Problems with AED Usage and Possible Solutions

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I Am Still Having Seizures! Why MyTreatment Did Not Work?

- **The AED prescribed was inappropriate**
- The AED prescribed was not used optimally
- Adherence to treatment has been suboptimal
- Patient is resistant to the prescribed AED

Which is the Best AED for my Patient? Properties to be Considered

- Spectrum of efficacy (seizure types and syndromes)
- Magnitude of efficacy
- Adverse effect profile (including teratogenicity)
- Impact on co-morbidities
- Drug interactions (and mechanisms of action)
- Ease of use
- Cost

Efficacy Spectrum of Available AEDs

Most seizures types/syndromes	Focal seizures and epilepsies*	Absence only
Valproic acid	Carbamazepine	Ethosuximide
Benzodiazepines	Phenytoin	
Phenobarbital°	Oxcarbazepine	
Primidone°	Pregabalin	
Levetiracetam	Gabapentin	
Lamotrigine°	Lacosamide	
Topiramate	Eslicarbazepine acetate	
Zonisamide	Brivaracetam (?)	
Perampanel (?)	Tiagabine	
Rufinamide	Vigabatrin	
Felbamate	Retigabine	

* Some of these AEDs may also protect against primarily generalized tonic-clonic seizures. Most can exacerbate myoclonic / absence seizures. Vigabatrin is effective in infantile spasms

° Phenobarbital and primidone are not effective against absences. Lamotrigine may aggravate severe myoclonic epilepsy of infancy.

Moshé, Perucca, Ryvlin & Tomson, The Lancet 2015;385: 884-898 (updated)

I can insert here a video of JME patient whose seizures were aggravated by prescription of the wrong treatment

Some Genetic Epilepsies for which Identification of the Molecular Defect has Treatment Implications

- *SCN1A* → avoid phenytoin and lamotrigine (generally)
- *SCN2A* → high-dose phenytoin helpful
- *SCN8A* → high-dose phenytoin helpful
- *SLC2A1* → ketogenic diet
- *PRRT2* → carbamazepine
- *PLCB1* → inositol
- *ALDH7A1* → pyridoxine
- *PNPO* → pyridoxal-5-phosphate
- *KCNQ2* → consider ezogabine for loss-of-function variants
- *KCNT1* → consider quinidine for gain-of-function variants (trials needed)
- *GRIN2A* → consider memantine, dextromethorphan for gain-of-function variants (trials needed)
- *TSC* → consider everolimus
- focal cortical dysplasia and other malformations of cortical development → consider everolimus or other mTOR inhibitors (trials needed)

Poduri, Epilepsy Currents 2017;17:16-22

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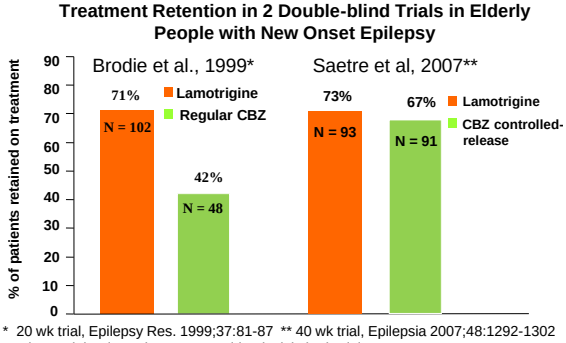
How Could an AED Be Used Suboptimally?

- Suboptimal formulation
- Suboptimal titration rate
- Subptimal maintenance dosage
- Subptimal dosing schedule

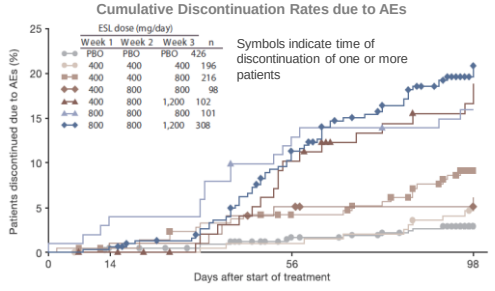
What Difference Can a Formulation Make?



* 20 wk trial, Epilepsy Res. 1999;37:81-87 ** 40 wk trial, Epilepsia 2007;48:1292-1302
Dosing and titration schemes were identical in both trials

Slow Titration Minimizes Incidence of Adverse Effects

Pooled Analysis of Placebo-Controlled EslicarbazepineTrials



Krauss et al, Epilepsy Res. 2018; 139:1-8

Epilepsia, 50(5):1072–1076, 2009
doi: 10.1111/j.1528-1167.2008.01799.x

FULL-LENGTH ORIGINAL RESEARCH

The role of titration schedule of topiramate for the development of depression in patients with epilepsy

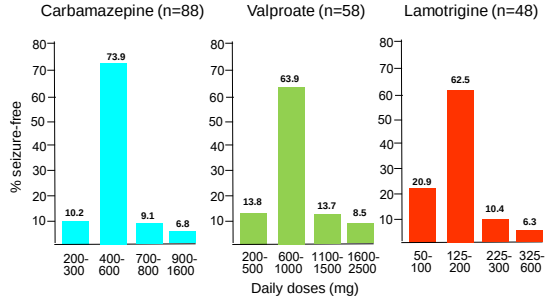
*Marco Mula, †Dale C. Hesdorffer, ‡Michael Trimble, and ‡§Josemir W. Sander

Rapid titration* increased the risk of developing depression by…

- 5-fold overall
- 12.7 fold if there was a hx of febrile convulsions
- 23.3 fold if there was a hx of depression

*50 mg starting dose with 50 mg increments every 1 to 2 weeks

A Review of Outcomes on the First Prescribed AED Doses at Which Seizure Freedom Was Achieved



Kwan & Brodie, *Epilepsia* 2001; 42:1255-60

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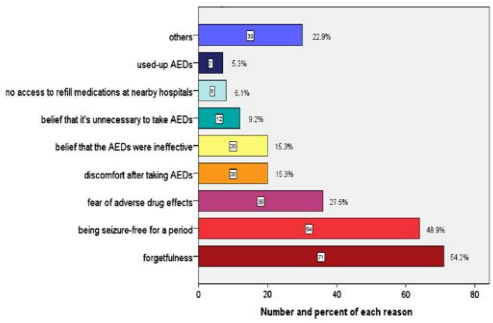
Some Major Causes of Poor Adherence to Prescribed AED Treatment

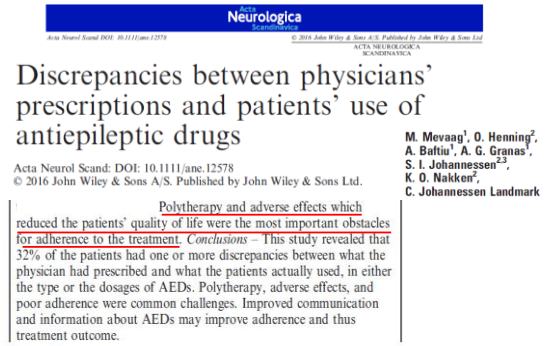
- Suboptimal physician-patient communication
- Low educational status
- Perceived stigma
- Complex treatment regimens
- Memory dysfunction
- Depressed mood
- Adverse effects
- Problematic access to medication, including cost

Faught, Epilepsy & Behav 2012;25:297-30; Liu et al, Epileptic Dis 2013; 15:289-94; McAuley et al, Epilepsy & Behav 2015;43:61-5; Meevag et al Acta Neurol Scand 2016 Epub ahead of print

Reason for Non-adherence among 131 Patients in China who Missed Taking their AEDs



Tang et al, Epilepsy & Behav 2013;27:85-9


Acta Neurologica Scandinavica

Discrepancies between physicians' prescriptions and patients' use of antiepileptic drugs

M. Mevaag[1], O. Henning[2], A. Baftiu[1], A. G. Granas[1], S. I. Johannessen[2,3], K. O. Nakken[2], C. Johannessen Landmark

Acta Neurol Scand: DOI: 10.1111/ane.12578
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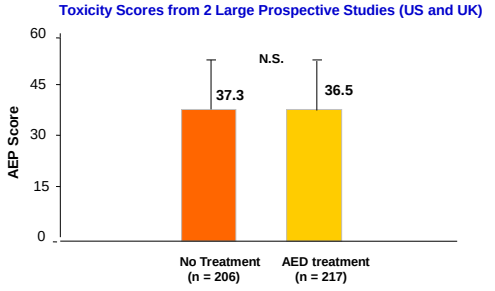
Polytherapy and adverse effects which reduced the patients' quality of life were the most important obstacles for adherence to the treatment. *Conclusions* – This study revealed that 32% of the patients had one or more discrepancies between what the physician had prescribed and what the patients actually used, in either the type or the dosages of AEDs. Polytherapy, adverse effects, and poor adherence were common challenges. Improved communication and information about AEDs may improve adherence and thus treatment outcome.

Many Adverse Effects Can Be Avoided!



Perucca P. et al. *Neurology* 2011;76:276-9.

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Failure to Respond to an Appropriately Selected and Used AED – What Do I Do Next?

- Decide whether to switch to an alternative monotherapy or move to combination therapy
- Best strategy is generally guided by considering why earlier treatment(s) failed
- In choosing the next treatment, consider risk of specific adverse effects, mechanism of action of alternative AEDs
- Be aware of drug interactions, avoid overtreatment, and giove early consideration to non-AED therapies!

I Am Still Having Seizures! Step by Step Solutions

1. Tailor AED selection to the characteristics of the individual – establish an alliance with your patient – good communication is everything!
2. Optimize starting dose, titration rate and dosing regimen
3. Monitor clinical response regularly and adjust treatment timely when adverse effects can be anticipated
4. Consider carefully alternative treatments when the initial AED(s) failed