Dealing with an Adult or Adolescent Presenting with a First-time Seizure:
A Pragmatic Approach

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“An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”

ILAE 2014
A person is considered to have EPILEPSY if they meet any of the following conditions:

1. At least two unprovoked seizures occurring more than 24 hours apart.

2. One unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.

3. Diagnosis of an epilepsy syndrome
The first question is: was this a seizure?

Think about seizure mimics:

- Functional non-epileptic attack (PNES)
- Syncope
- Migraine equivalents
- Panic attack
- Parasomnias (cataplexy, night terrors, etc.)
- Movement disorders (paroxysmal dyskinesias)
- Malingering (secondary gain)
- Metabolic (hypoglycaemia)
- Etc.
What are functional seizures?

- Psychogenic non-epileptic seizures (PNES) are clinical events resembling epileptic seizures but *lacking abnormal cortical electrical discharges*.

- They are *involuntary* and may be manifestations of a psychological distress.
Functional seizure (PNES)

Keep in mind:

• PNES is *common* (up to 20% of patients attending seizure clinics!)

• It is *NOT* malingering

• May be *difficult to distinguish* from an epileptic seizure (especially focal frontal seizures)

• *PNES and epileptic seizures may coexist* in the same patient
PNES: Suggestive clinical features:

- Eyes often closed rather than open
- Longer duration (minutes to hours)
- Waxing and waning motor signs
- Bilateral motor jerking with maintained awareness
- Asynchronous movements (L vs R side of the body)
- Bizarre movements: pelvic thrusting and cycling of the legs (may also occur in frontal lobe seizures)
- Often precipitated by an emotional event
- Often a history of emotional or sexual abuse
Video-EEG monitoring is the most reliable way to confirm the diagnosis

- It is important to be empathetic and non-judgemental
- **Cognitive behavioural therapy** is the only intervention for which there is evidence of benefit
- Appropriate use of anti depressants and anxiolytics is likely to be helpful

Anzelotti, et al. Frontiers Neurology 2020;11 art 461
Differentiating an epileptic seizure from syncope is important:

- Syncope may be associated with a *risk of cardiac death*
- Misinterpretation of syncope as a seizure may be associated with:
  - *Inappropriate long-term AED treatment*
  - Significant *negative quality of life and medico-legal implications*
Syncope: some suggestive clinical features

- Typically occurs in the upright position
- Different prodromal symptoms:
  - light headedness
  - palpitations
  - dizziness
- Duration shorter (*seconds with rapid recovery*)
- Little if any post-event confusion
Clonic jerking:

• May be associated in up to 20% of syncope events
• Typically occur immediately after the syncope
• In focal seizures they may precede the event, even while awareness is maintained.
In order to satisfy yourself that your patient has suffered a seizure

History is absolutely crucial:

• From a witness
  and
• From the patient
History: from a witness & the patient

You will be asking yourself:

1. Are the clinical features in keeping with an epileptic seizure, and, if so:

2. Do these features suggest a **focal** or **generalised** onset

3. Any obvious risk or **provoking factors**
From the witness:

- Seizure onset and duration
- Description of seizure semiology
  - generalised onset
  - focal onset
    - turning of head
    - version of gaze
    - focal jerking
    - stiffening or jerking of an upper limb
History from the WITNESS

Keep in mind any reversible provoking factors!

Ask About:

- Comorbidities
- Medications
- Childhood febrile convulsions
- Psychiatric history (depression overdose?)
- Recreational drug use (recent and past)
- Recent or distant head injury
- Preceding febrile or other illnesses (meningitis/encephalitis?)
- Prodromal psychiatric / behavioural changes (auto-immune encephalitis?)
Especially in children and adolescents, ask the parents about any previous:

- Intermittent myoclonic jerks
- Blank stares (absences)

Which may support the diagnosis of genetic generalised epilepsy syndromes such as:

- Juvenile myoclonic epilepsy
- Juvenile-onset absence epilepsy
- Childhood-onset absence epilepsy
Aura

• Typically indicates a focal seizure:

Commonly:

• Gustatory olfactory hallucinations
• Epigastric “rising” sensation (“heat” or “nausea”)
• Déjà vu / Jamais vu
• Emotion (dread / ecstasy)

These auras are common because they localise to the temporal lobe, and temporal lobe epilepsy is the most focal epilepsy
Other auras include:

- Sensory hallucinations (sensory cortex)
- Flashing lights (occipital lobe)
- Visual patterns or hallucinations (visual assoc. cortex)
- Focal motor jerking (motor cortex)
- Micropsia, macropsia, alien limb (R parietal lobe)
Examination:

Perform a detailed systemic- & neurological examination:

Again keeping in mind potentially reversible systemic and intracranial provoking factors

- Fever, rash,
- Signs of head trauma
- Meningism
- GCS
- Lateralising or localising neurological signs
If your patient is still confused or not back to base-line after the seizure, make sure that he / she is **STABLE**

**ABC (defg = “don’t ever forget the glucose”)**

- **Secure airway, decubitus position.**
- O2 Sats monitor, **Face mask O2 / nasal prongs**
- Send an **urgent blood gas** with electrolytes
- **IV line**
- **Finger prick blood glucose ( ? Rx Thiamine & glucose)**
- Blood pressure (hyper/hypotension)
- **ECG**
If your patient remains persistently confused:

Request an urgent EEG

? Subclinical electrographic status epilepticus

? encephalopathy
Patient not back to baseline? URGENT LABS!

Also send urgent Labs:

- Arterial blood gas
- Na K Ca Mg PO
- Acid-base & lactic acid
- FBC, CRP, ESR
- Renal & liver function (ammonia?)
- Toxicology screen
- AED drug level
- Cardiac Markers

If you suspect bacterial meningitis: blood culture & start IV antibiotics – remember some are epileptogenic
Urgent contrasted CT brain imaging if

- Prolonged post ictal confusion / depressed level of consciousness
- (new) localising or lateralising neurological signs
- Features of raised ICP
- Suspected head trauma
- You’re planning a LP to exclude meningitis/encephalitis

Remember renal function before administering contrast
In most instances, if your patient is asymptomatic and back to baseline:

- blood work up, EEG and brain scanning may be done routinely.
- follow up at OPD for results and management
Why is it important to determine whether a seizure was focal or generalised?
Classification: **FOCAL vs. GENERALISED**

- **Focal**
- **Focal with Tonic-Clonic Jerking**
- **Generalised**

A  
B  
C
Determining whether a seizure has focal or generalised onset is important because it has implications with respect to:

- **Aetiology** (a focal structural brain lesion may require specific treatment)
- **Choice of Anti Epileptic Drugs**
- **Prognosis**
For instance:

In a child or adolescent presenting with a seizure, this is likely to be of generalised onset and familial with a relatively good prognosis (although a structural intracranial or metabolic cause is not excluded)

In an adult, a first time seizure is much more likely to have a focal onset and indicate structural intracranial pathology or a metabolic cause.
You will have to decide:

- Whether or not to treat your patient?
- Which drug to use?
- How to start?
- How to alter treatment if first-line drug fails?
- If/when to stop treatment in seizure-free patients?
Consider:

Risk of recurrence:
- Number of seizures
- Seizure type/Syndrome
- Underlying structural cause
- Abnormal EEG

Risk-benefit of Drug Treatment:
- Seizure-related morbidity (risk of injury, SUDEP, etc.) vs.
- Drug-related side effects

Implications of an Incorrect Diagnosis:
- Social, vocational, medico-legal

There is no place for “trial of AED therapy!”
What is the lifetime risk of recurrence if untreated?

After a first single seizure 46%

After a second seizure 70%
FIRST Study (1993)

- 419 adults and children enrolled within a week of a first unprovoked seizure
- Randomised to immediate vs. deferred treatment

Recurrence at 2 years after a single seizure was:

24% in the AED-treated group

42% in the untreated group
After a single seizure:
To treat or not to treat? THE EVIDENCE

MESS Study (2005)

- Enrolled patients in whom there was uncertainty whether or not to start treatment including 812 who had experienced a single seizure.
- Randomised to immediate vs. deferred treatment

Recurrence at 2 years after a single seizure was:

32% in the AED-treated group

39% in the untreated group

Importantly:

Both these studies found that deferring treatment after a single seizure *DID NOT* result in subsequent poorer control of seizures.
After a single seizure: To treat or not to treat?

Not all first seizures are created equal

First Seizure vs. First seizure:
- Provoked
- Plus
  - epileptiform EEG
  - abnormal neuro examination
  - abnormal brain imaging

AEDs may be indicated after a first seizure under certain circumstances
RECOMMENDATIONS: for initiating AED treatment

1. Treat after 2 seizures if their severity is significant for the individual, if the interval between seizures is not more than 1 – 2 years and if the informed patient so wishes.

2. Defer treatment after a first seizure in most cases

3. Consider treatment after a first seizure if high risk of recurrence (>60%) For example: post-brain injury, tumour, abnormal EEG, structural abnormality on brain imaging)

4. Consider treatment after a first seizure in elderly/frail patients where a second seizure could result in injury

5. Take vocation and other circumstances into consideration: drivers, construction workers.
Which AED?

“Standard” vs. “New” AEDs
Which AED?
“STANDARD” AEDs

- Phenobarbital 1912
- Phenytoin 1938
- Carbamazepine 1960
- Valproate 1970

Effective and cheaper, but ↑side effects
Which AED?
“NEW” AEDs

- Lamotrigine
- Oxcarbazepine
- Gabapentin
- Topiramate
- Levetiracetam
- Pregabalin
  - Felbamate
  - Vigabatrin
  - Zonisamide
  - Lacosamide
  - Rufinamide
  - Carisbamate
  - Tiagabine
  - Perampanel

• **Benefits**
  
  - Effective
  - ↓ Adverse effects
  - ↓ drug-drug interactions

• **Disadvantage**
  
  - Expensive
Which AED?
Head-to-head controlled AED trials?

2006 ILAE Review of controlled trials comparing efficacy and effectiveness of AEDs in newly diagnosed epilepsy:

Conclusions: MAJOR WEAKNESSES

Most head-to-head trials comparing standard and new AEDs are:

- Funded by the pharmaceutical industry
- Biased in the choice of formulation and target dosages, favouring the sponsors’ product.
- Too short
- Regulatory trials designed to obtain a licence.

ILAE Treatment Guidelines: Evidence-based analysis of anti epileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes: Epilepsia 2006; 47: 1094-1120
Efficacy and Effectiveness

**2007 SANAD Study: “Standard” vs. “New” AEDs**

Disadvantages: Non-controlled, open label, unblinded
Advantages: Long follow up (6 years), large number of participants (1700), pragmatic: non fixed drug dosages

Findings:

- For **focal seizures**: lamotrigine better than carbamazepine, oxcarbamazepine, topiramate and gabapentin
- For **primary generalised seizures**: valproate better than lamotrigine and topiramate

Which AED? Phenobarbital

- Most commonly used AED world-wide

- Advantages
  - Efficacy
  - Cost
  - Once daily dose
  - Oral and IV forms

- Disadvantages
  - Cognitive effects?
  - Liver enzyme inducer
  - Teratogenic
  - Dependency
Major Epilepsy Treatment Guidelines all differ in their recommendations WRT first-line AEDs:

**AAN:** no preference between old and new drugs

**NICE:** preferential use of older agents (except phenytoin because of complicated pharmacokinetics) unless specific reason to do otherwise

**ILAE:** phenytoin and carbamazepine have highest quality of evidence of efficacy and effectiveness

*All guidelines stress the need to consider individual patient characteristics when choosing an AED*

Neurology 2018: 91;74-81
Which AED?

Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy


Andres M. Kanner, MD, Eric Ashman, MD, David Gloss, MD, MPH&TM, Cynthia Harden, MD, Blaise Bourgeois, MD, Jocelyn F. Bautista, MD, Bassel Abou-Khalil, MD, Evren Burakgazi-Dalkilic, MD, Esmeralda Llanas Park, MD, John Stern, MD, Deborah Hirtz, MD, Mark Nespeca, MD, Barry Gidal, PharmD, Edward Faught, MD, and Jacqueline French, MD

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Neurology® 2018;91:74-81. doi:10.1212/WNL.0000000000005755
Taylor your choice of AED to each patient!

Factors affecting choice:

1. Seizure Type/Epilepsy Syndrome
2. Tolerability/side effect profile
3. Gender (child bearing potential & potential teratogenicity)
4. Intellectual function
5. Comorbid illnesses (renal failure, hepatic failure, depression, mood instability, dementia)
6. Cost
Focal Epilepsy

All drugs regarded as having roughly equal efficacy

But differ according to:

- Cost
- Side-effect profile (idiosyncratic/chronic)
- Incidental beneficial effects (e.g. mood stabilising)
- Pharmacokinetics
- Drug-drug interactions

Generalised Epilepsy:

lamotrigine, levetiracetam, gabapentin, valproate
## Which AED?

### Generalised Epilepsy Syndromes

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Valproate: not the drug of choice:

- A higher risk of severe congenital abn (e.g. ASD, spina bifida, cleft palate) compared with other AEDs like CBZ and lamotrigine.

- Children with mothers treated with valproate during pregnancy have lower IQ at 3 and 6 years.

Alternatives to Valproate:
- Lamotrigine (especially with absence & myoclonic epilepsy)
- Levetiracetam (focal and generalised)
- Carbamazepine (focal)
Which AED? The ELDERLY

Elderly:  
*Increased incidence epilepsy*  
*Less tolerance for SE of AEDs*  
*Usually on numerous other medications*

Avoid Enzyme-inducing drugs (carbamazepine, phenytoin, phenobarbital):

- drug-drug interactions
- endocrine disturbance (e.g. hyponatraemia)
- bone problems
- higher rates of discontinuation compared with lamotrigine and gabapentin

RCTs:

**Lamotrigine:** fewer drug-drug interactions than CBZ and Phenytoin  
**Levetiracetam:** fewer drug-drug interactions than CBZ and Phenytoin  
**Valproate:** similar side effect profile to LEV, better than CBZ  
**(Topiramate):** fewer drug-drug interactions but cognitive side effects

BMC Neurology;2016 16:149-153. Psychogeriatrics;2017; 17; 208-209
Comorbidities influence AED choice:

- Hepatic failure: levetiracetam / topiramate
- Anticoagulation/warfarin: levetiracetam / topiramate
- ↑ other medications: levetiracetam / topiramate
- Migraine: topiramate, valproate
- Mood disorders: valproate, carbamazepine
- Depression: lamotrigine
- Neuropathic pain: valproate, gabapentin, pregabalin, carbamazepine
- Renal failure: use levetiracetam with caution
HIV

AEDs and ARVs have complex and extensive interactions

Avoid enzyme inducing AEDs:

*Phenytoin, phenobarbital, carbamazepine result in reduced levels of non-nucleotide transcriptase inhibitors and protease inhibitors.*

**Drugs of Choice in HIV:**

- **Levetiracetam:**
- **Valproate:** (increases levels of zidovudine)
- **Lamotrigine:** (levels reduced by raltegavir/atazanivir)
- **(Gabapentin):** (focal onset seizures)

**Brand name vs. Generic**

2010: Systematic review of RCTs comparing efficacy of trade-name vs generic AEDs: “Generic substitution is not associated with loss of seizure control”.

2011: Review of bioavailability of generic vs brand-name AEDs “Most generic AEDs provide total drug delivery similar to brand-name products”

**Recommendations:**

- No contraindication to substituting generic for a brand-name agents,
  
  But

- Frequent changes between brand-name and generics or between different generics are not advised

What dose?

Aim: the lowest dose which effectively controls seizures

Most patients achieve seizure-freedom on relatively low doses of AEDs

- Valproate: 600-1000 mg / d
- Carbamazepine: 400 mg / d
- Levetiracetam: 1000 mg / d
- Lamotrigine: 125-200 mg / d

Elderly patients generally require lower dosages
What dose?

A law of diminishing returns!
How to initiate treatment?

Start with a low/moderate therapeutic dose

Increase drug dose gradually until either:

- Seizure control achieved, or
- Unacceptable side effects occur

Titration dose dependant on the individual drug:

Valproate, Levetiracetam, Phenytoin: possibly rapid

Topiramate, Lamotrigine: slow
50% of adult patients will achieve seizure-freedom without intolerable S/E on the initially prescribed AED

Reasons for failure:

• **Intolerable side effects:** (e.g. Nausea, drowsiness, cognitive difficulties)

• **Idiosyncratic reaction:** (e.g. rash, anaphylaxis)

• **Lack of efficacy:** (i.e. persisting seizures despite maximum recommended dose of first line drug)

Kwan P & Brodie MJ. NEJM 2000; 342: 314-319
Failure of First AED: What to do?

If Idiosyncratic Reaction:
- Stop offending drug
- Introduce a different drug (remember cross-reactivity)

If Lack of Efficacy:
- Reassess diagnosis
- Check compliance (? serum drug level)
  Then....
- Introduce second agent
- Increase second agent to therapeutic dose
- Wean off first agent

Epilepsia. 2010 51: 7-26; Epilepsia. 2011 52: 219-33
Serial AEDs: “Another Law of Diminishing Returns”

20-30% of patients resistant to the initial AED will achieve seizure-freedom on an alternative monotherapy

BUT

Only 10% of patients resistant to two drugs will become seizure-free with the addition of a third AED.

ILAE Definition of **Pharmaco-Resistance**: 

“Failure to achieve sustained seizure-freedom after adequate trials of at least 2 appropriate AEDs given alone or in combination”.

Epilepsia 2010; 52: 219-33
Pharmaco-resistance: what next?

- Review your diagnosis of epilepsy
- Interrogate compliance (serum blood levels)
- Refer to a specialist epilepsy centre for:
  - Review of pharmacotherapy
  - Candidate for epilepsy surgery

“The greatest threat for pharmaco-resistant patients is the use of excessive AED dosages and polytherapy”

Perucca. CNS Drugs 2005; 19: 897-908
Discontinuation of AED therapy?

Discontinuation: when?

Seizure-free for 2-4 years

But consider:

Risk and implications of seizure recurrence

vs

Adverse drug effects of continuing AEDs
2008: Double blind placebo-controlled trial looking at outcome after AED withdrawal.

160 adults seizure-free for between 2 to 5 years

At one year:

• 15% seizure recurrence in withdrawal (placebo) group
• 7% seizure recurrence in continued treatment group

2004, Review of 28 non-blinded studies (4571 patients)

Seizure-recurrence after AED withdrawal in adults:
26-61% at 1 year
43-65% at 2 years

Higher risk of recurrence if:
- Adolescent/adult onset
- Focal seizures
- Underlying neurological disorder
- Abnormal EEG at the time of withdrawal

CNS Drugs. 2004; 18: 201-212
Weaning AEDs: how fast?

Over 3-4 weeks for most AED’s

Over 2-3 months for phenobarbital or benzo’s
Serum Drug Levels?

Serum AED Levels: What is the utility?

Indications:
- Compliance
- Toxicity

Many patients are well controlled on “sub-therapeutic” serum AED levels

“The Modern approach is to underemphasise reference ranges when making therapeutic decisions on AED dose”

Epilepsia 2008: 49: 1239-76
1. Convince yourself that your patient had a seizure and not a mimic (syncope, PNES, etc.)

2. If so, decide whether it was of focal or generalised onset

3. AEDs indicated after:
   - Two seizures
   - Single seizure if there is a high risk of recurrence (> 60% chance of recurrence in 10 years)

4. AED choice is based on:
   - Seizure type (focal vs generalised or syndrome)
   - Side-effect profile
   - Patient characteristics (sex, age, comorbidity, etc.)
5. Serial monotherapy before combination therapy

6. Avoid overtreatment (over-dosage and polytherapy)

7. Diagnose pharmaco-resistance after 2 adequate trials of AEDS

8. Refer sooner rather than later for epilepsy surgical assessment

9. Consider AED withdrawal after 2-4 years seizure-free.
Thank you