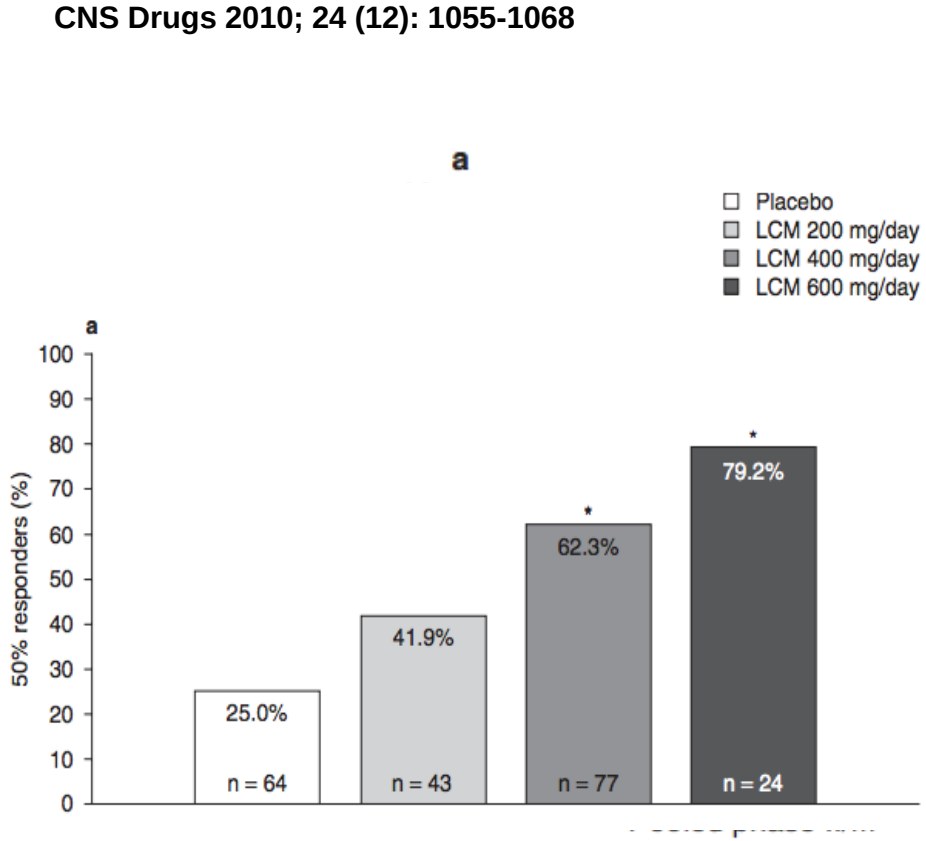


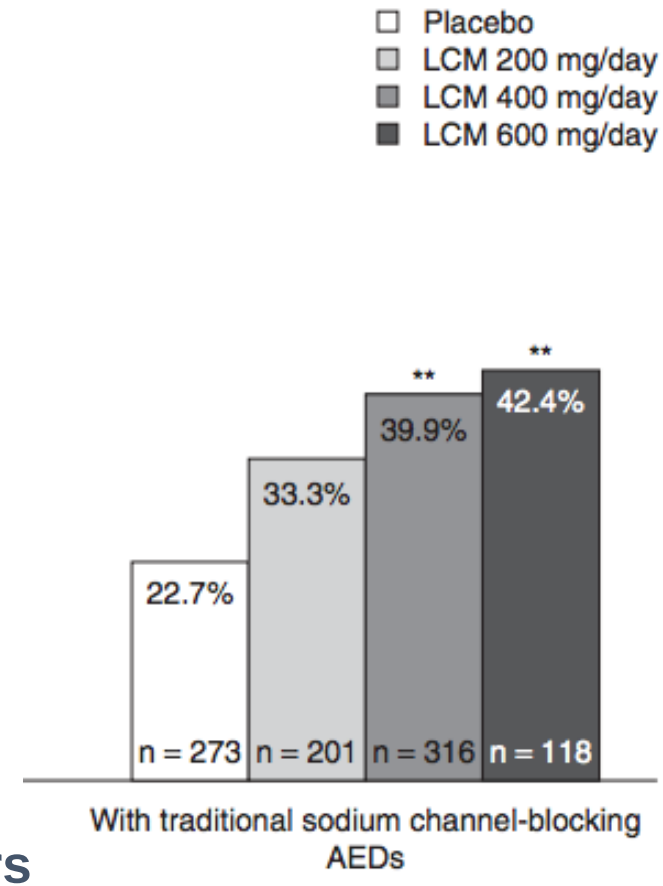
Kwan and Brodie Seizure 2000; 9: 464–468



Rationale for selecting multiple mechanism of actions

CNS Drugs 2010; 24 (12): 1055-1068





Concomitant non Na channel blockers

Combining ASMs

Predominant Mechanism of Action	ASM
Fast Na	PHT, CBZ, OXC, ESL, LTG, VPA,TPM, ZNS
Slow Na	Lacosamide (LCM)
Ca T type	ESM, VPA, ZNS
Ca α2δ voltage-gated	GBP, PGB
K	Ezogabine (EZG)
GABA	VPA, PB, Benzos, TBG, VGB (FBM, TPM)
Glutamate	FBM, LTG,TPM, Perampanel (PER)
SV2	LEV

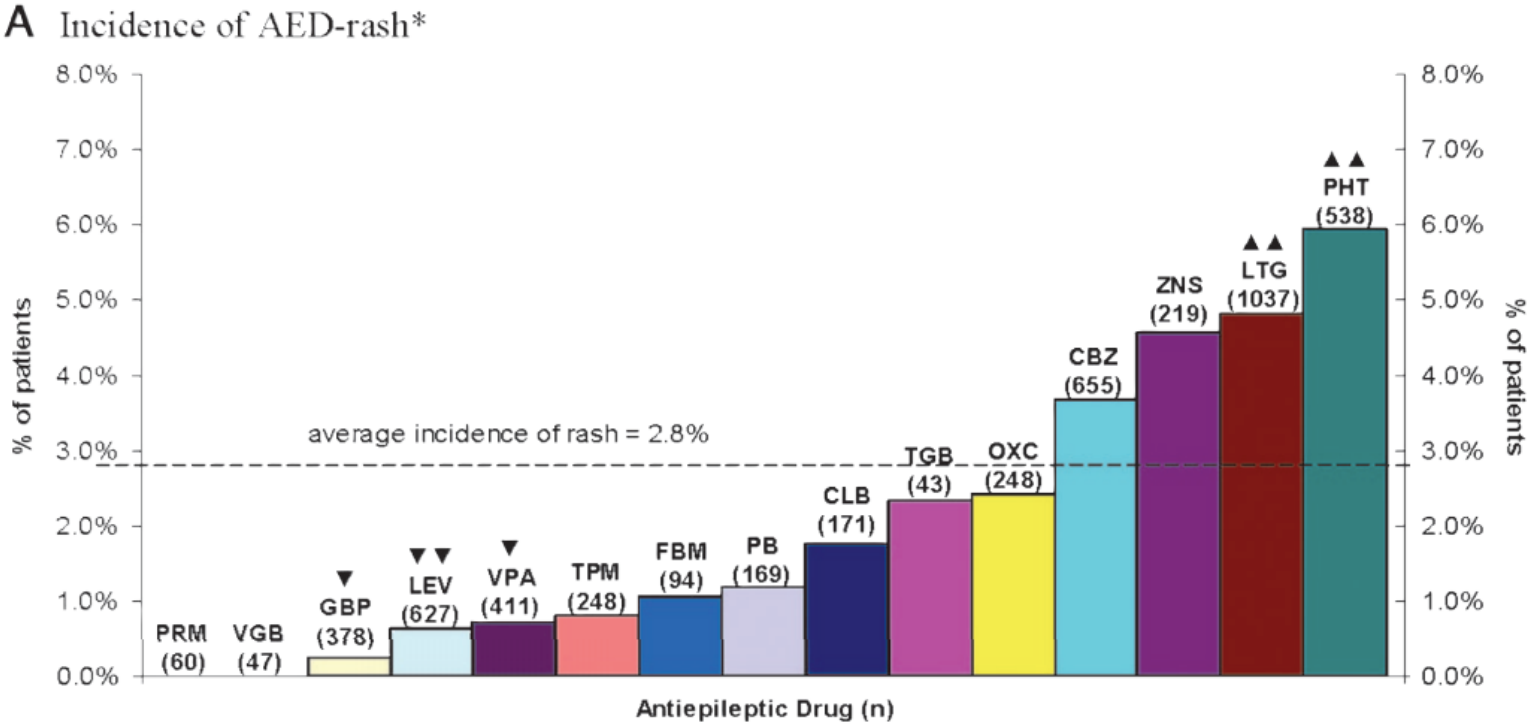
ASM Hepatic Induction

AED	Selective CYP	Broad CYP	UGT
CBZ		++	+
PB		++	+
PHT		++	+
VPA	- 2C9	-	-
Clobazam	- 2D6		
BRV	+ 2C19, - epoxide OHase		
ESL	+ 3A4, - 2C19		Weak +
FBM	+ 3A4, - 2C19		
LCM	Weak - 2C19		
OXC	+ 3A4, - 2C19		Moderate ++
RUF	Weak + 3A4, - 2E1		
TPM	Weak + 3A4, - 2C19		

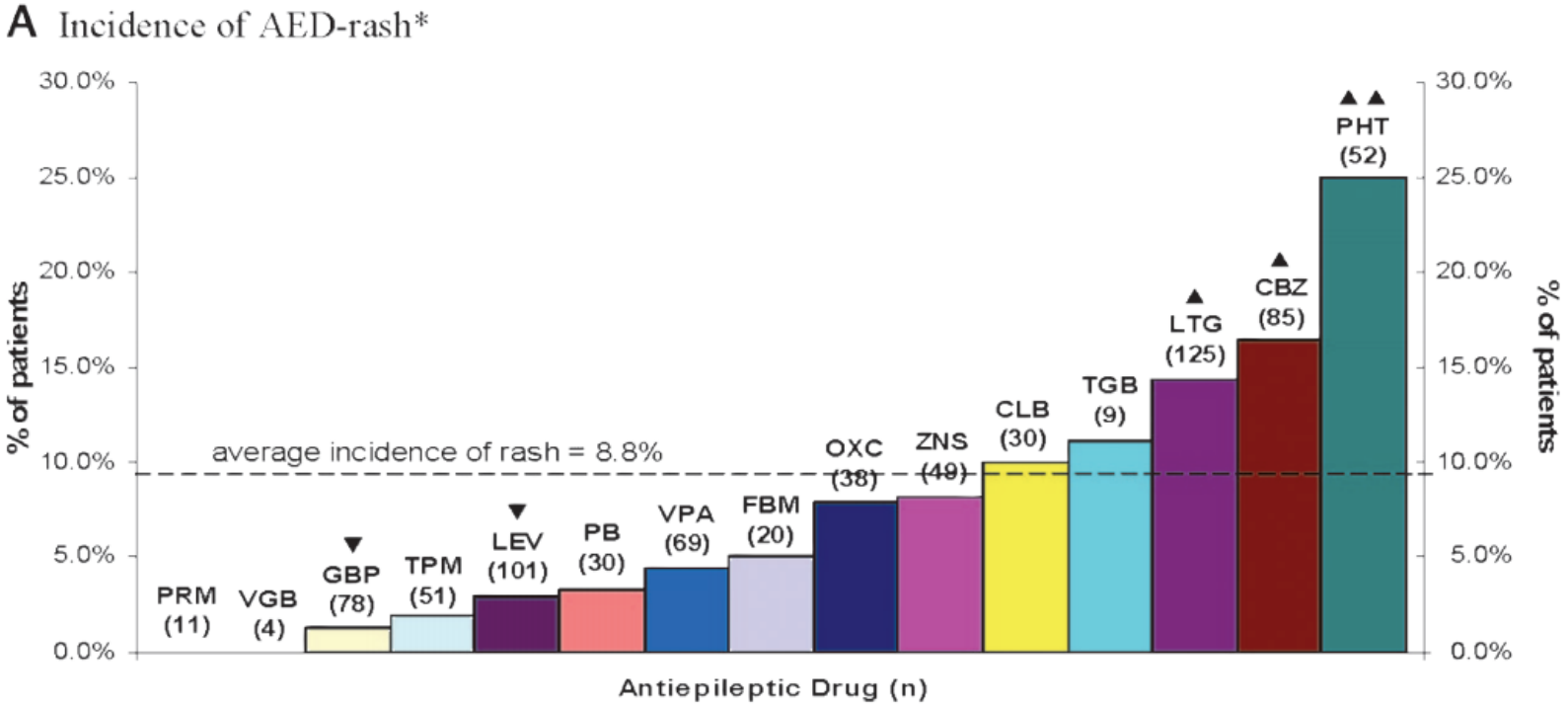
Neither inducers nor inhibitors : ESL, LTG, GBP, PGB, TGB, LEV, PER, ZNS
But may be subject to interaction from other AEDs

Mixing ASMs & Adverse effects

ASMs & Rash


A Incidence of AED-rash*
8.0%
7.0%
6.0%
5.0%
4.0%
3.0%
2.0%
1.0%
0.0%
% of patients
average incidence of rash = 2.8%
PRM (60)
VGB (47)
▼ GBP (378)
▼▼ LEV (627)
▼ VPA (411)
TPM (248)
FBM (94)
PB (169)
CLB (171)
TGB (43)
OXC (248)
CBZ (655)
ZNS (219)
▲▲ LTG (1037)
▲▲ PHT (538)
Antiepileptic Drug (n)

Mixing ASMs & Rash



Mixing ASMs

Rash Cross Sensitivity rates:

- CBZ ↔ OXC (33-71%)
- CBZ ↔ PHT (42-57%)
- CBZ ↔ PB (27-66%)
- ZNS ↔ PHT (21%)

No specific cross reactivity between LTG and any other ASM

ASMs with small chance of a Rash

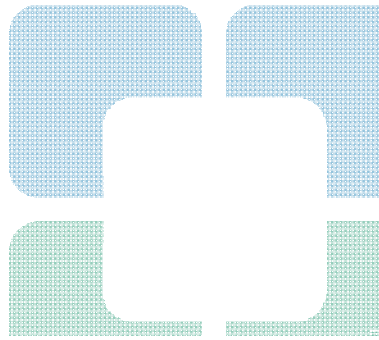
Gabapentin

Levetiracetam

Pregabalin

Topiramate

Valproic Acid

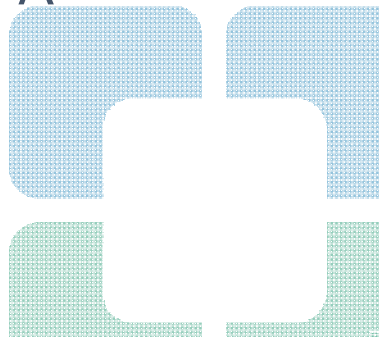


Additive Adverse Effects

- **Somnolence**: nearly all AEDs except LTG, FBM
- **Insomnia**: LTG, FBM
- **Dizziness/imbalance**: PHT, PRM, CBZ, OXC, ESL, LCM, LTG, TGB, PGB, PER
- **Blurred vision**: CBZ, OXC, LTG, LCM
- **Tremors**: VPA, LTG
- **Weight gain**: CBZ, VPA, GBP, PGB, VGB
- **Weight loss**: FBM, TPM, ZNS
- **Mood changes**: ESM, PB, LEV, TPM, ZNS, PER, paradoxical effects of benzos

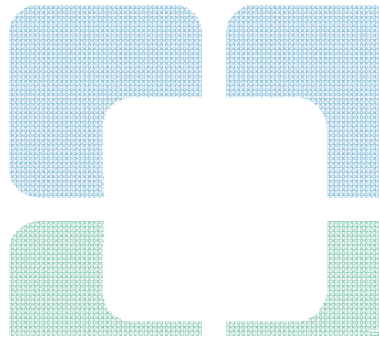
Not easy ASM combinations

- **LCM + Na+ drugs (PHT, CBZ, OXC, LTG):** dizziness, blurred vision, LCM metabolism inducible
- **TPM + ZNS**: doubling side effects: cognitive slowing, weight loss, kidney stones
- **LTG + VPA**: inhibition of LTG clearance, increased risk of rash
- **CBZ + LTG**: hepatic induction of LTG clearance, additive dizziness and blurred vision
- **PHT + VPA**: PHT induces VPA metabolism (reduces to 50%). VPA displaces PHT (decreases total, increases free)
- **PB + VPA**: idiosyncratic hypersomnolence/encephalopathy
- **CBZ + OXC**: doubling side effects: dizziness, diplopia



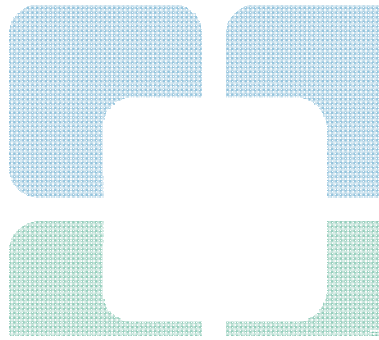
Easy ASM combinations

- **Levetiracetam:** An easy add on to all ASMs
- **Lacosamide**: An easy add on to non Na+ channel blocking ASMs
- **Topiramate**: Add on to non-inducing drugs other than ZNS; ?VPA
- **Gabapentin and Pregabalin**: Can be added to all ASMs



Combining ASMs

- Different mechanism of action
- Minimal pharmacokinetic interaction
- Minimal additive side effects
- Potential for synergism

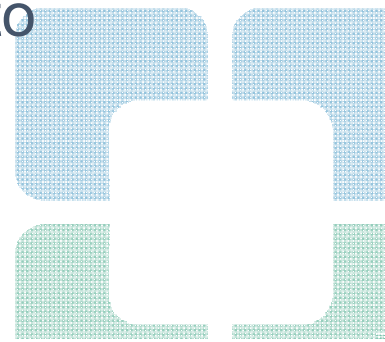


ASMs: Letting go is not easy

Discontinuation of ASM

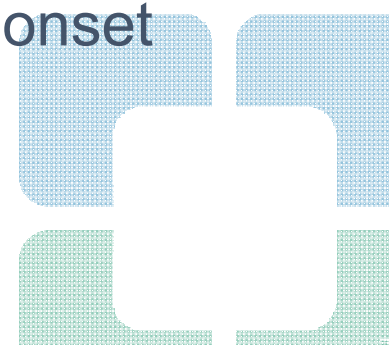
AAN Practice Parameter 1996; Discontinuation may be considered if -

- Seizure free 2-5 years on AEDs (mean 3.5 years)
- Single type of partial or generalized seizure
- Normal neurological exam and normal IQ
- EEG normalized with treatment
- Adults have a 61% chance and Children 69% chance to remain Seizure Free



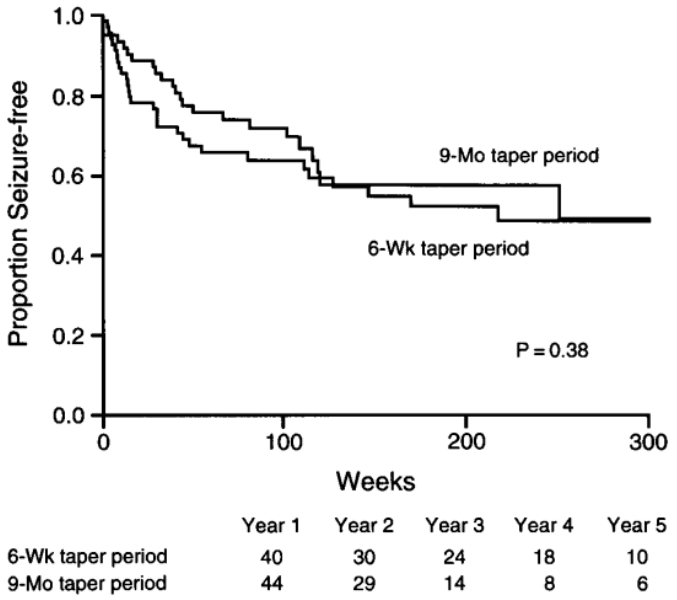
Discontinuation of ASMs

- Prospective and Retrospective studies over last 25 years suggest
  - Relapse risk 25% at 1 year and 29% at 2 years
- Childhood onset epilepsy, Neurologically normal children, Normal EEG (8-12% relapse)
- Differences in Adults are smaller than thought (RR 1.3)
  - Much of the increased risk is due to the adolescent onset seizures



Duration of ASM taper

- Considerable variability; taper lasting months or even years
- Prospective, randomized clinical trial (1994) in Children with epilepsy with >2 year seizure freedom
  - 6 week or 6 month taper
  - No difference in recurrence at 2 years

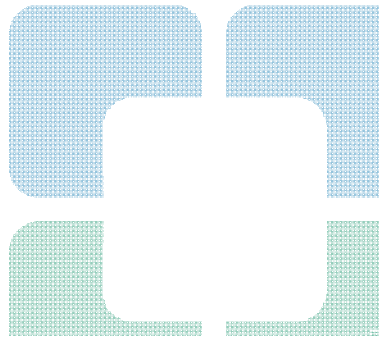


	Year 1	Year 2	Year 3	Year 4	Year 5
6-Wk taper period	40	30	24	18	10
9-Mo taper period	44	29	14	8	6

N Engl J of Med 1994, 330

Prognosis after ASM Discontinuation

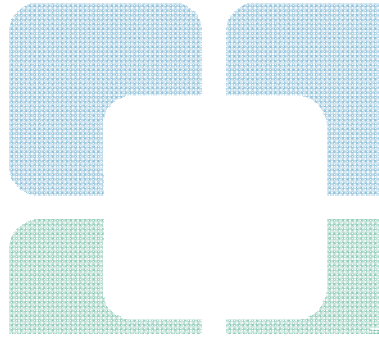
- Majority of patients who relapse after medication withdrawal will become seizure free and in remission after ASMs are restarted
- Seizure control may not be immediate
- Prognosis for seizure control after recurrence in well controlled patients is no different in those in whom ASM withdrawn and relapsed or those who remained on ASM and still relapsed



ASM Discontinuation after Epilepsy Surgery

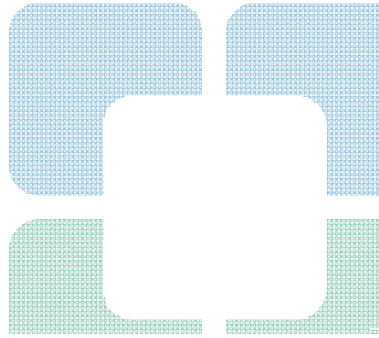
- 60% remain seizure free after ASM withdrawn
- Good prognosis: Younger age at surgery, HS on MRI
- Not so Good prognosis: >30 years at surgery, long duration of epilepsy, persistent SWs on EEG, Normal MRI (specially with neocortical resections)
- Berg et al: Much of the relapses after 1 year seizure freedom, occurred while reducing ASMs; the risk of recurrence was not higher in those who continued ASMs

Berg et al, Epilepsia, 2006; 47
Lee et al, Seizure 2008;17
Al-Kaylani et al, Seizure 2007;16
Tellez-Zenteno, Epilepsy Res 2012



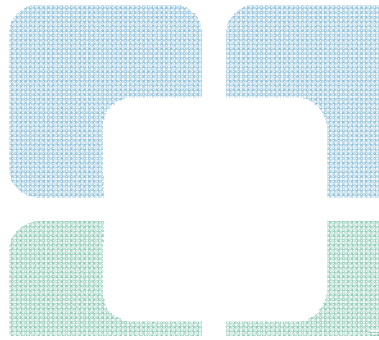
ASM Discontinuation after Non Epileptiform EEG

- ASM started for prophylaxis after CNS insult: 1-3 months
- ASM started after single symptomatic seizure from CNS insult: 12 months
- ASM after single unprovoked seizure: 2 years, if no risk for recurrence
- ASM after first remote symptomatic seizure: 2 years and reconsider
- ASM after at least 2 unprovoked seizures: 2 years and reconsider
- ASM after successful epilepsy surgery: after 1-2 years



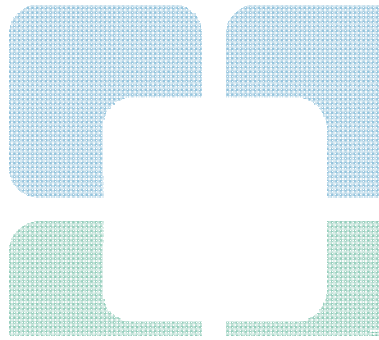
ASM Discontinuation – a highly individualized decision

- Patient discussion and complete buy in
- EEG while still on ASM
- Advice on Driving and Activities
- Withdraw one drug at a time
- Taper one ASM over 6-12 weeks
- Close follow up (EEG optional)



All of the following about ASM taper in children are true except

1. Tapering each ASM over 1 year is safer for seizure prevention than a taper over 6-12 weeks
2. Taper after successful epilepsy surgery may be an option
3. Majority of patients who relapse after ASM taper will regain seizure control after restarting ASM
4. Taper after 2 years of an unprovoked seizure may be an option



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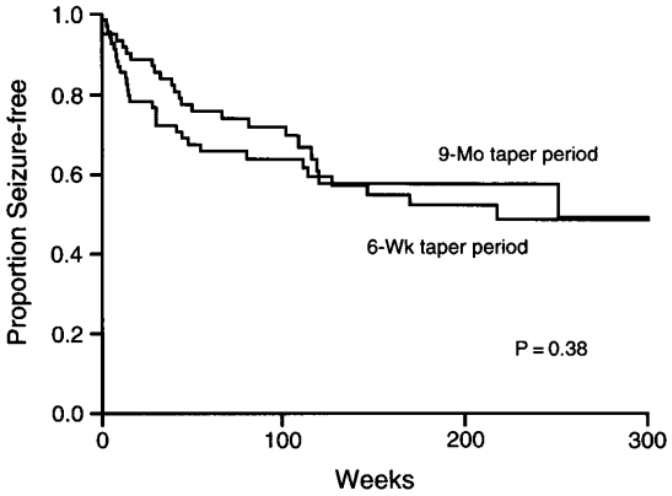

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6-Wk taper period	40	30	24	18	10
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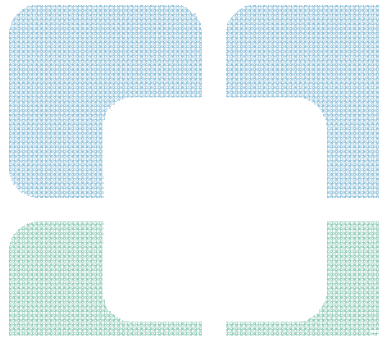
N Engl J of Med 1994, 330

Correct answer 1

There is high risk of seizure recurrence after first unprovoked seizure in all of the following except:

1. There is h/o prior brain injury or insult causing the seizure
2. The patient presents with a nocturnal seizure
3. EEG shows epileptiform abnormality
4. Patient presents with multiple discrete seizures within 24 hours



There is high risk of seizure recurrence after first unprovoked seizure in all of the following except:

4. Patient presents with multiple discrete seizures within 24 hours

Other factors that did not make a difference included Age, Sex, FMH of seizures, Seizure Type, Presentation with Status Epilepticus

Neurology 2007;69;1996-2007
N Eng J Med 1982;307;522-528
Neurology 1990;40;1163-1170
Neurology 2006;67;1047-1049
Neurology 1991;41;965-972
Epilepsia;2008;49(suppl 1)13-18

Correct answer 4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