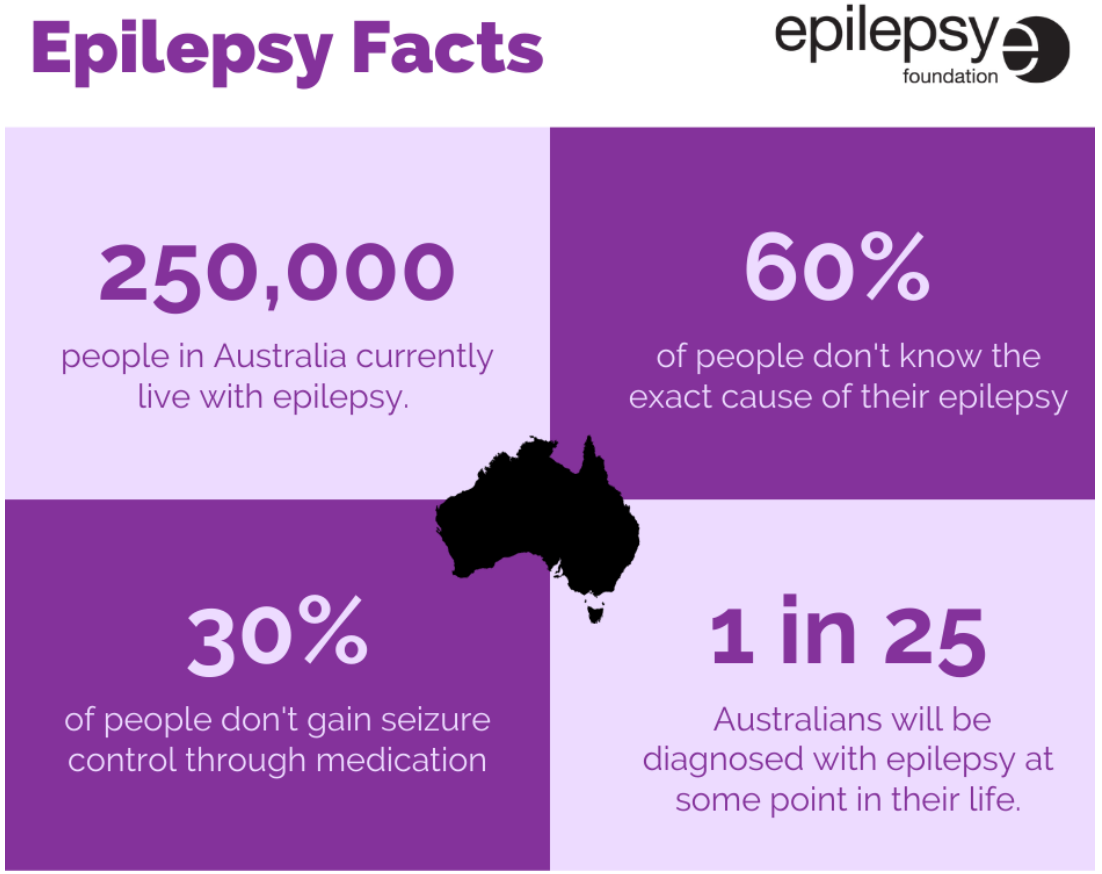
Epilepsy

- Most common serious neurological disease
- Around 1 in 10 people will develop epilepsy during their lifetime
- Around 250,000 Australians live with epilepsy
- **Seizures** are the symptom
- Shift in the balance between neuronal excitation (glutamate) and inhibition (GABA)



Seizures- the tip of an iceberg

Drug-resistant epilepsy

- Failure of two anti-seizure medications to achieve sustained seizure freedom
- **The greatest impact to quality of life is seizure control**

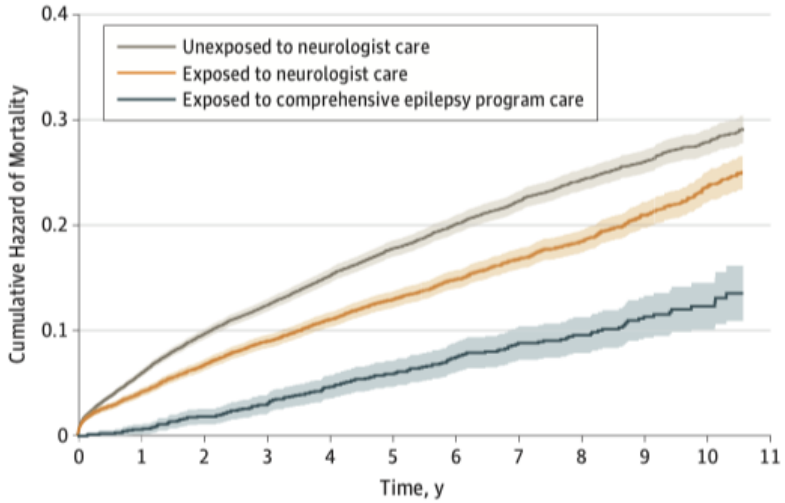
- **Consequences of drug resistant epilepsy**

- Major contributor to the overall societal and economic burden of epilepsy (Foster et al Neurology 2020)
- Psychological, educational, social and vocational impacts (Laxer et al Epilepsy Behav 2014)
- Higher co-morbidity rates (Cramer et al Epilepsy Behav 2014)
- Greater use of health services, incur higher costs to health system (Cramer et al Epilepsy Behav 2014)
- Increased incidence SUDEP 2-10/1000 patient years (chronic epilepsy 1-2/1000 patient-years) (Shankar et al, Epileptic Disord 2017)

Comprehensive Epilepsy Program- Advantages

- Reduction premature mortality risk
- Multi-disciplinary team approach
- Early access to surgical assessment
  - Admission for video EEG-monitoring
  - Neuroradiology- MR and nuclear medicine
  - Neuropsychology
  - Neuropsychiatry
- Neuromodulation
- Dietary intervention- modified Atkins diet
- Drug trials

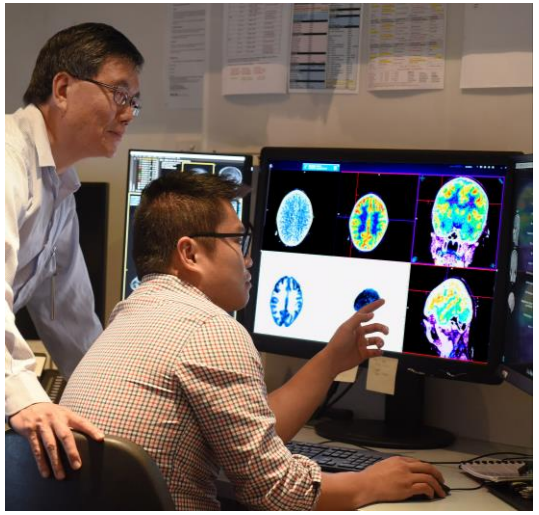
Figure 2. Mortality Over Time in Incident Epilepsy Cases



No. at risk by time											
Exposed to comprehensive epilepsy program care	16865	13200	11829	10648	9258	7970	6875	5889	4615	3277	2040
Exposed to neurologist care	5746	7167	6997	6772	6128	5262	4462	3679	2916	2120	1450
Unexposed to neurologist care	683	1284	1498	1608	1586	1443	1244	1033	805	598	355

Lowerison et al. AMA Neurol. 2019;76(11):1352-1358.

RBWH Comprehensive Epilepsy Program



CASE 1

IS IT EPILEPSY? CAN I DRIVE?

CASE 1

- 23 year old female medical student
- Celebrating after exams, sleep deprived , 3 standard drinks
- Fell over , hit head hard on cement
- 2 minute bilateral tonic clonic seizure, 10 mins post ictal confusion
- Lateral tongue bite, no incontinence

- Nil previous seizure
- “Do I have epilepsy? Can I drive?

FURTHER HISTORY

- Mild ADHD, anxiety/depression
- Lisdexamfetamine 40 mg
- Escitalopram 20 mg
- Progesterone IUS
- Drinks 5-10 standard drinks once a month
- Class C licence

- Risk factors:
  - 20 sec febrile convulsion age one
  - Cousin with epilepsy

- Exam normal
- ECG, CT normal
- Put on RBWH First seizure pathway
- Routine EEG next day normal

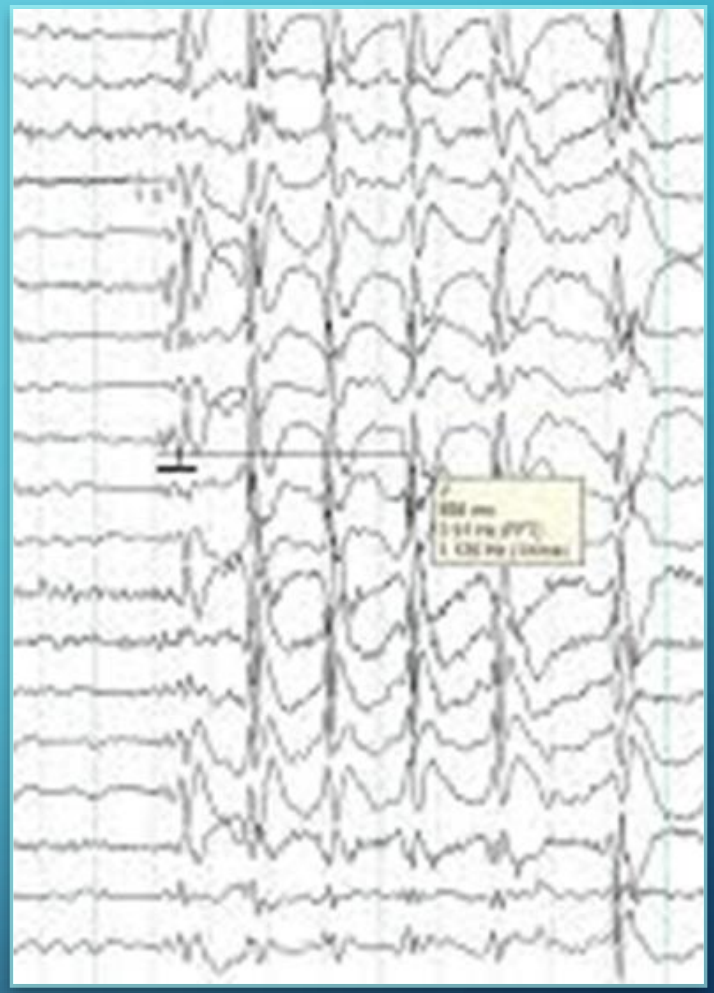
CONSIDER

- *What is her driving restriction? What if the seizure was caused by the head injury?*
- *Can you diagnose epilepsy after one seizure?*
- *Does a normal EEG make it unlikely that a patient has epilepsy?*
- *How would you advise a patient who had normal investigations after one seizure?*

INVESTIGATIONS

Sleep deprived EEG: 3-6 Hz generalized spike wave with photo-paroxysmal response

One myoclonic jerk during recording



TREATMENT

Lamotrigine 25 mg nocte 2 weeks, increasing by 25 mg every 2 weeks target dose 50 mg bd

“what about my ADHD and anxiety meds”

CONSIDER

What sort of epilepsy does she have?

What lifestyle advice should she be given?

Would you make psychiatric medication adjustments based on the patient's new diagnosis?

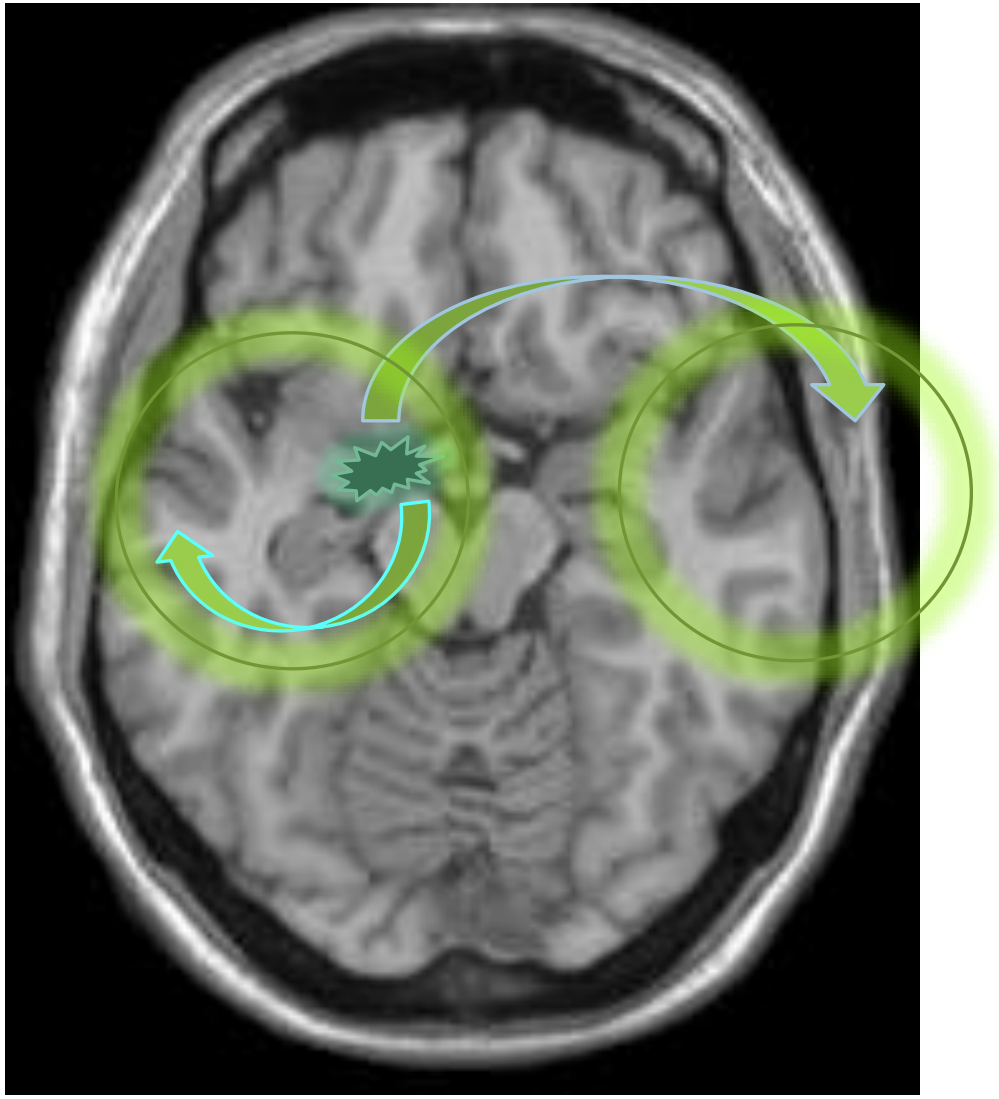
BREAKOUT GROUP DISCUSSIONS

- *What is her driving restriction? What if the seizure was caused by the head injury?*
- *Can you diagnose epilepsy after one seizure?*
- *Does a normal EEG make it unlikely that a patient has epilepsy? How would you advise a patient who had normal investigations after one seizure?*
- *What sort of epilepsy does she have?*
- *What lifestyle advice should she be given?*
- *Would you make psychiatric medication adjustments based on the patient's new diagnosis?*

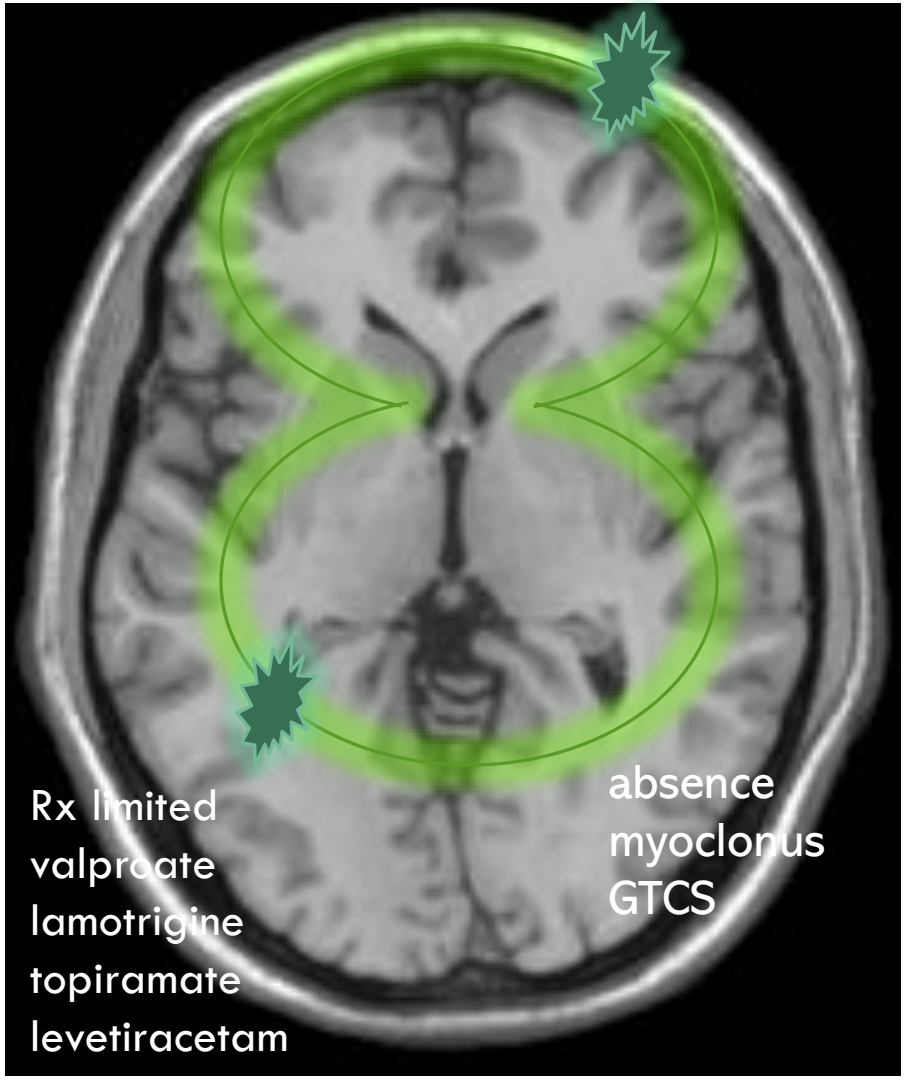
FEEDBACK

- *What is her driving restriction? What if the seizure was caused by the head injury?*
- *Can you diagnose epilepsy after one seizure?*
- *Does a normal EEG make it unlikely that a patient has epilepsy? How would you advise a patient who had normal investigations after one seizure?*
- *What sort of epilepsy does she have?*
- *What lifestyle advice should she be given?*
- *Would you make psychiatric medication adjustments based on the patient's new diagnosis?*

Focal seizures



Generalized seizures



ILAE OFFICIAL REPORT

Epilepsia
The Journal of the International League Against Epilepsy

A practical clinical definition of epilepsy

*Robert S. Fisher, †Carlos Acevedo, ‡Alexis Arzimanoglou, §Alicia Bogacz, ¶J. Helen Cross, #Christian E. Elger, **Jerome Engel Jr, ††Lars Forsgren, ‡‡Jacqueline A. French, §§Mike Glynn, ¶¶Dale C. Hesdorffer, ##B.I. Lee, ***Gary W. Mathern, †††Solomon L. Moshé, ‡‡‡Emilio Perucca, §§§Ingrid E. Scheffer, ¶¶¶Torbjörn Tomson, ###Masako Watanabe, and ****Samuel Wiebe

Epilepsia, 55(4):475–482, 2014

Epilepsy is a disease of the brain defined by any of the following conditions

1. A least two unprovoked (or reflex) seizures occurring >24 h apart
2. One unprovoked (or reflex) 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

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

(Fisher et al., 2014)

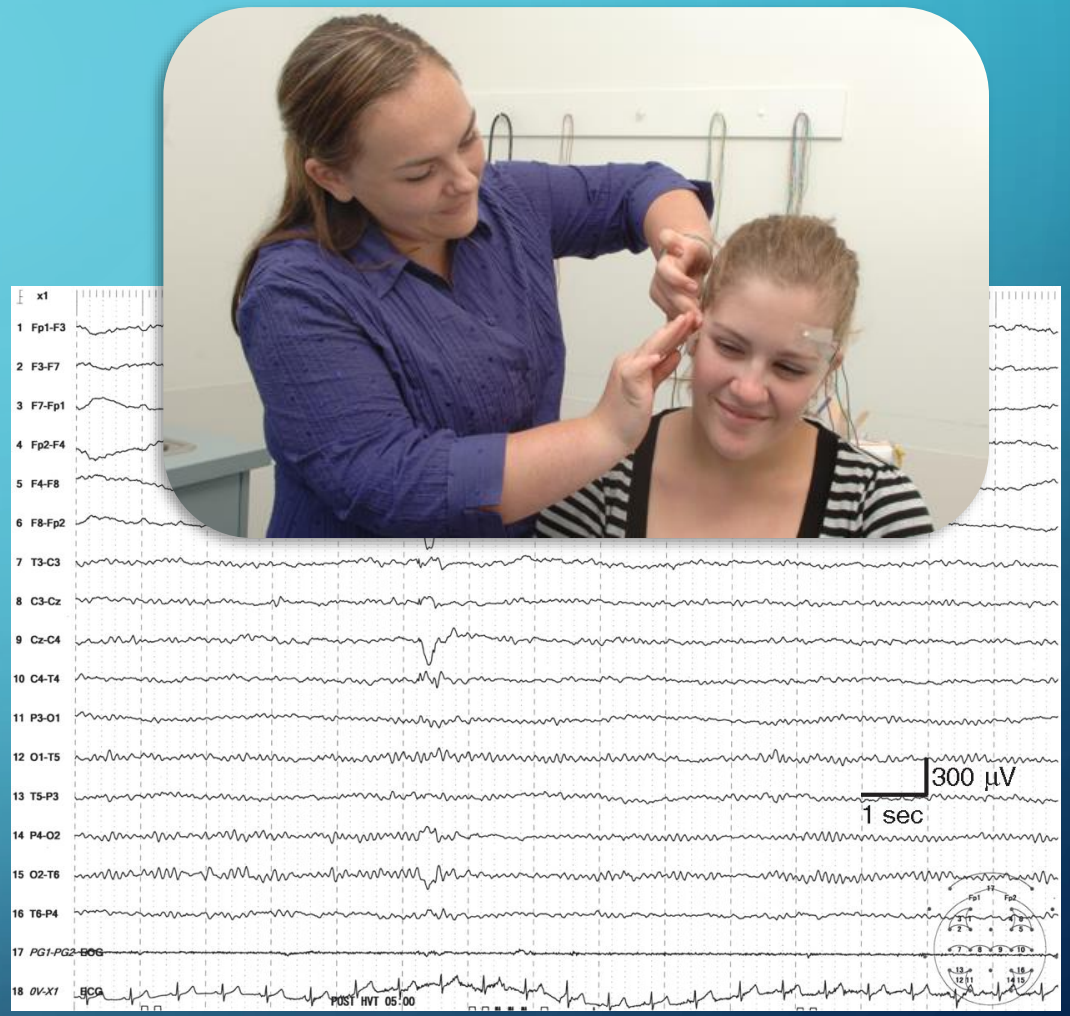
RISK FACTORS FOR RECURRENCE (AAN EVIDENCE BASED GUIDELINES)

Risk of recurrence: 21-47% (Krumholz 2015), almost half (Bonnett, seizure 2022)

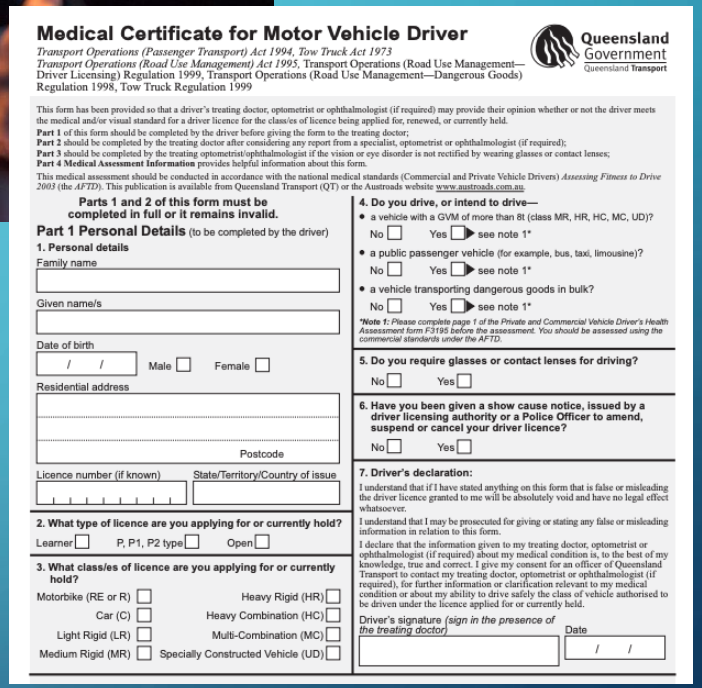
Variable	Relative rate
Nocturnal seizure	2.1 (1-4 year seizure risk)
EEG abnormalities (epileptiform discharges – spikes/ sharp waves)	2.16 (1-5 year seizure risk)
Neuroimaging abnormalities	2.44 (1-4 year seizure risk)
Prior brain insult (cf. patients with seizures of unknown cause)	2.55 (1-5 year seizure risk)

(Krumholz et al., 2015)

- Routine scalp EEG is an insensitive test
- In a meta-analysis of previous studies, routine EEG identified epileptiform abnormalities in 10–27% of adults and in 32–43% of children (Bouma et al., 2016)
- Sensitivity increases with sleep deprived and 24 hour ambulatory EEG
- NOTE: Epilepsy is a clinical diagnosis!



DRIVING RULES



Medical Certificate for Motor Vehicle Driver

Transport Operations (Passenger Transport) Act 1994, Tow Truck Act 1973
Transport Operations (Road Use Management) Act 1995, Transport Operations (Road Use Management—Driver Licensing) Regulation 1999, Transport Operations (Road Use Management—Dangerous Goods) Regulation 1998, Tow Truck Regulation 1999

Queensland Government
Queensland Transport

This form has been provided so that a driver's treating doctor, optometrist or ophthalmologist (if required) may provide their opinion whether or not the driver meets the medical and/or visual standard for a driver licence for the class/es of licence being applied for, renewed, or currently held.

Part 1 of this form should be completed by the driver before giving the form to the treating doctor;
Part 2 should be completed by the treating doctor after considering any report from a specialist, optometrist or ophthalmologist (if required);
Part 3 should be completed by the treating optometrist/ophthalmologist if the vision or eye disorder is not rectified by wearing glasses or contact lenses;
Part 4 Medical Assessment Information provides helpful information about this form.

This medical assessment should be conducted in accordance with the national medical standards (Commercial and Private Vehicle Drivers) *Assessing Fitness to Drive 2003* (the *AFTD*). This publication is available from Queensland Transport (QT) or the Austroads website www.austroads.com.au.

Parts 1 and 2 of this form must be completed in full or it remains invalid.

Part 1 Personal Details (to be completed by the driver)

1. Personal details

Family name

Given name/s

Date of birth / / Male ☐ Female ☐

Residential address

Postcode

Licence number (if known) State/Territory/Country of issue

2. What type of licence are you applying for or currently hold?

Learner ☐ P, P1, P2 type ☐ Open ☐

3. What class/es of licence are you applying for or currently hold?

Motorbike (RE or R) ☐ Heavy Rigid (HR) ☐
Car (C) ☐ Heavy Combination (HC) ☐
Light Rigid (LR) ☐ Multi-Combination (MC) ☐
Medium Rigid (MR) ☐ Specially Constructed Vehicle (UD) ☐

4. Do you drive, or intend to drive—

- a vehicle with a GVM of more than 8t (class MR, HR, HC, MC, UD)? No ☐ Yes ☐ ▶ see note 1*
- a public passenger vehicle (for example, bus, taxi, limousine)? No ☐ Yes ☐ ▶ see note 1*
- a vehicle transporting dangerous goods in bulk? No ☐ Yes ☐ ▶ see note 1*

*Note 1: Please complete page 1 of the Private and Commercial Vehicle Driver's Health Assessment form F3195 before the assessment. You should be assessed using the commercial standards under the AFTD.

5. Do you require glasses or contact lenses for driving?

No ☐ Yes ☐

6. Have you been given a show cause notice, issued by a driver licensing authority or a Police Officer to amend, suspend or cancel your driver licence?

No ☐ Yes ☐

7. Driver's declaration:

I understand that if I have stated anything on this form that is false or misleading the driver licence granted to me will be absolutely void and have no legal effect whatsoever.

I understand that I may be prosecuted for giving or stating any false or misleading information in relation to this form.

I declare that the information given to my treating doctor, optometrist or ophthalmologist (if required) about my medical condition is, to the best of my knowledge, true and correct. I give my consent for an officer of Queensland Transport to contact my treating doctor, optometrist or ophthalmologist (if required), for further information or clarification relevant to my medical condition or about my ability to drive safely the class of vehicle authorised to be driven under the licence applied for or currently held.

Driver's signature *(sign in the presence of the treating doctor)* Date / /

Default restriction 12 months

Epilepsy first diagnosed: 6 months on medication
First seizure, no evidence of epilepsy: 6 months
Acute symptomatic seizure* (e.g. head injury, alcohol withdrawal): 6 months
Black out of undetermined cause: 6 months

Acute symptomatic seizure : seizures only occurring during a temporary brain disorder or metabolic disturbance

FIRST SEIZURE GENERAL ADVICE

Provide First Aid for support person:
1. protect from injury and time seizure.
2. when possible gently roll on side.
3. calmly talk to person and reorientate them.
4. Stay with person.

Call 000 straight away, as diagnosis still ongoing

Seizure Triggers
Avoid Alcohol
Avoid sleep deprivation
Avoid recreational drugs – eg cannabis, MDMA etc

Seizure Safety
Don't be in or near water without someone being within arms reach (swimming/baths/fishing etc)
Don't climb ladders
Consider safety around the home
Consider occupational health and safety

No Driving
Read Jet's Law, leaflet provided
Initial non driving time: private 6-12 months; commercial 5-10 years. The fitness to drive conditions vary so this is not a guarantee.
QLD transport need to be informed
When able to drive again avoid driving after Seizure Triggers (or missed medications if applicable)

If further Events:
□ Call ambulance and go to emergency if concerned
□ GP review and letter to clinic
□ Contact clinic for advice
□ Keep seizure diary, if possible video events

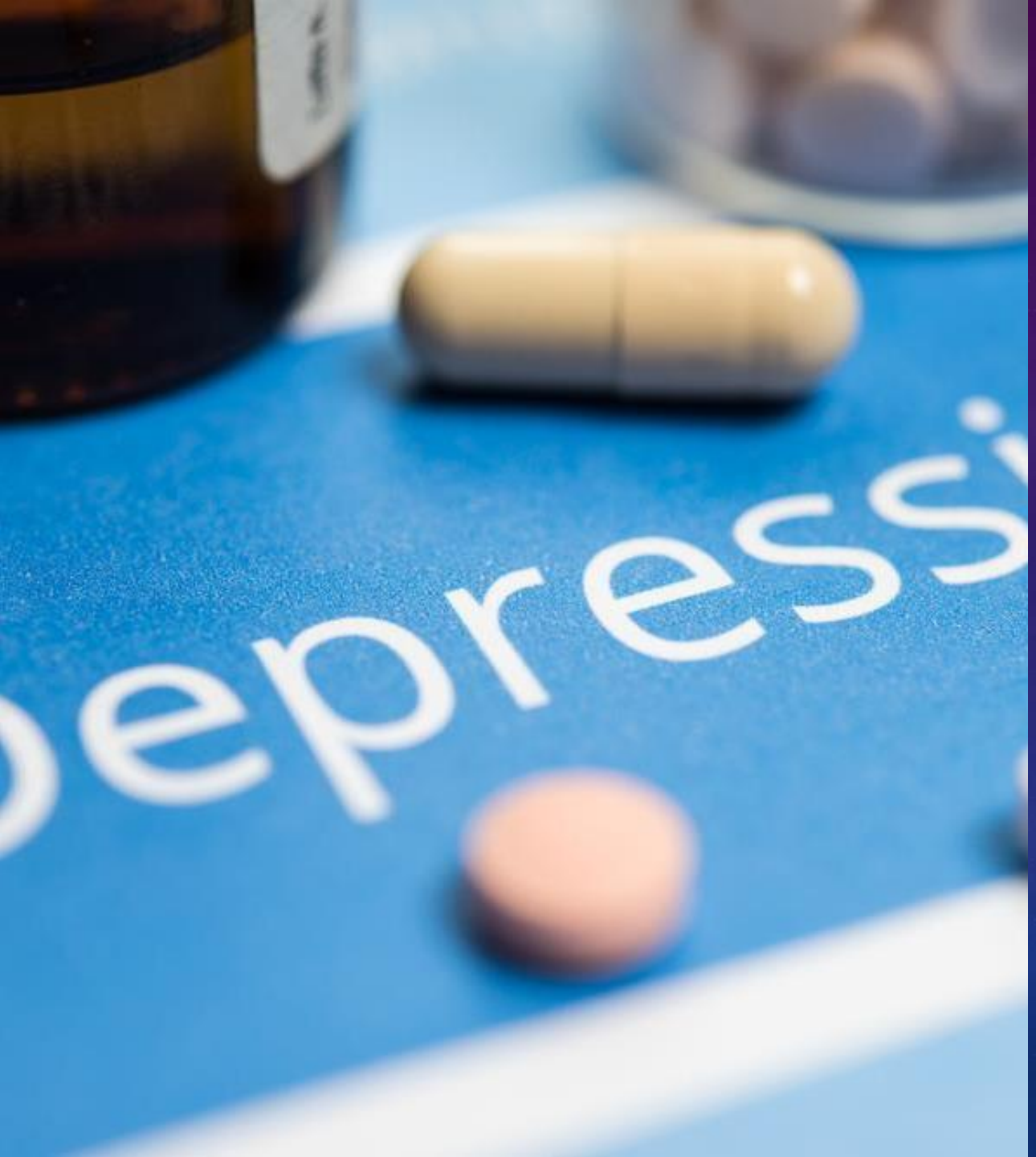
Support
www.epilepsyqueensland.com.au

ADHD, DEPRESSION AND ANTI-ANXIETY DRUGS IN EPILEPSY

- Taken by a high proportion of Australians (I in 7)
- People with epilepsy 4-6x more likely to suffer from depression (likely biological factors)
- Depression Is a common comorbidity of any chronic disease.

EPILEPSY AND ADHD MEDICATION

- Swedish registry study: same number of seizures after ADHD meds compared to same period previous year (Epilepsia 2019)
- NICE guidelines for ADHD 2019 stimulants (methylphenidate, dexamphetamine, lisdexamfetamine) for persons with epilepsy: "*ensure dose titration is slower and monitoring more frequent*"
- Shared decision making if epilepsy poorly controlled, a generalised tonic-clonic seizure in the last three months, or those with a history of status epilepticus



EPILEPSY AND DEPRESSION MEDICATIONS

- ILAE practice recommendations for the medical treatment of depression in adults with epilepsy (2021):
  - Selective serotonin receptor inhibitors (SSRIs - sertraline, escitalopram, citalopram, fluoxetine, fluvoxamine) are not associated with seizure worsening in people with epilepsy.
  - Switching from a SSRI to venlafaxine XR appears appropriate – I tend to avoid doses above 225 mg daily.
  - Tricyclic antidepressants (TCAs - amitriptyline, doxepin etc.): higher-dose clomipramine associated with a 4x greater incidence of seizures.
  - Sustained-release bupropion – similar to SSRIs at a dose up to 300 mg daily.

EPILEPSY AND DEPRESSION MEDICATIONS CONT.

- Mirtazapine alone or with an SSRI can be considered; greater incidence of side effects with venlafaxine.
- Lithium for augmentation: seizures tend to occur in the context of toxic lithium levels (> 3mmol/L).
- Quetiapine or aripiprazole augmentation: quetiapine (and olanzapine) associated with a slightly increased risk of seizures; other second-generation antipsychotics placebo-level.
- First-generation antipsychotics e.g. haloperidol, chlorpromazine evidence a slightly higher risk of seizures than placebo.
- Generally start lower and increase more slowly.

EPILEPSY AND ANTI-ANXIETY MEDICATIONS

- SSRIs first line.
- Silexan 1-2 lavender capsules at bedtime with a trial for six weeks at each dose.
  - main side effect is lavender-flavoured burping.
  - helpful for generalised anxiety symptoms (worrying), sleep quality, and depression.

SO…..WOULD YOU MAKE PSYCHIATRIC MEDICATION ADJUSTMENTS?.....

- Not necessarily
- Starting or increasing such drugs requires careful choice and titration
- Important to treat psychiatric co-morbidities of epilepsy

CASE 2

“No Seizures, but I think I might be pregnant”

HISTORY

- 27 year old woman
- Epilepsy, Valproate 500 mg bd
- Thinks she is 6-7 weeks pregnant.
- Unplanned, not on folate
- Worried about risk of malformation
- Wants to cease valproate
- Wants to know what her options are

FURTHER HISTORY

- “blank spells “ in childhood, on valproate at 5 years, weaned off at 12
- 2 generalised tonic-clonic seizures age 16 years led to reinstitution of Valproate
- Last seizure during back-packing holiday more than 5 years ago, when ran out of tablets for 2 days

FURTHER HISTORY

Epilepsy specialist advice: institute changeover from valproate to lamotrigine.

Lamotrigine 50 mg bd established, valproate fully weaned, seizure free

Pregnancy managed in conjunction with epilepsy specialist advice

Has a healthy baby

Asks about contraception after the birth: not sure what she wants:

OCP? Implant? IUD?

QUESTIONS:

- *What are the risks of seizures in pregnancy?*
- *What are the risks of valproate in pregnancy?*
- *Do they relate to dose? Do they relate to stage of pregnancy?*
- *Should she be taking folate? If so , what dose?*
- *What happens to lamotrigine levels during pregnancy?*
- *What are the risks of epilepsy for her baby?*

- *What effect will OCP agents have on lamotrigine?*
- *What effect will lamotrigine have on OCP agents?*
- *How will long term agents/implanted devices affect lamotrigine?*
- *What contraceptive method is least interfering with antiseizure medication?*

BREAK-OUT DISCUSSION

DILEMMA

Risk of seizures: harm to mother and foetus

Risk of harm to foetus from

anti seizure medication

Important not to stop medications suddenly

Seek neurological advice and urgent referral to the Comprehensive Epilepsy Program

https://brisbanenorth.communityhealthpathways.org/108657.htm

MATERNAL AND FOETAL RISKS OF SEIZURES

Maternal

- Risk of injury
- Risk of sudden unexpected death with epilepsy
- 10 x increased risk of death with delivery
- Increased risk of adverse outcome- pre-eclampsia, preterm labour, stillbirth
- Increased health care use, prolonged hospital admission, increased LUSCS

Foetal

- Prolonged seizure - foetal hypoxia
- Small for gestational age (some agents)
- Frequent of seizures may be a risk factor for low IQ in child
- Seizure-related falls, risk of trauma to uterus
- Foetal decelerations with focal seizures

RISKS OF VALPROATE (VPA)

- **Major congenital malformations (MCM)**
  - Most common- cardiac, neural tube, hypospadias
  - Dose dependent
  - First trimester critical
- **Developmental and behavioural outcomes**
  - VPA > 800 mg/day, 10-point decease in IQ
  - VPA < 800 mg/day impaired verbal abilities
  - Dose dependent
  - Risk likely the whole pregnancy
- **Autism spectrum disorder (ASD)**
  - 4x increase,
  - Risk likely the whole pregnancy
- **Genetic contribution**
  - If family history of ASD and previous MCM, likely higher baseline risk irrespective of VPA

VPA dose (mg/day)	Approximate Risk of MCM (Population risk 2-3%, no ASM)
> 1500	25 %
700-1450	10%
500-700	6.3 %
< 500	5%

ASM- anti-seizure medication

FOLIC ACID

Optimal dose and duration unclear

Aim 1 mg/day for 3 months prior to pregnancy and then at least 0.5 mg/day through-out pregnancy

- General population evidence for benefits
- Lack of evidence for women taking ASMs
- Literature supports at least 0.4mg/day

Benefits

- **Reduced risk of autism and language delay** in the children (Bjork et al JAMA Neurol 2018;160-168)
- **Improved IQ at 6 years**, exposed to ASMs in utero (Meador et al Neurology 2020 94:e729-e740)

Potential Risks of high dose folic acid

- Animal studies
- Observational study- pre-natal high-dose folic **increased risk of cancer** in children of mothers with epilepsy (Vegrim et al JAMA Neurol.doi10.1001/jamaneurol.2022.2977)

LAMOTRIGINE LEVELS DURING PREGNANCY

- ASM dependent and substantial inter-individual variability
- Decline in serum concentration > 35% from pre-pregnancy level associated with increased risk of seizure
- Increase in estrogen-driven glucuronidation leads to decreased levels
- As early as the 3rd week of pregnancy
- Importance of a baseline pre-pregnancy drug level

WILL MY CHILD DEVELOP EPILEPSY?

- If you have generalised epilepsy the chance your child will develop epilepsy is only 1 in 12
- If you have focal epilepsy the chance your child will develop epilepsy is 1 in 50

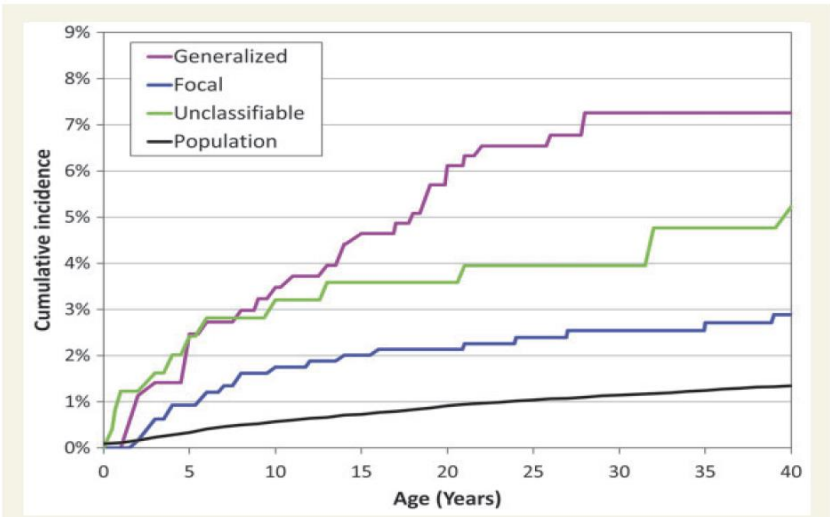


Figure 1 Age-specific cumulative incidence of epilepsy in first-degree relatives of probands with epilepsy, by proband epilepsy type.

(Peljto et al Brain 2014;137:795-805)

CONTRACEPTIVE CHOICES

- Enzyme-inducing anti-seizure medications
  - carbamazepine, phenytoin
  - increase the activity of the CYP3A4 enzymes
  - increases the metabolism of estrogen and progesterone, decreasing their levels
- Lamotrigine
  - elimination is by glucuronide conjugation (enzyme UGT1A4)
  - can cause a modest decrease in progestins likely due to induction of clearance
  - probably not an inducer of the CYP3A as no change to estrogen levels
- Bi-directional impact- estrogen induces lamotrigine glucuronidation and increases elimination
  - combined OC pill can **lower lamotrigine levels** by 40-60%
- Contraceptive options
  - Combined OC pill
  - Progesterone only
  - **IUD- preferred option**

LAMOTRIGINE AND CONTRACEPTION CHOICE

Contraception choice	PROS	CONS
Barrier methods	No interactions with lamotrigine	**High failure rate**
OC pill	Non-invasive	User-dependent **reduces lamotrigine level (estrogen-driven)** Modest decrease in progestin
Mini-pills (low dose progestin-only) 0.03 mg levonorgestrel 0.35mg norethisterone	No change to estrogen levels No change to lamotrigine levels	User-dependent **Does not inhibit ovulation** Break through bleeding
68 mg etonogestrel implant (intermediate dose progestin-only)	User-independent No change to estrogen levels No change to lamotrigine levels	Modest decrease in progestin **Failures have been documented**
Depo medroxyprogesterone acetate (high dose progestin-only)	User-independent No change to estrogen levels No change to lamotrigine levels	Modest decrease in progestin **Impacts on bone, delayed return to fertility, acne, hair loss, depression**
20 ug levonorgestrel releasing IUD	**User-independent** **No change to lamotrigine level**	Possible concerns of infertility
4mg Drospirenone	No estrogen **Dose inhibits ovulation**	User-dependent Modest decrease in progestin No data with lamotrigine use

SUMMARY

- **Important not to stop medications suddenly**
- **Seek neurological advice and urgent referral to the Comprehensive Epilepsy Program**
  - https://brisbanenorth.communityhealthpathways.org/108657.htm
- Tonic-clonic seizures - risks to both foetus and mother
- Valproate has dose dependent risks
  - major congenital malformations
  - developmental and behavourial outcomes
- Folate should be used preconception and throughout pregnancy
- Lamotrigine levels can fall with pregnancy
- Baseline lamotrigine level important for drug monitoring
- The genetics of epilepsy is complex
  - rarely caused by a single gene
- Combined oral contraceptive pill can reduce lamotrigine levels
- IUD is the preferred contraception option

Case 3

Can I ever get better control of my seizures?

Would medical marijuana help?

Learning objectives

- Epilepsy types and the definition of Drug Refractory Epilepsy.
- When to refer patients to a comprehensive epilepsy unit for presurgical epilepsy evaluation.
- SUDEP risk in epilepsy patients.
- Role of epilepsy surgery in the treatment of epilepsy.
- Medical marijuana in Epilepsy in Australia

Case 3 - Background

- Fred is a 27-year-old man, new to your practice and coming in to request a new script with some questions regarding his treatment
- Background:
  - Normal birth and developmental history.
  - No antecedents for epilepsy (CNS insults, family history)
- Social history
  - He works full-time as an investment banker.
  - Lives with his partner and has no dependents.
  - Currently driving with a conditional license.
  - Rare social alcohol and lifelong non-smoker.
- No other past medical history and no known drug allergies

Case 3 – Epilepsy history

- Diagnosed with epilepsy at the age of 22 after an unprovoked tonic-clonic seizure at work.
- First seizure:
  - Fred describes his first seizure initially starting with a sudden familiar sensation, as if knowing the current situation has been encountered before (déjà vu).
  - This was followed by an intense nausea and rising sensation in the epigastrium before losing consciousness.
  - Fred's first memory following the seizure was being in an ambulance.
  - Witness accounts of Fred's seizure described him looking absent and confused before progressing into a generalised convulsion.

Case 3 – Progress history

- Started on anti-seizure medication – gradually increased over years
- Unfortunately continues to have convulsive seizures every two months.
- Fred continues to drive, as his seizures only occur in his sleep and have remained that way for the past four years.
- Fred's seizures usually wake up his wife when they occur. She will roll him onto his side and Fred will usually be able to recover and go to work the following day. He does report frequent tongue bites from these seizures.
- Medication:
  - Lamotrigine 200mg BD
  - Levetiracetam 1500mg BD
  - Lacosamide 200mg BD

Case 3

- Fred moved to Brisbane from Sydney 6 months ago, and has provided a folder with some old clinic notes and investigation reports
- He presented today to request repeats for his regular anti-seizure medication and mentioned that he read on some online forums about the benefits of medical marijuana in epilepsy and asked if that was something he could try to improve his seizures.

Questions

1. Fred’s previous investigations revealed a normal MRI brain with no focal abnormalities. What type of epilepsy does Fred have and does it matter?
2. Are you happy that Fred’s epilepsy is adequately controlled?
3. What are the major risks to this patient if no change is made to his management and treatment?
4. What is SUDEP? Is this something important to discuss with the patient?
5. What are the likely outcomes with additional medicines vs epilepsy surgery in this patient?
6. Should medical marijuana be considered for this patient?

Breakout rooms

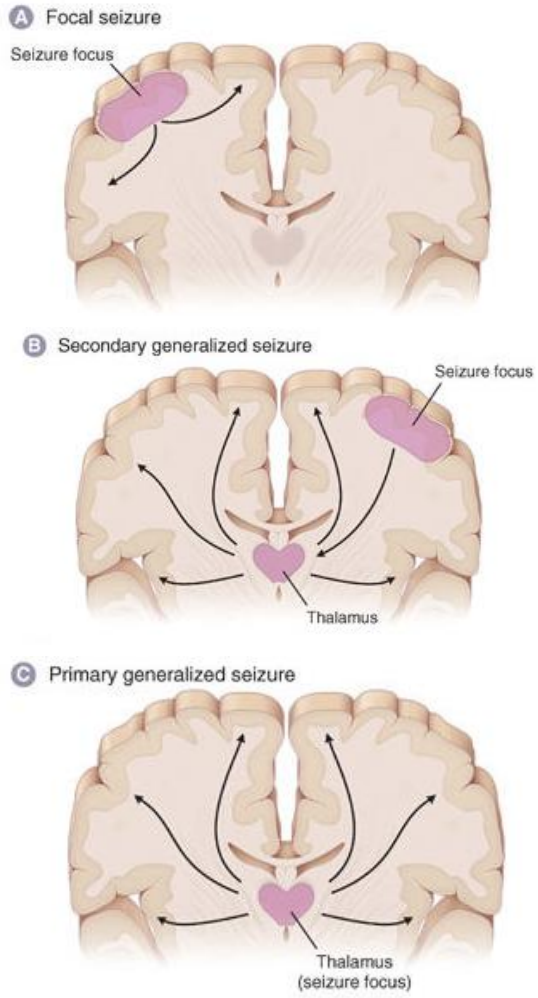
Expert opinion

1. Fred’s previous investigations revealed a normal MRI brain with no focal abnormalities. What type of epilepsy does Fred have and does it matter?
2. Are you happy that Fred’s epilepsy is adequately controlled?
3. What are the major risks to this patient if no change is made to his management and treatment?
4. What is SUDEP? Is this something important to discuss with the patient?
5. What are the likely outcomes with additional medicines vs epilepsy surgery in this patient?
6. Should medical marijuana be considered for this patient?

1 - Fred's Ix revealed a normal MRI brain with no focal abnormalities. What type of epilepsy does Fred have and does it matter?

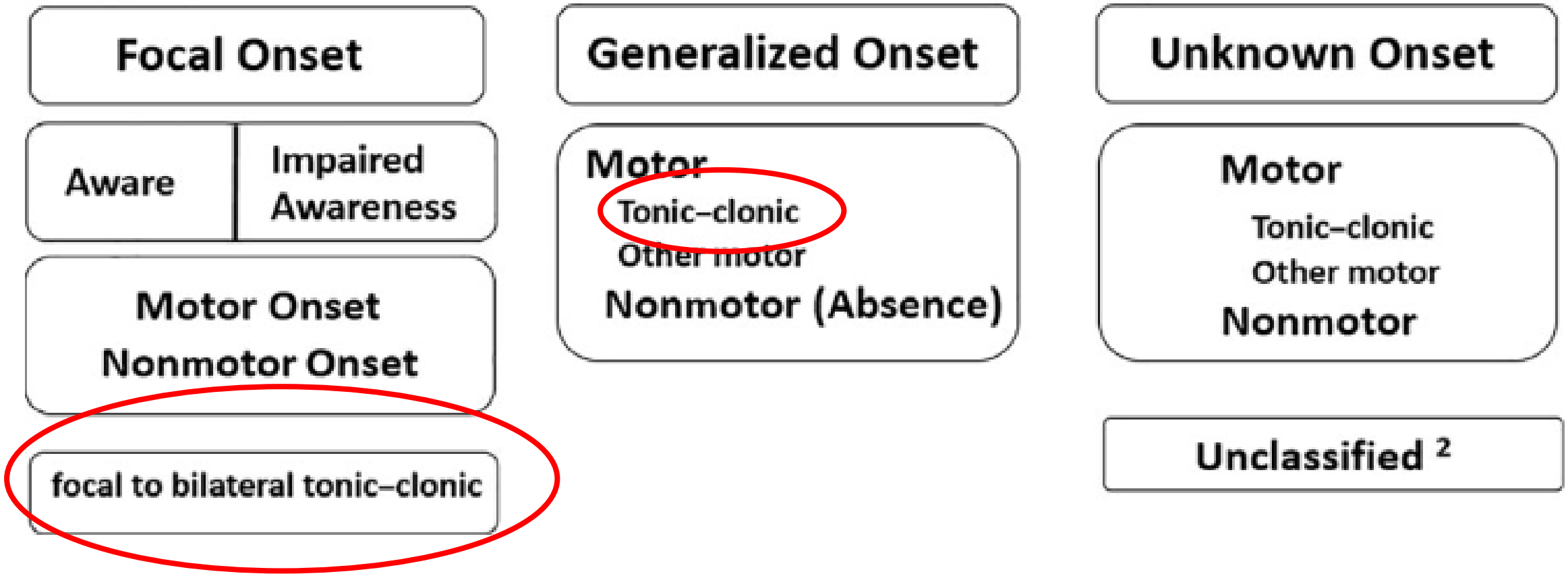
- Focal vs generalised epilepsy?

	Focal onset	Generalised onset
Aura	Yes	
Focal/asymmetric ictal features	Yes	
Post-ictal focal signs	Yes	
Neurological abnormalities on exam	Yes	
Age of onset		< 20 years
Time of day: On waking From deep sleep	Yes	Yes
Myoclonus		Yes
Low frequency		Yes
100% generalised tonic clonic		Yes



Focal vs generalised epilepsy

- Both focal and generalised onset seizures can cause tonic-clonic (grand mal seizures)



Focal vs generalised: Implications

- Implications understanding if focal vs generalised epilepsy?
  - Helps guide investigations
    - Focal → Imaging to find lesion (MRI, PET brain, ictal SPECT)
  - Improves choice of therapy
    - Valproate (effective for generalised epilepsies)
    - Carbamazepine and oxcarbazepine (effective mainly for focal epilepsies, can worsen some generalised epilepsies)
  - Prognosis
    - Childhood absence epilepsy (CAE) usually remits as adult
    - Focal → surgery as potential therapy
    - Generalised → resective surgery not a therapy

MRI negative epilepsy

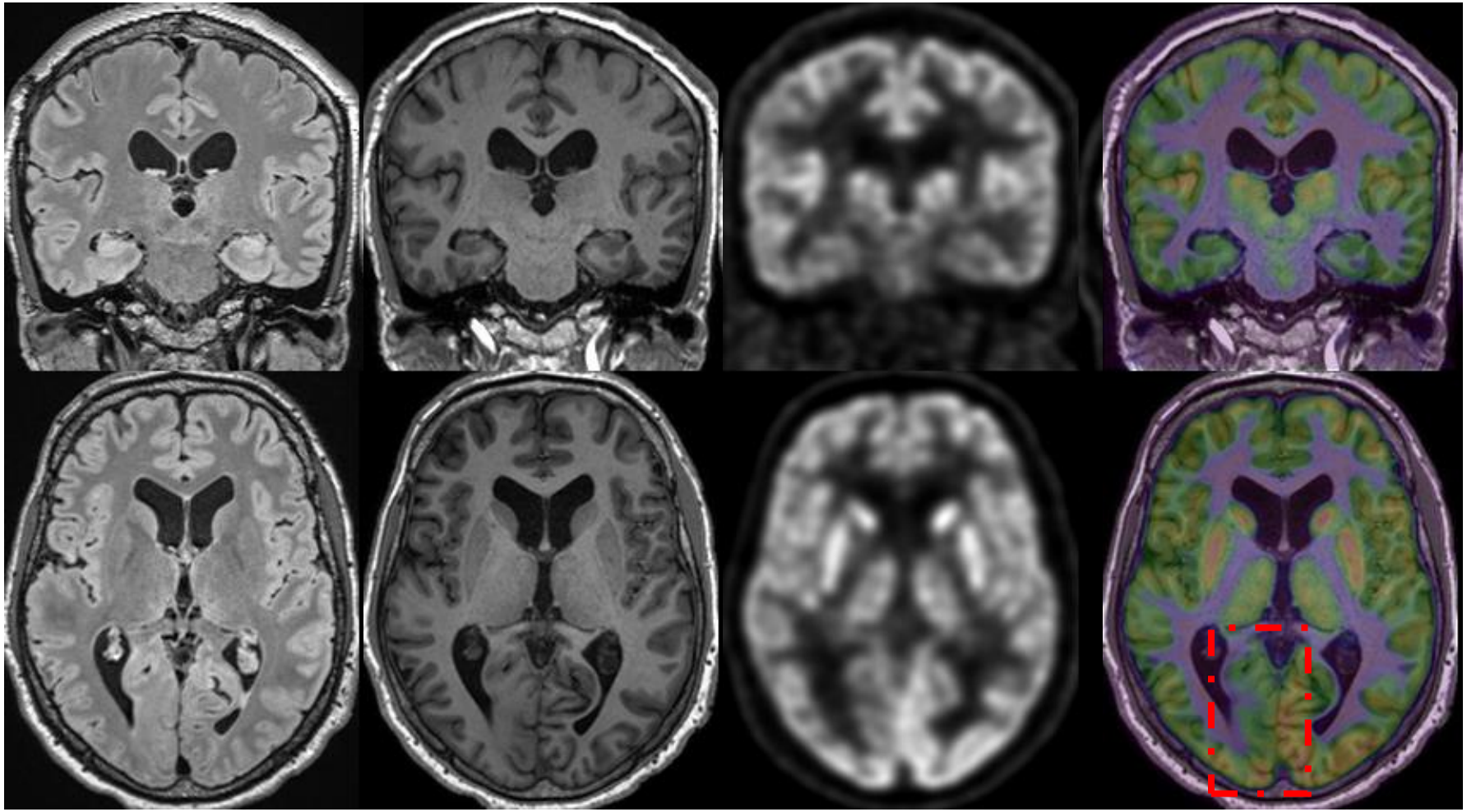
- 30% of patients in surgical studies have MRI-negative (non-lesional) focal epilepsy
- Even with a negative MRI, other modalities can help localise the epileptogenic lesion
- Standard MRI in epilepsy – 57% false negative rate
- Epilepsy protocol MRI by neuroradiologist – 11% false negative rate (89% correct)

Téllez-Zenteno, J. F., Hernández Ronquillo, L., Moien-Afshari, F., & Wiebe, S. (2010). Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy research, 89(2-3), 310–318. https://doi.org/10.1016/j.eplepsyres.2010.02.007

Wang, Z. I., Alexopoulos, A. V., Jones, S. E., Jaisani, Z., Najm, I. M., & Prayson, R. A. (2013). The pathology of magnetic-resonance-imaging-negative epilepsy. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc*, *26*(8), 1051–1058. https://doi.org/10.1038/modpathol.2013.52

Von Oertzen, J., Urbach, H., Jungbluth, S., Kurthen, M., Reuber, M., Fernández, G., & Elger, C. E. (2002). Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. *Journal of neurology, neurosurgery, and psychiatry*, *73*(6), 643–647. https://doi.org/10.1136/jnnp.73.6.643

Seeing the invisible – multimodal imaging



2 – Are you happy that Fred's epilepsy is adequately controlled?

- No
- Fred has **drug resistant epilepsy** with tonic-clonic seizures
- International League Against Epilepsy definition:
  - Failure of adequate trials of two (or more) tolerated and appropriately chosen and used antiepileptic drugs to achieve sustained seizure freedom
- Indication for referral to comprehensive epilepsy program is **failure of only two appropriately chosen anti-epileptic drugs** (i.e. drug resistant epilepsy)

3- What are the major risks to this patient if no change is made to his management and treatment?

- Patient has drug resistant epilepsy and ongoing tonic-clonic seizures
- Active tonic-clonic seizures are associated with
  - Negative stigmatisation
  - Lower quality of life quotients
  - Seizure related injuries
  - Unfavourable treatment outcomes
  - Increased risk of **SUDEP**

4 - What is SUDEP? Is this something important to discuss with the patient?

SUDEP

SUDEP stands for Sudden Unexpected Death in Epilepsy.

Defined as the sudden and unexpected death of a person with epilepsy without apparent cause.

1 in 1000 patient risk of SUDEP

Tonic-clonic seizure in preceding year– 27x risk

Nocturnal seizure in preceding year – 8x risk

Sveinsson, O., Andersson, T., Mattsson, P., Carlsson, S., & Tomson, T. (2020). Clinical risk factors in SUDEP: A nationwide population-based case-control study. Neurology, 94(4), e419–e429. https://doi.org/10.1212/WNL.0000000000008741

5 - What are the likely outcomes with medication trials vs epilepsy surgery in this patient?

- Drug resistant epilepsy (DRE) remission rates
  - ASM drug trials have a small likelihood of inducing remission 4-6% per year (15-20% cumulative)
- Remission rates from medication have not improved despite new medications

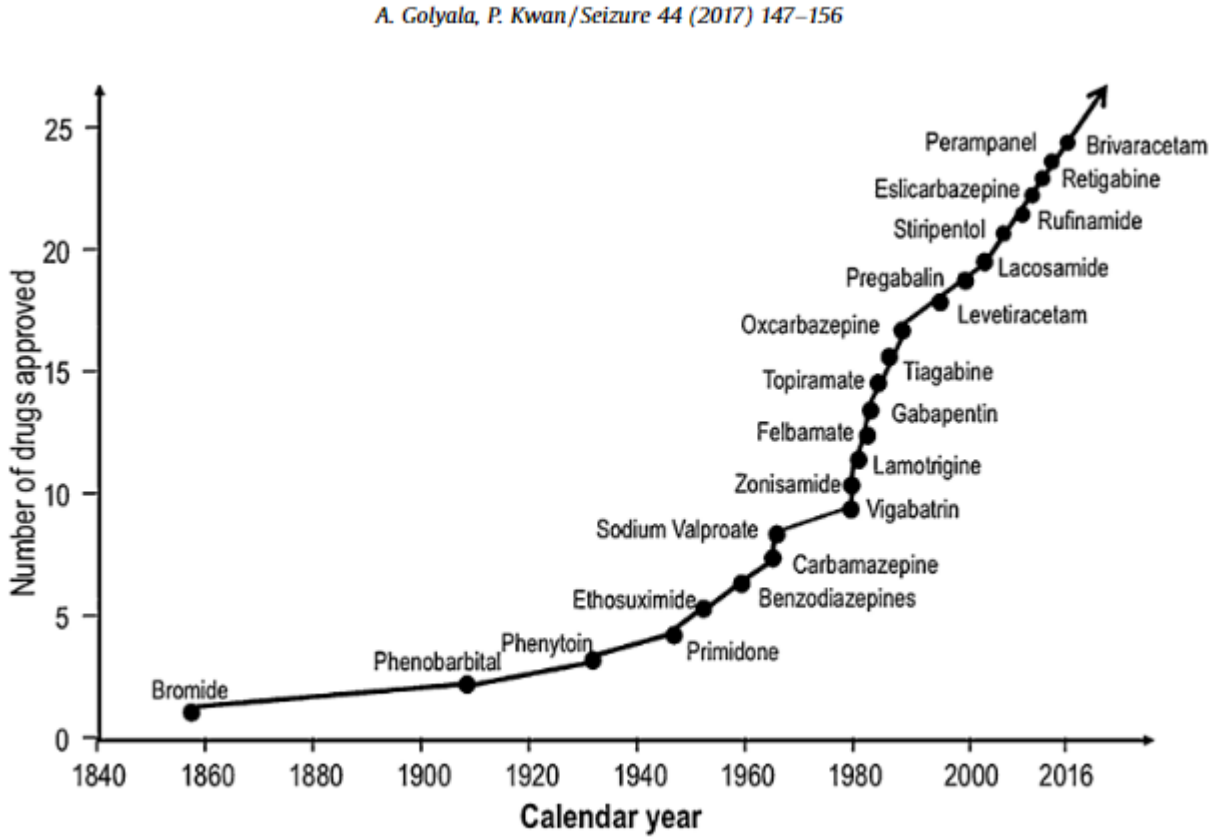


Fig. 1. Chronological development of antiepileptic drugs.

Kwan, P., Schachter, S. C., & Brodie, M. J. (2011). Drug-resistant epilepsy. The New England journal of medicine, 365(10), 919–926. https://doi.org/10.1056/NEJMra1004418

Epilepsy surgery is effective!

JAMA Neurology | Original Investigation

Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs

A 30-Year Longitudinal Cohort Study

Zhibin Chen, PhD; Martin J. Brodie, MD; Danny Liew, MD, PhD; Patrick Kwan, MD, PhD

Cochrane Library

Cochrane Database of Systematic Reviews

Surgery for epilepsy (Review)

West S, Nolan SJ, Cotton J, Gandhi S, Weston J, Sudan A, Ramirez R, Newton R

182 studies, 16756 patients
65% Engel I at 12+ months

Long-term reduction of health care costs and utilization after epilepsy surgery

*†Nicholas K. Schiltz, ‡Kitti Kaiboriboon, *Siran M. Koroukian, *Mendel E. Singer, and *§¶Thomas E. Love

Epilepsia, 57(2):316–324, 2016
doi: 10.1111/epi.13280

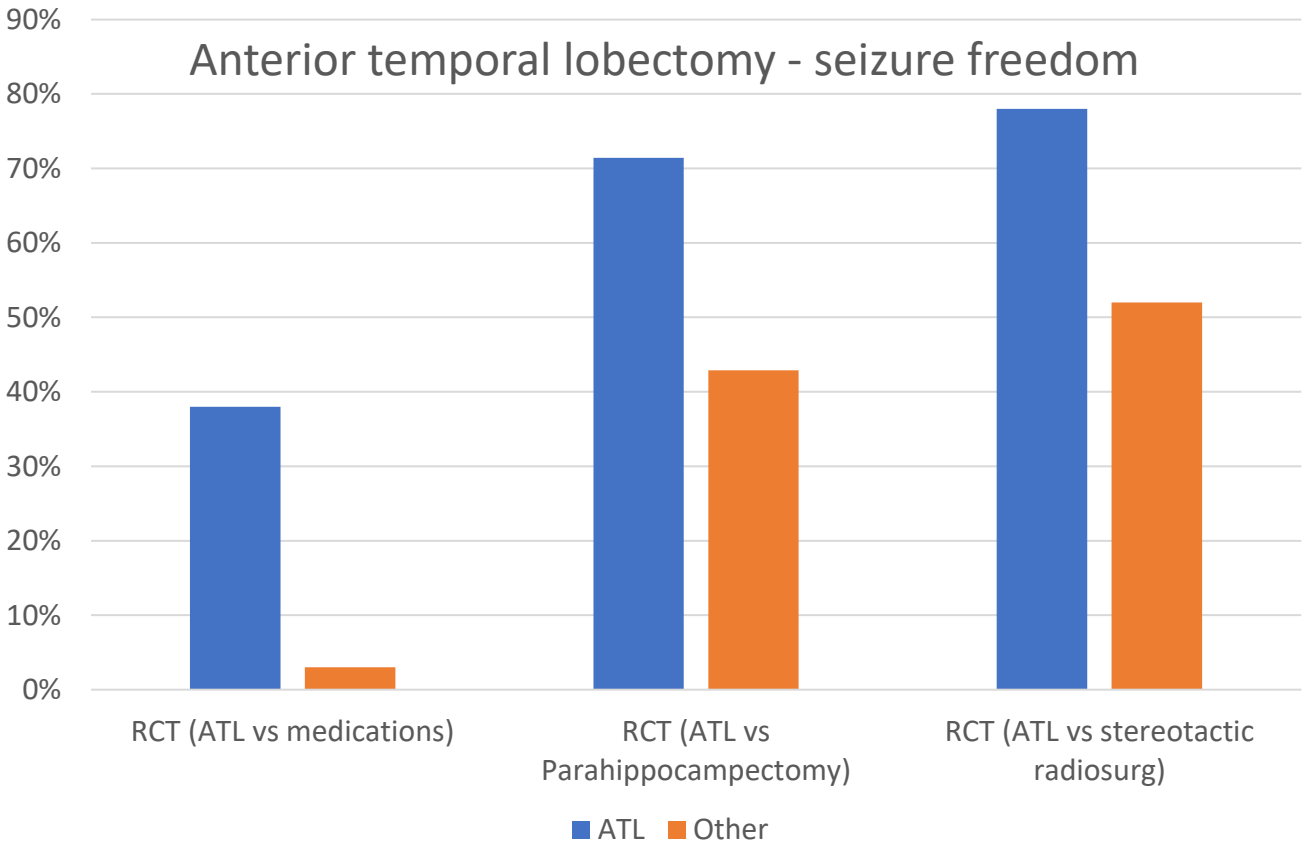
CrossMark

Epilepsy surgery in children and adults

Philippe Ryvlin, J Helen Cross, Sylvain Rheims

Lancet Neurol 2014; 13: 1114–26

Anterior temporal lobectomy (ATL)



A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY

SAMUEL WIEBE, M.D., WARREN T. BLUME, M.D., JOHN P. GIRVIN, M.D., PH.D., AND MICHAEL ELIASZIW, PH.D., FOR THE EFFECTIVENESS AND EFFICIENCY OF SURGERY FOR TEMPORAL LOBE EPILEPSY STUDY GROUP*

Original Article

Parahippocampectomy as a New Surgical Approach to Mesial Temporal Lobe Epilepsy Caused By Hippocampal Sclerosis: A Pilot Randomized Comparative Clinical Trial

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

Radiosurgery versus open surgery for mesial temporal lobe epilepsy: The randomized, controlled ROSE trial

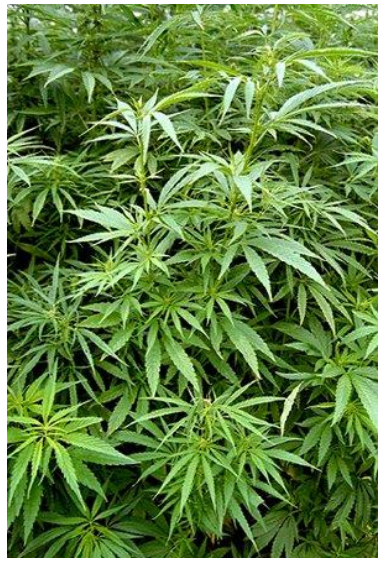
Wiebe, S., Blume, W. T., Girvin, J. P., Eliasziw, M., & Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group (2001). A randomized, controlled trial of surgery for temporal-lobe epilepsy. *The New England journal of medicine*, *345*(5), 311–318. https://doi.org/10.1056/NEJM200108023450501

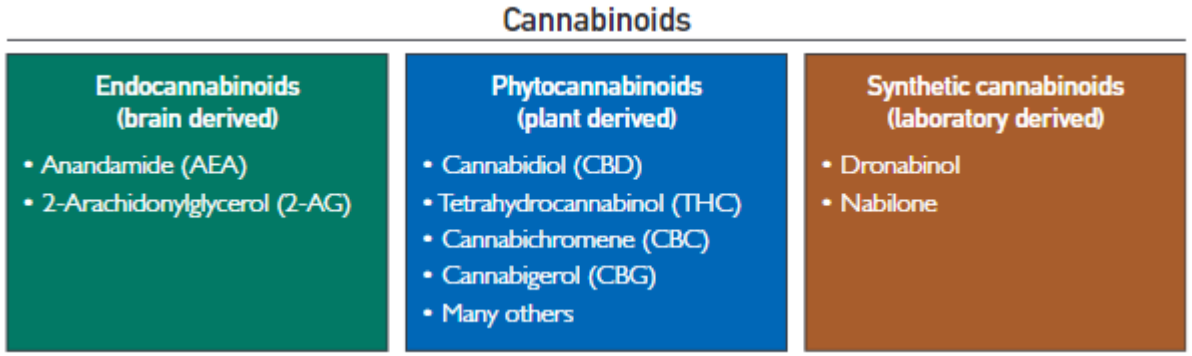
Alonso-Vanegas, M. A., Freire Carlier, I. D., San-Juan, D., Martínez, A. R., & Trenado, C. (2018). Parahippocampectomy as a New Surgical Approach to Mesial Temporal Lobe Epilepsy Caused By Hippocampal Sclerosis: A Pilot Randomized Comparative Clinical Trial. World neurosurgery, 110, e1063–e1071. https://doi.org/10.1016/j.wneu.2017.11.170 Barbaro, N. M., Quigg, M., Ward, M. M., Chang, E. F., Broshek, D. K., Langfitt, J. T., Yan, G., Laxer, K. D., Cole, A. J., Sneed, P. K., Hess, C. P., Yu, W., Tripathi, M., Heck, C. N., Miller, J. W., Garcia, P. A., McEvoy, A., Fountain, N. B., Salanova, V., Knowlton, R. C., … Tecoma, E. (2018). Radiosurgery versus open surgery for mesial temporal lobe epilepsy: The randomized, controlled ROSE trial. *Epilepsia*, *59*(6), 1198–1207. https://doi.org/10.1111/epi.14045

6 – Should medical marijuana be considered for this patient?

Epilepsy treatment book (Gowers Neurology textbook 1885)

Treatment	Efficacy
• Bromide	+++
• Digitalis	+
• Belladonna	+
• Cannabis	+
• Zinc/iron	+
• Opium	-
• Arsenic	-
• Turpentine	-
• Mistletoe	-





6 – Should medical marijuana be considered for this patient?

- Cannabidiol (CBD), a non-psychoactive phytocannabinoid, has been of great public interest for drug-resistant epilepsy

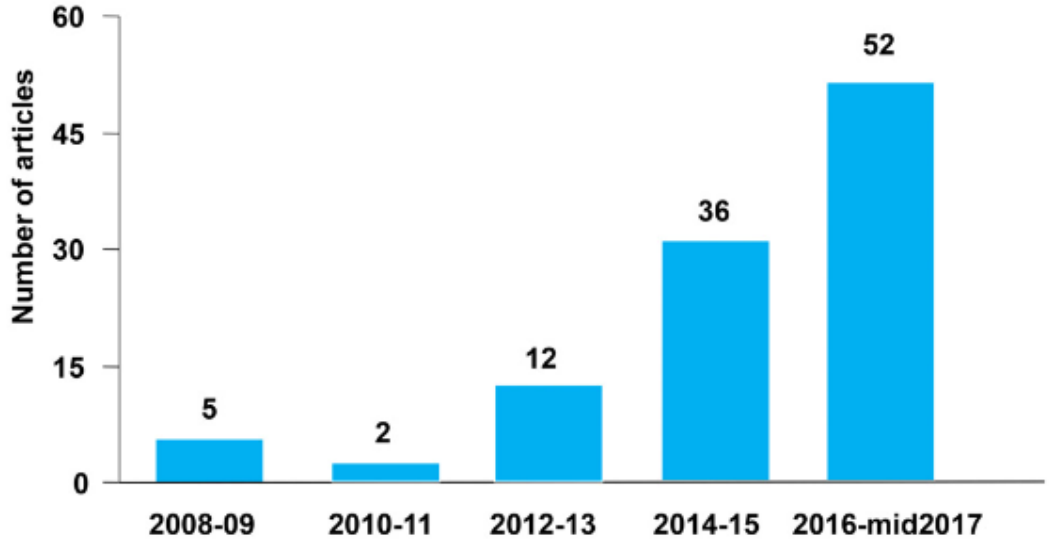
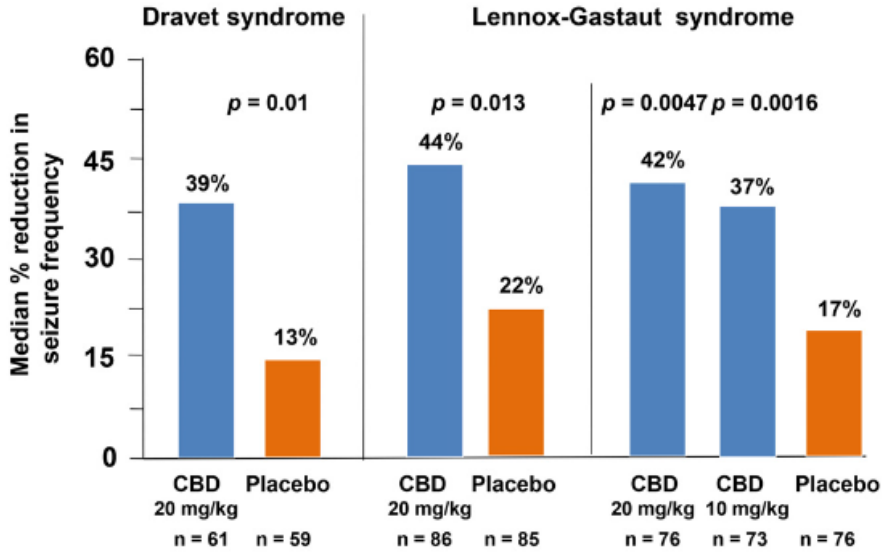


Figure 1. Number of articles retrieved in PubMed by using the search terms 'cannabis and epilepsy', grouped by year of publication.

- Tetrahydrocannabinol (THC)
  - Has been suggested in several studies to demonstrate **proconvulsant** effect
  - The psychotropic properties, inconsistent activity in seizure models have rendered THC undesirable for development of treatment of epilepsy

CBD evidence



- Dravet syndrome (RCT NEJM 2017)
  - >50% reduction in convulsive seizures
    - 43% in CBD group vs 27% in placebo group
  - No difference with non-convulsive seizure group
  - Adverse effects (75% in CBD group vs 36% in placebo)
- Lennox-Gastaut Syndrome
  - Drop seizure reduction (44% CBD vs 24% placebo) (RCT GWPCARE4)
  - Drop seizure reduction (42% CBD vs 17% placebo) (RCT GWPCARE3)
- Lack of RCT evidence for CBD use as monotherapy for any seizure type
- Many underpowered and poorly design studies in epilepsy

Side effects are common

Adverse event	Percentage of patients with adverse event	
	CBD group (n = 61)	Placebo group (n = 59)
Somnolence	36%	10%
Diarrhea	31%	10%
Decreased appetite	28%	5%
Fatigue	20%	3%
Vomiting	15%	5%
Fever	15%	8%
Lethargy	13%	5%
Convulsion	11%	5%
Upper respiratory tract infection	11%	8%

Only events occurring with a frequency > 10% in either group are listed.
CBD, cannabidiol.

Dose of 20mg/kg in positive RCT studies

CBD – indications in epilepsy (Australia)

- Cannabidiol is **TGA approved** as an adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) for patients 2 years and older
- This drug is only Medicare approved for Dravet syndrome
- Non-PBS cost of drug (100g/mL oral liquid, 100mL = $2006.49)
- 60kg with LGS using 20mg/kg dose of cannabidiol= $2000/week

- Lack of RCT evidence for less rigorously prepared CBD preparations

Important notes

- Patients purchasing cannabis-based products need to understand that product may not only contain CBD but other phytocannabinoids such as THC
- CBD can result in drug-drug pharmacokinetic interactions with current anti-seizure drugs (demonstrated in RCT)
- 2020 – TGA released top 25 cannabis products sold under the special access scheme
  - 3 products failed with too low CBD or THC content
  - 2 products failed with too high CBD content
- Recent study in USA demonstrated low level heavy metal and phthalate contamination in edible CBD

Heavy metal and phthalate contamination and labeling integrity in a large sample of US commercially available cannabidiol (CBD) products

Hannah Gardener [a], Chela Wallin [b], Jaclyn Bowen [c]

42%

Of the 516 commercially available CBD products tested fell within ±10% of the CBD content claimed on the manufacturer label

Of the **121** edible CBD products tested

42% contained at least trace levels of lead

8% contained at least trace levels of cadmium

28% contained at least trace levels of arsenic

37% contained at least trace levels of mercury

Gardener, H., Wallin, C., & Bowen, J. (2022). Heavy metal and phthalate contamination and labeling integrity in a large sample of US commercially available cannabidiol (CBD) products. *The Science of the total environment*, *851*(Pt 1), 158110. https://doi.org/10.1016/j.scitotenv.2022.158110

Summary

- Understanding the epilepsy type (focal vs generalised) has implications on investigations, treatment and prognosis in epilepsy
- Drug resistant epilepsy is defined by the failure to achieve seizure freedom after the trial of 2 or more appropriate anti-seizure drugs
- Drug resistant epilepsy is an indication for referral to a comprehensive epilepsy service
- SUDEP occurs in 1 in 1000 epilepsy patients, with a 27-fold risk in patients with recent tonic-clonic seizures over the past year
- Seizure freedom from medication after drug resistance is <10%
- Epilepsy surgery can provide much higher seizure freedom rates
- Cannabidiol currently only has evidence for Lennox-Gastaut and Dravet syndrome (both severe epileptic encephalopathies)

GP MANAGEMENT OF EPILEPSY

- Where to from here?

WHAT LEADS TO BETTER OUTCOMES IN EPILEPSY IN PRIMARY CARE? (FROM NCGC)

- Regular structured review with GP (are they having events, Encourage compliance, about potential triggers alcohol/sleep/drugs, Check for side effects of medications, Check on mood, Women – check contraception/pregnancy planning)
- Consider regular pathology FBE/ELFT (use recall systems)
- Maximum interval between review should be 1 year
- Having a comprehensive care plan
- Managing lifestyle and medical issues (especially mental health and substance abuse)
- https://www.epilepsyingeneralpractice.com/gp-care-plans

Discuss and agree patient management goals and actions. These might include:

- ☐ **Optimum seizure control, and reduction of risk factors**
- ☐ **Successful self-management with good general health and quality of life**
- ☐ **Continuity of care with one GP, if possible, and perhaps an annual specialist review**
- ☐ **Agreement to join epilepsy register for recalls and follow up**
- ☐ **Discussion with an epilepsy educator**
- ☐ **Other**

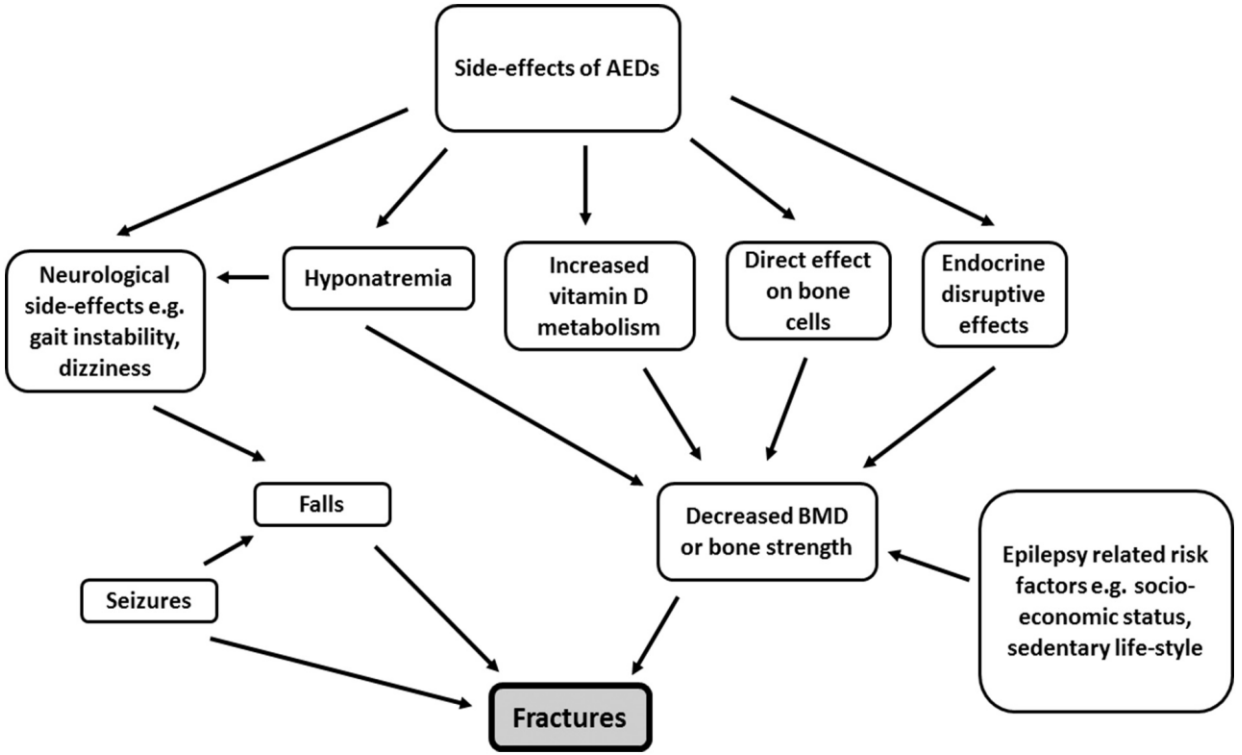
Issues for consideration	**Comments if required**
Patient understanding of condition	
AEDs, side effects, interactions	
Driving	
Lifestyle / Risk & triggers	
First Aid	
Mood	
Bone Health	
Social / Employment issues	
Epilepsy Action Plan if needed	
Women's issues	
Contraception	
Planning pregnancy	
Folic acid	
Polycystic Ovary Syndrome	

Epilepsy and Bone Disease

- All patients with epilepsy have increased risk of metabolic bone disease.
  - Osteoporosis affects 10-30% of all patients with epilepsy.
  - Fracture risk 2-6x that of the background risk.

- Multifactorial fracture risk
  - Falls and physical trauma
  - Underlying disease eg stroke, cerebral palsy
  - Effects of ASMs on gait and balance

- Various mechanisms:
  - Enzyme induction increasing catabolism of vitamin D.
  - Cytochrome induced increase in metabolism of sex steroids
  - Direct inhibitory effect on intestinal calcium absorption (eg phenytoin)



Diemar, S et al, An explorative literature review of the multifactorial causes of osteoporosis in epilepsy, Epilepsy & Behaviour 2019: 100(Pt A):106511

Prevention and Treatment

- No consensus on optimal screening, diagnosis, or prevention.
- Treatment of established osteoporosis is the same for those not on ASMs.

Table 1. Indications for performing DXA in patients with epilepsy.

- Patients treated with EIASM >2 years
- Patients treated with any type of ASM together with one of the following risk factors for bone loss:
- High-dose ASM treatment (dose above the recommended)
- ASM polytherapy (2 or more ASM)
- Co-morbidities known to increase risk of osteoporosis
- Patients with decreased mental capacity and low physical activity
- Concomitant treatment with medications known to induce bone loss (e.g., prednisolone >5 mg)
- One or more clinical risk factors for fractures (e.g., age >80 years, smoking, excessive alcohol intake, secondary osteoporosis, low BMI, and previous low-energy fracture)

Andersen N and Jorgensen N, Impaired bone health as a comorbidity of epilepsy. Best Pract Res Clin Rheumatol. 2022 Sep;36(3):101755

Sleep Disorders

- Obstructive sleep apnoea
  - 20-40% of adults with refractory epilepsy
  - Associated with worse seizure control
- Indications for PSG in patients with epilepsy
  - Daytime sleepiness, loud snoring, witnessed pauses etc
- Management has consequent benefits to seizures
  - Associated with reduced seizure control and reduced interictal discharges.
  - 50% of patients achieve >50% reduction in seizures with effective treatment

Table 2. Comparisons between CPAP-compliant group and CPAP-noncompliant group

	CPAP-compliant (n = 28) mean, median (IQR)	CPAP-noncompliant (n = 13) mean, median (IQR)	Statistical analysis
ESS	12, 11 (8.2–15)	13.3, 14 (9.5–16.5)	p = 0.3
AHI	17.1, 12 (9–21)	17, 10 (7.8–29)	p = 0.29
Optimal CPAP pressure (cm)	10.5, 10 (8–12)	9.4, 8 (8–11)	p = 0.31
Actual CPAP treatment (cm)	10, 10 (8–12)	n/a	n/a
Baseline seizure frequency (/month)	1.8, 1 (1–3)	2.1, 1 (1–3.5)	p = 0.48
Post-CPAP seizure frequency (/month)	1.1, 1 (0–2)	1.8, 1 (0.5–2.5)	p = 0.2
N (%) of patients seizure-free post-CPAP	16 (57%)	3 (23%)	RR = 1.54 (CI = 1.017–2.039); p = 0.05
AEDs, median daily dose (median baseline and treatment levels)	LEV (n = 14) 2,000 (10, 23) PHT (n = 9) 300 (15, 17) OXC (n = 6) 900 (18, 13) LMG (n = 6) 300 (14, 17) VPA (n = 6) 1,500 (67, 54) TPM (n = 4) 150 (9, 8) GBP (n = 2) 1,800 (9, 10) CBZ (n = 2) 800 (10, 11)	LEV (n = 6) 1,500 (12, 22) PHT (n = 5) 300 (18, 14) OXC (n = 5) 900 (9, 18) GBP (n = 3) 1,500 (4, 7) LMG (n = 2) 250 (13, 12) TPM (n = 2) 200 (10, 7) VPA (n = 1) 1,500 (71, 69)	n/a
Follow-up time	12 months (6–25)	10.5 months (6–19)	p = 0.1

CPAP, continuous positive airway pressure; IQR, interquartile range; ESS, Epworth Sleepiness Scale; AHI, Apnea–hypopnea Index; AED, antiepileptic drug; LEV, levetiracetam; PHT, phenytoin; OXC, oxcarbazepine; LMG, lamotrigine; VPA, valproic acid; TPM, topiramate; GBP, gabapentin; CBZ, carbamazepine.

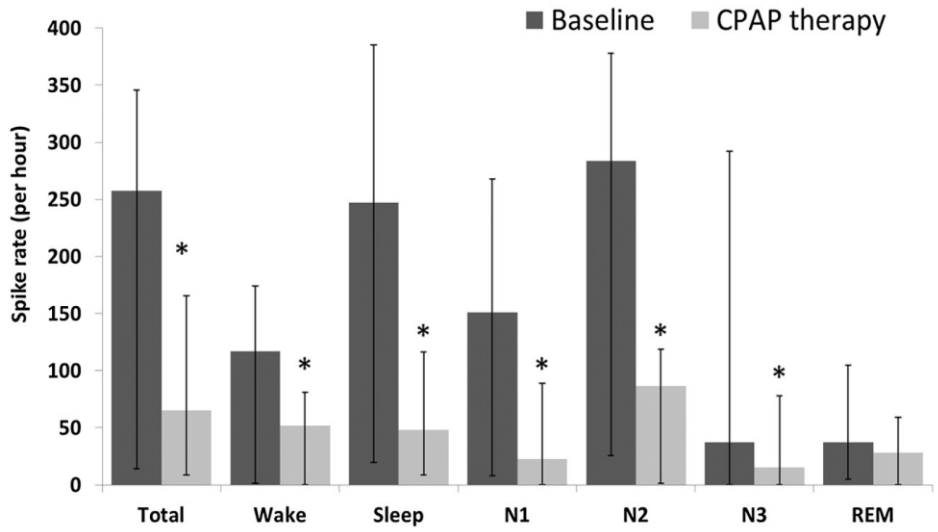


Fig. 1. Median (P25–P75) spike rates at baseline and with therapeutic CPAP therapy. *p < 0.05 (Wilcoxon signed-rank test).

Pornsriniyom D et al. Continuous positive airway pressure therapy for obstructive sleep apnea reduces interictal epileptiform discharges in adults with epilepsy. Epilepsy Behav 2014 Aug;37:171-4

Vendrame M et al. Effect of continuous positive airway pressure treatment on seizure control in patients with obstructive sleep apnea and epilepsy. Epilepsy 2011 Nov;52(11):e168-71

Mental Health Comorbidities

- Prevalence of specific disorders from meta-analyses:
  - Depression (active or within last 12mths) 23%.
  - Anxiety disorders 20%
  - Psychotic disorders 5% (7% in the TLE cohort).

- Why is it important?
  - Severity of depression correlates to lower chance of seizure-freedom
  - Psychiatric disorders are associated with higher risk of adverse effects from ASMs.
  - Psychiatric comorbidities are associated with premature mortality in epilepsy.

- Patients with epilepsy should be screened for depression:
  - At time of diagnosis.
  - Prior to and following ASM initiation or change.
  - At least annually.

TABLE. THE NEUROLOGIC DISORDER DEPRESSION INVENTORY EPILEPSY (NDDIE)

In the past 2 weeks how often have you felt:	Always or often	Some of the time	Rarely	Never
Everything is a struggle	4	3	2	1
Nothing I do is right	4	3	2	1
Feel guilty	4	3	2	1
I'd be better off dead	4	3	2	1
Frustrated	4	3	2	1
Difficulty finding pleasure	4	3	2	1

Antiseizure Medication Level Monitoring

- Generally, routine ASM level monitoring is not routinely indicated.
  - Dose titration is to effect rather than serum level.
  - ASM levels in seizure-free patients may be above or below reference ranges.
  - Others may demonstrate toxicity at levels below the reference range.

- Indications for level monitoring:
  - Obtaining a baseline in a seizure-free patient.
  - Assessing compliance.
  - Guiding titration when changes in levels may be expected (eg pregnancy, adding another medication).

Medication	Blood monitoring suggestions per AMH
Valproate	Check blood count prior to treatment; routine monitoring of aminotransferases does not predict the occurrence of hepatic failure
Carbamazepine	Check blood count before treatment, and periodically thereafter
Phenytoin	Nil
Perampanel	Nil
Levetiracetam	Nil
Topiramate	Serum bicarbonate at baseline and periodically
Zonisamide	Serum bicarbonate at baseline and periodically
Lamotrigine	Nil
Oxcarbazepine	Sodium concentration after two weeks, then each month for three months
Ethosuximide	Nil
Lacosamide	Nil
Cannabidiol	LFTs at baseline, then at one, three, and six months; then periodically thereafter.