Pharmacological treatment

Prof. Dieter Schmidt

Pharmacological Treatment

Professor Dieter Schmidt

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Outline

- The art of pharmacological epilepsy treatment includes matching the profile of the individual patient with profile of the individual antiepileptic drug (AED);

1. How and when to start AEDs? Which AED?
2. How to optimize the benefit/risk balance of pharmacological treatment for your patient?
3. How and when to stop AEDs?
4. Outlook?

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Why treat epilepsy?

- Make sure it is epilepsy and the patient wants to be treated
- AEDs offer symptomatic seizure control, *i.e.*, a lower risk of seizure recurrence
- Ideally: no seizures, no side effects
- Realistically: 70% seizure free, 50% no side effect
- AEDs allow most patients to live a normal life

Elger CE, Schmidt D, Modern management of epilepsy: a practical approach; *Epilepsy Behav.* 2008; **12**: 501-539

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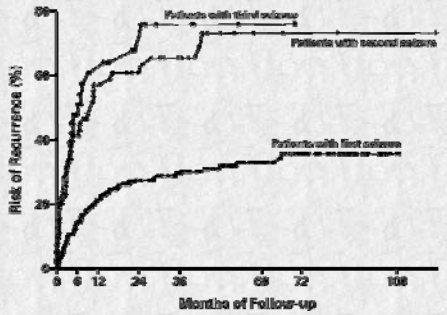
The risk of seizure recurrence



Hauser *et al.*, Risk of recurrent seizures after two unprovoked seizures; *N. Engl. J. Med.* 1998; **338** (7): 429-434

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Who may not need AEDs

- Children with febrile seizures, idiopathic focal epilepsies of childhood *e.g.,* Rolandic epilepsy
- Adolescents or adults with drug-induced seizures, single seizures, isolated clusters of seizures or rare seizures
- Immediate or posttraumatic seizures

Elger CE, Schmidt D. Modern management of epilepsy: a practical approach; *Epilepsy Behav.* 2008; **12**: 501-539

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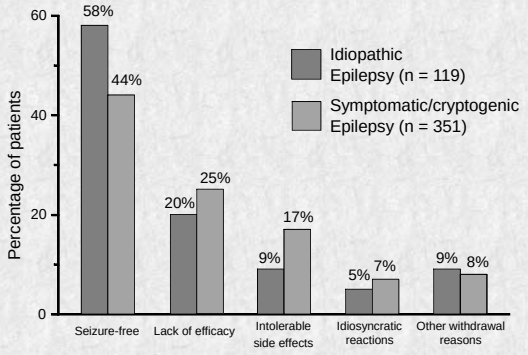
Response to first-ever AED



mod. from Kwan and Brodie; Effectiveness of first antiepileptic drug; *Epilepsia* 2001; **42**: 1255-1260

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Which AED?

- Match the need of the individual patient (seizure type, gender, comorbidity, past treatment)
- The best tolerated AED for the seizure type: no side effects, no drug interaction, no monitoring = no unnecessary interference
- Start low, go slow
- Consider: in 30% AEDs are for life
- AEDs allow most patients to live a normal life

Elger CE, Schmidt D. Modern management of epilepsy: a practical approach; *Epilepsy Behav.* 2008; **12**: 501-539

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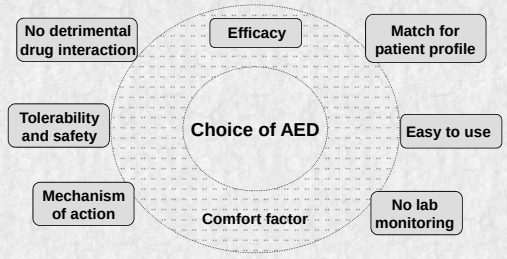
Choice of AED: considerations



Elger CE, Schmidt D. Modern management of epilepsy: a practical approach; *Epilepsy Behav.* 2008; **12**: 501-539

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AEDs: mechanism of action of AEDs and clinical efficacy

Drug	Anticonvulsant effect in rodent models			Clinical efficacy (seizure suppression)		
	MES*	s.c. PTZ**	Amyg.-kindling***	Partial seizures	Generalized seizures	
Predominant Na^+/Ca^{2+} activity					Convulsive	Nonconvulsive
Phenytoin	+	NE	+	+	+	NE
Carbamazepine	+	NE	+	+	+	NE
Oxcarbazepine	+	NE	+	+	+	NE
Lamotrigine	+	±	+	+	+	+
Zonisamide	+	±	+	+	+	+
Predominant Ca^{2+} activity						
Ethosuximide	NE	+	NE	NE	NE	+
GABA systems						
Benzodiazepines	+	+	+	+	+	+
Vigabatrin	NE	+	+	+	+	NE
Tiagabine	NE	+	+	+	+	NE
Mixed						
Valproate	+	+	+	+	+	+
Felbamate	+	+	+	+	+	+
Topiramate	+	NE	+	+	+	+
Phenobarbital	+	+	+	+	+	±
Novel targets						
Gabapentin	±	±	+	+	+	NE
Pregabalin	+	NE	+	+	+	NE
Levetiracetam	NE	NE	+	+	+	±
Lacosamide	+	NE	+	+		
Retigabine	+	+	+	+		

Table 2. Anticonvulsant spectrum of AEDs in models and man,
"NE" = not effective; * mice/rats, mice/cats, *** rats, focal seizures,amygd=amygdala, + = effective, ± insufficient data,**
Adapted from Rogawski and Löscher (2004a) and Bialer *et al*., (2009), Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: Ways out of the current dilemma; *Epilepsia* 2011 (in press)

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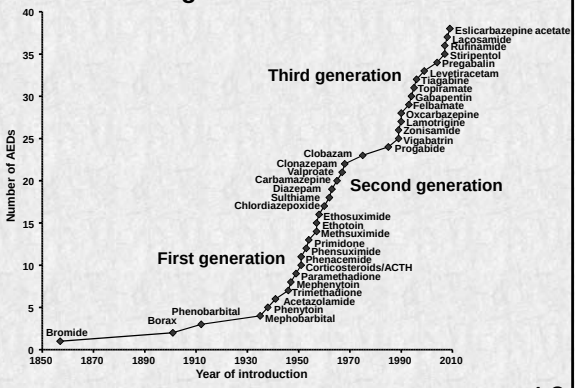
Three generations of AEDs



Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: Ways out of the current dilemma; *Epilepsia.* 2011 (in press)

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Major first generation AEDs

AED	PRO	CON
Phenobarbital / Primidone	Long experience, intravenous, broad efficacy, low cost[1]	Interaction, sedation, depression, rheumatism, less effective than Carbamazepine[2]
Phenytoin	Long experience, intravenous, non-sedative, well tolerated in the elderly[1]	Interaction, rash, cerebellar toxicity, non-linear kinetics[1]

1. Elger CE, Schmidt D, Modern management of epilepsy: a practical approach; *Epilepsy Behav.* 2008; **12**: 501-539
2. Mattson *et al.*, Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures; *N. Engl. J. Med.* 1985; **313**: 145-151

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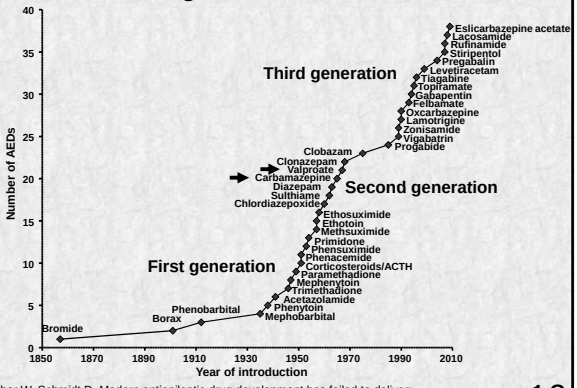
Three generations of AEDs



Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: Ways out of the current dilemma; *Epilepsia* 2011 (in press)

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Major second generation AEDs

AED	PRO	CON
Carbamazepine	Long experience, in general well tolerated, unsurpassed efficacy[1]	Interactions, not well tolerated in children and elderly, rash, aplastic anemia[3]
Valproate	Long experience, intravenous use, broad efficacy, unsurpassed efficacy for idiopathic generalized epilepsy[1]	Weight gain, liver failure, high teratogenicity, interaction[3], VPA less effective than CBZ for cps[2]

1. Mattson *et al.*, Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures; *N. Engl. J. Med.* 1985; **313**: 145-151
2. Schmidt and Beyenburg, Antiepileptic drugs; *Side Effects of Drugs*. Annual 31, Aronson JK (ed) 2009; pp. 105-148; *Elsevier:* Amsterdam
3. Mattson *et al.*, A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic- clonic seizures in adults; The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group; *N. Engl. J. Med.* 1992; **327**: 765-771

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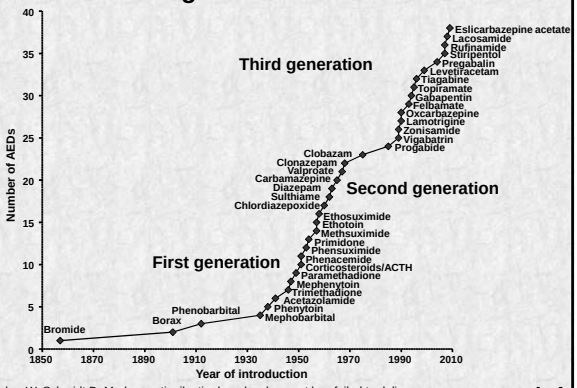
Three generations of AEDs



Löscher W, Schmidt D, Modern antiepileptic drug development has failed to deliver: Ways out of the current dilemma; *Epilepsia* 2011 (in press)

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Third generation AEDs

AED	PRO	CON
Gabapentin	Well tolerated, safe, no interaction, no rash	T.i.d., weaker efficacy *vs.* CBZ[2]
Lamotrigine	Well tolerated, safe, mood-stabilizer (Grumpy Old Men!)	Interaction, slow titration
Levetiracetam	Well tolerated, safe, few interactions, no idiosyncratic reaction	Psychiatric adverse effects
Oxcarbazepine	Well tolerated, safe, better tolerated than Carbamazepine, particularly in children	Interaction, hyponatremia (elderly, comedication)

1. Elger CE, Schmidt D, Modern management of epilepsy: a practical approach; *Epilepsy Behav.* 2008; **12**: 501-539
2. Marson *et al.*, A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs; The SANAD trial; *Health Technol. Assess.* 2007; **11**: 1-134

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Third generation AEDs (2)

AED	PRO	CON
Topiramate	Generally well tolerated, safe, no interactions below 200 mg/d, broad efficacy	Cognitive side effects, weight loss, depression, rare nephrolithiasis, metabolic acidosis
Pregabalin	Generally well tolerated, safe analgesic action	Weight gain, edema, no monotherapy
Tiagabine	Well tolerated, safe no interactions	Non-convulsive status epilepticus, depression, no monotherapy

Elger CE, Schmidt D, Modern management of epilepsy: a practical approach; *Epilepsy Behav.* 2008; **12**: 501-539

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Which AED for focal seizures?

Classification	Recommended	Other
Focal, including tonic clonic seizures	Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine	Valproate, Carbamazepine, Clobazam, Phenytoin, Pregabalin, Topiramate, Vigabatrin, *etc.*
Unclear, if focal or generalized seizure	Valproate, Lamotrigine, Levetiracetam, Clobazam	Phenobarbital Topiramate, Zonisamide, *etc.*

Mod. from Elger CE, Schmidt D. Modern management of epilepsy: a practical approach; *Epilepsy Behav.* 2008; **12**: 501-539

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Which AED for generalized seizures?

Classification	Recommended	Other
Generalized, including tonic-clonic seizures	Valproate, Levetiracetam, Lamotrigine	Phenobarbital Carbamazepine, Clobazam? Topiramate *etc.*
Absence seizures only	Valproate, Ethosuximide Clobazam	Levetiracetam Lamotrigine, Phenobarbital Topiramate, Zonisamide, *etc.*
Myoclonic seizures	Valproate, Clobazam	Levetiracetam Phenobarbital Lamotrigine Topiramate, Zonisamide, *etc.*

? = Uncertain utility

Elger CE, Schmidt D, Modern management of epilepsy: a practical approach; *Epilepsy Behav.* 2008; **12**: 501-539

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Starting dose, titration and drug interaction

AED	Starting dose mg/d (maintenance)	Titration in weeks	Major elimination /metabolic pathways	CYP- P450 inducer	Enzyme inhibitor
Clobazam	10 (10)	0.2	Hepatic	No	No
Gabapentin/Pregabalin	300 (2400)/75(300)	1	Renal	No	No
Vigabatrin	500 (3000)	1.5	Renal	No	No
Carbamazepine	200 (800)	2	Hepatic	Yes	No
Oxcarbazepine	150 (1200)	2	Hepatic	Yes	Yes
Phenytoin	100 (300)	2	Hepatic	Yes	No
Valproate	600 (1200)	2	Hepatic	No	Yes
Lacosamide	50 (400)	2	Hepatic	No	No
Eslicarbazepine	400 (800)	2	Hepatic	Yes	No
Zonisamide	25 (300)	3	Hepatic	No	No
Levetiracetam	500 (2000)	4	Renal	No	No
Felbamate	300 (3600)	4	Hepatic	no	No
Tiagabine	6 (35)	7	Hepatic	No	No
Ethosuximide	250 (1000)	8	Hepatic	No	No
Phenobarbital	50 (200)	8	Hepatic	Yes	No
Bromide	300 (2100)	8	Hepatic	No	No
Primidone	125 (250)	8	Hepatic	Yes	Yes
Topiramate	25 (200)	9	Hepatic	Yes*	Yes
Lamotrigine	25 (300)	10	Hepatic	No	No

*>200mg

Mod. from Shorvon S. *et al.*, *The Treatment of Epilepsy*; Oxford Blackwell Publishing 2004
Patsalos PN. *Anti-Epileptic Drug Interactions: A clinical Guide*; Cranleigh: Clarius Press Ltd. 2005

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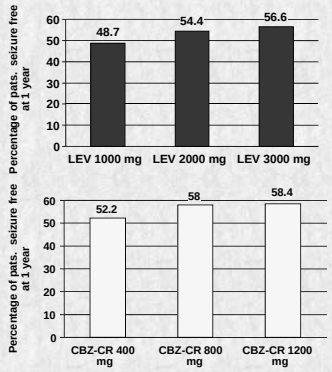
Limited effectiveness of dose increase



Mod. from Brodie *et al.*, Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy; *Neurology,* 2007; **68**: 402-408

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Which dose is optimal?

- The optimal dose is the lowest dose (at whatever serum concentration) that achieves seizure freedom and at the lowest possible rate of adverse effects[1]
- While young children may need higher mg/kg dose or more frequent dosing because they metabolize AEDs more rapidly than adults, the elderly often require lower mg/kg dose as they metabolize and eliminate slower and are more responsive to drug effects[1,2]
- Avoid overtreatment = unnecessary and excessive drug load that leads to a suboptimal risk-benefit balance[1]

1. Schmidt D. Strategies to prevent overtreatment with antiepileptic drugs in patients with epilepsy; *Epilepsy Res.* 2002; **52**: 61-69
2. Brodie *et al.*, Epilepsy in later life; *Lancet Neurol.* 2009; **8**: 1019-1030

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Adverse events of AEDs

	Carbamazepine	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate	Total
Number randomised	378	377	378	210	378	1721
Total number (%) of patients with at least one adverse event	183 (48%)	178 (47%)	169 (45%)	100 (48%)	200 (53%)	830 (48%)
Tiredness/drowsiness/fatigue/lethargy	48 [36]	46 [34]	31 [17]	22 [16]	43 [33]	190 [136]
Depression	14 [8]	18 [10]	20 [13]	7 [5]	29 [24]	88 [60]
Headache	21 [9]	20 [15]	21 [13]	9 [6]	17 [11]	88 [54]
Allergic rash	38 [32]	13 [4]	17 [15]	20 [16]	17 [8]	105 [75]
Memory problems	20 [12]	22 [19]	13 [10]	13 [8]	26 [19]	94 [68]
Dizziness/vertigo	14 [10]	23 [15]	15 [9]	13 [12]	15 [8]	80 [54]
Other psychiatric	16 [7]	17 [9]	11 [7]	7 [5]	37 [31]	88 [59]
Worsening of seizures	17 [5]	22 [13]	17 [12]	3 [1]	17 [8]	76 [39]
Other neurological	9 [6]	21 [14]	15 [9]	8 [5]	18 [12]	71 [46]
Other general	13 [6]	19 [11]	19 [13]	9 [6]	16 [12]	76 [48]
Behaviour/personality change/aggression	12 [4]	9 [6]	12 [7]	2 [1]	24 [19]	59 [37]
Ataxia	9 [6]	24 [12]	14 [9]	8 [6]	9 [3]	64 [36]
Confusion/difficulty thinking/disoriented	9 [9]	16 [15]	8 [4]	8 [6]	22 [19]	63 [53]
Anxiety/agitation/nervousness	7 [7]	15 [11]	8 [5]	7 [6]	15 [12]	52 [41]
Weight loss	2 [1]	4 [2]	4 [2]	3 [1]	29 [27]	42 [33]
Diplopia	5 [2]	11 [4]	4 [2]	8 [6]	6 [3]	34 [17]
Nausea	9 [6]	7 [3]	9 [6]	15 [13]	4 [4]	44 [32]
Weight gain	9 [7]	15 [12]	4 [1]	1 [0]	5 [4]	34 [24]
Accidental injury	7 [2]	11 [6]	12 [8]	3 [1]	8 [3]	41 [20]
Pins and needles/dysaesthesia	4 [1]	5 [1]	3 [1]	0 [0]	26 [24]	38 [27]
Sleep disturbance	5 [2]	4 [4]	9 [8]	4 [2]	9 [8]	31 [24]
Other events*	108 [71]	113 [73]	110 [70]	46 [38]	103 [64]	480 [316]

Marson *et al.*, A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs; The SANAD trial; *Health Technol. Assess.* 2007; **11**: 1-134

No brackets = intention-to-treat analysis, Brackets = per protocol analysis

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AED-associated disease

	CBZ	PB	PHT	VPA	ESM	CLB	FBM	GBP	LEV	LTG	OXC	PGB	TGB	TPM	VGB	ZNS	ESL	LCM
CNS																		
Encephalopathy			●	●											●			
Cognitive changes		●												●		●		
Depression/ behavior/psychosis		●	●		●	●	●		●				●		●	●		
Non-CNS																		
Rash	●	●	●							●	●							
Leucopenia/anemia/ thrombopenia	●	●	●	●			●											
Pancreatitis				●				●										
Nephrolithiasis														●		●		
Hepatic failure				●			●											
Osteoporosis	●	●	●	●														
Hyponatremia	●										●						●	
Weight change				●				●				●		●	●			
Drug interaction	●	●	●	●						●	●					●		
Highest teratogenicity				●														

mod. from Schmidt D. Drug treatment of epilepsy: options and limitations; *Epilepsy and Behavior* 2009; **15**: 56-65

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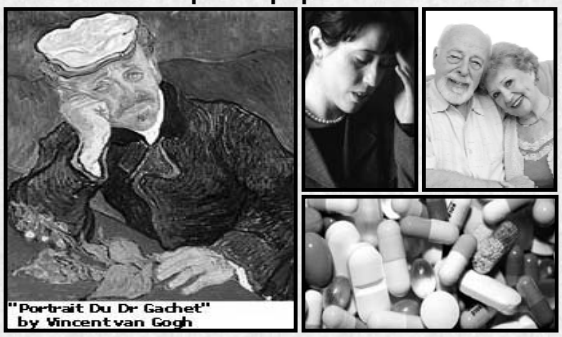
Pharmacological treatment in special populations



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Effect of AEDs on other drugs

Table 4. Common Drugs with Either Increased or Reduced Clearance in the Presence of Antiepileptic Drugs.*

Type of Medication	Increased Clearance (and Need for Higher Doses) with Phenytoin, Phenobarbital, Carbamazepine	Decreased Clearance (and Need for Lower Doses) with Valproic Acid
Cardiac	Disopyramide, quinidine, amiodarone, propranolol, metoprolol, nifedipine, felodipine, nimodipine, digoxin, lisinopril, simvastatin, atorvastatin, warfarin	Nimodipine
Psychiatric	Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, citalopram, paroxetine, bupropion, haloperidol, chlorpromazine, clozapine, olanzapine, risperidone, quetiapine	Amitriptyline, nortriptyline, clomipramine, paroxetine
Antineoplastic	Cyclophosphamide, busulfan, etoposide, methotrexate, teniposide, vinca alkaloids	
Antifebrile	Praziquantel, albendazole, doxycycline, ketoconazole, clindamycin, chloroquine, mefloquine, rifampin, saquinavir	Zidovudine, pentobarbitone
Other	Cyclosporine, tacrolimus, diazepam, dexamethasone, prednisone, oral contraceptive pills, theophylline, methadone	Lorazepam, diazepam

*Data are from: Patsalos PN and Perucca E. Cnteractions between antiepileptic drugs and other drugs; *Lancet Neurol.* 2003; **2**: 473-481; This list is not comprehensive
French JA, Pedley TA, Clinical practice; Initial management of epilepsy; *N. Engl. J. Med.* 2008; **359** (2): 166-176

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Metabolic consequences of enzyme-inducing AEDs

- AEDs which induce the cytochrome P450 system adversely affect bone, lipid, and gonadal steroid metabolism
- Although patients treated with inducing AEDs are at increased risk of fracture, it is still controversial whether bone mass is truly related to enzyme induction, and analogously, whether reductions in testosterone truly account for male sexual dysfunction
- Data showing elevations of surrogate cardiovascular and cerebrovascular risk endpoints with epilepsy patients, mostly inducing AED treated, are consistent and concerning, however
- Newer, non-inducing AEDs are preferable, if possible

Mintzer S. Metabolic consequences of antiepileptic drugs; *Curr. Opin. Neurol.* 2010; **23**: 164-169

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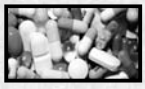
ILAE definition of drug resistant epilepsy



- Failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom

Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen HW, Mathern G, Moshe SL, Perucca E, Wiebe S, French J, Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies; *Epilepsia* 2010; **51**: 1069-1077

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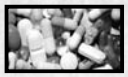
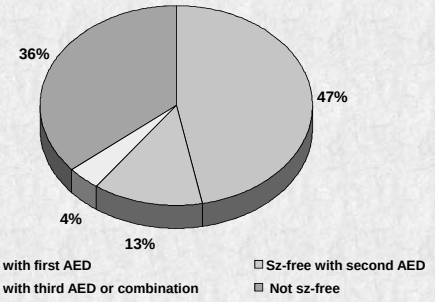
Drug-resistant epilepsy





Sz-free = 12 Mo. no seizures; clinical observation of 470 previously untreated patients

Kwan P, Brodie MJ. Early identification of refractory epilepsy; *N Engl J Med.* 2000; **342**: 314-319

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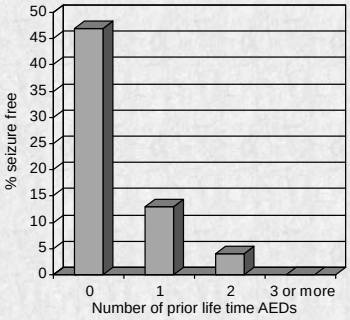
Number of prior life-time AEDs and drug response



Schiller and Najjar; Quantifying the response to antiepileptic drugs: effect of past treatment history; *Neurology*, 2008; **70**: 54-65

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Why combine AEDs?

- **Advantages**
  - Immediately effective and intuitively appropriate
  - Works even if the add-drug is less effective
  - Add an AED with a different mechanism of action*
  - No withdrawal effects
  - Prefer interaction-free AEDs

Disadvantages

- Higher drug load = more side effects
- Effect of individual drug often difficult to discern
- Not more effective than substitution
- Not useful in case of drug-specific side effects
- Risk of unwanted interactions

*So-called "Rational polytherapy"

Elger CE, Schmidt D, Modern management of epilepsy: a practical approach; *Epilepsy Behav.* 2008; **12**: 501-539

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Epilepsia, 51(1):7–26, 2010
doi: 10.1111/j.1528-1167.2009.02299.x

CRITICAL REVIEW AND INVITED COMMENTARY

Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: Systematic review and meta-analysis

*Stefan Beyenburg, †‡Knut Stavem, and §Dieter Schmidt

The overall weighted pooled-risk difference in favor of AEDs over placebo for seizure-freedom in the total sample of adults and children was 6% [95% confidence interval (CI) 4–8, z = 6.47, p < 0.001] and 21% (95% CI 19–24, z = 17.13, p < 0.001) for 50% seizure reduction. Although the presence of moderate heterogeneity may reduce the validity of the results and limit generalizations from the findings, we conclude that the placebo-corrected efficacy of adjunctive treatment with modern AEDs is disappointingly small and suggest that better strategies of finding drugs are needed for refractory epilepsy, which is a major public health problem.

KEY WORDS: Refractory epilepsy, Antiepileptic drugs, Placebo, Placebo-corrected seizure outcome.

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Add-on or substitution?

Elger CE, Schmidt D, Modern management of epilepsy: a practical approach; *Epilepsy Behav.* 2008; **12**: 501-539

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Depression and suicidality

- Depression and anxiety are clinically import in epilepsy, not only in drug-resistant cases[1]
- In general, AEDs are not increasing the risk of suicidality, unless the patient has a depression[2]
- However, some AEDs such as LEV, TGB,TPM, VGB that cause depression[3] seem to be associated with suicidal behavior[4]
- Fortunately, other AEDs such as OXC, GBP, LTG, PGB are not associated with suicidal behavior[4]

1. Elger CE and Schmidt D. *Epilepsy Behav.* 2008; **12**: 501-539
2. Arana *et al., NEJM,* 2010; **363**: 542-551
3. Mula and Sander, *Drug Saf.* 2007; **30**: 555-567
4. Andersohn *et al.,* Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior; *Neurology,* 2010; **75**: 335-340

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Natural history of treated epilepsy

- Summary after 37 years of follow-up
  - 48% Terminal remission from the start
  - 19% Late remission (Relapsing-remitting course)
  - = *67% Good outcome with terminal remission*
  - 14% Worsening course (Remitting-relapsing)
  - 19% Drug resistant epilepsy from the start
  - = *33% Poor outcome without remission*

Sillanpää M, Schmidt D. Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study; *Brain*; 2006; **129**: 617-624

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AEDs for the elderly

- Given the adverse metabolic effects induced by enzyme-inducing AEDs discussed earlier, metabolically inert modern AEDs such as gabapentin, lamotrigine or levetiracetam are preferable for the elderly[1,2]
- AEDs should be given at a low maintenance dose and only after slow titration as the elderly are more sensitive to adverse effects and often respond well to low doses[2]
- As many elderly take antihypertensive drugs that cause hyponatremia, Oxcarbazepine, which also causes hyponatremia, should be used with caution[3]

1. Mintzer S. Metabolic consequences of antiepileptic drugs; *Curr. Opin. Neurol.* 2010; **23**: 164-169
2. Brodie *et al.*, Epilepsy in later life; *Lancet Neurol.* 2009; **8**: 1019-1030
3. Arif *et al.*, Comparative effectiveness of 10 antiepileptic drugs in older adults with epilepsy; *Arch Neurol.* 2010; **67**: 408-415

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Stopping AEDs

- Despite its benefits, stopping AEDs in patients seizure free for several years is associated with doubling the risk of seizure recurrence for up to 2 years compared with continued treatment[1]
- Nevertheless, stopping all AEDs is recommended,
  - If it turns out that the patient has no epileptic seizures
  - If the risk of recurrence is small (about in 25% of patients), as in children with self-limiting course, particularly in those with childhood absence epilepsy or those with non-symptomatic etiology and rare seizures[2]
- Discontinuation of AEDs should be very slow, over weeks and months and, in those on several drugs, be done for one drug at the time. Rapid discontinuation of certain AEDs (*e.g.,* Phenobarbital) may cause withdrawal seizures

1. Randomised study of antiepileptic drug withdrawal in patients in remission; Medical Research Council Antiepileptic Drug Withdrawal Study Group; *Lancet*; 1991; **33**: 1175-80
2. Sillanpää M, Schmidt D. Prognosis of seizure recurrence after stopping antiepileptic drugs in seizure-free patients: A long-term population-based study of childhood-onset epilepsy; *Epilepsy Behav.* 2006; **8**: 713-19

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Stopping AEDs (2)

- However, on average, one in three adults has a seizure recurrence, though the range can go up to 66% (34%, range 12-66%, CI 95%: 27-43)[1]
- The risk of seizure recurrence is particularly high for those with juvenile myoclonic epilepsy and symptomatic focal epilepsy, the most frequent epilepsy in adults[1]
- Patients who did become seizure-free only after a number of years or after a number of AEDs may have a higher risk of seizure recurrence than those who became seizure-free with the first adequate AED
- Furthermore, seizure freedom is surprisingly neither guaranteed nor immediate in some patients when being treated for a seizure recurrence[2]; On the other hand, continued treatment does not guarantee uninterrupted seizure freedom in those who have become seizure free[3]

1. Schmidt D and Löscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience; *Acta neurol scand*. 2005; **111**: 291-300
2. Sillanpää M, Schmidt D. Prognosis of seizure recurrence after stopping antiepileptic drugs in seizure-free patients: A long-term population-based study of childhood-onset epilepsy; *Epilepsy Behav.* 2006; **8**: 713-19
3. Randomised study of antiepileptic drug withdrawal in patients in remission; Medical Research Council Antiepileptic Drug Withdrawal Study Group; *Lancet*; 1991; **33**: 1175-80

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Visions for the future

- As four decades ago, one in three new-onset patients has drug-resistant seizures
- Current AEDs do not seem to prevent epilepsy or block its progression or affect the underlying natural history of epilepsy
- Thus, there is an unmet need for AEDs that better block seizure generation and the underlying epilepsy, or ideally both, *i.e.*, offer a complete cure of epilepsy

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Summary

- Current AED treatment is generally well-tolerated and provides seizure freedom in 2 out of 3 patients with new-onset epilepsy
- However, we do not seem to have made substantial improvements in effectiveness since the introduction of Carbamazepine and Valproate over 40 years ago
- Unmet needs include seizure-freedom in patients with previously drug-resistant seizures, prevention of epilepsy and control of the underlying epilepsy, in short, a cure for epilepsy

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