Dr Ian Rosemergy

Consultant Neurologist

Capital and Coast DHB

Sunday, August 11, 2019

(Room 3)

8:30 - 9:25 WS #153: Update on Epilepsy

9:35 - 10:30 WS #163: Update on Epilepsy (Repeated)

Epilepsy Update

Ian Rosemergy

Neurologist

Disclosures

- Nil

Plan

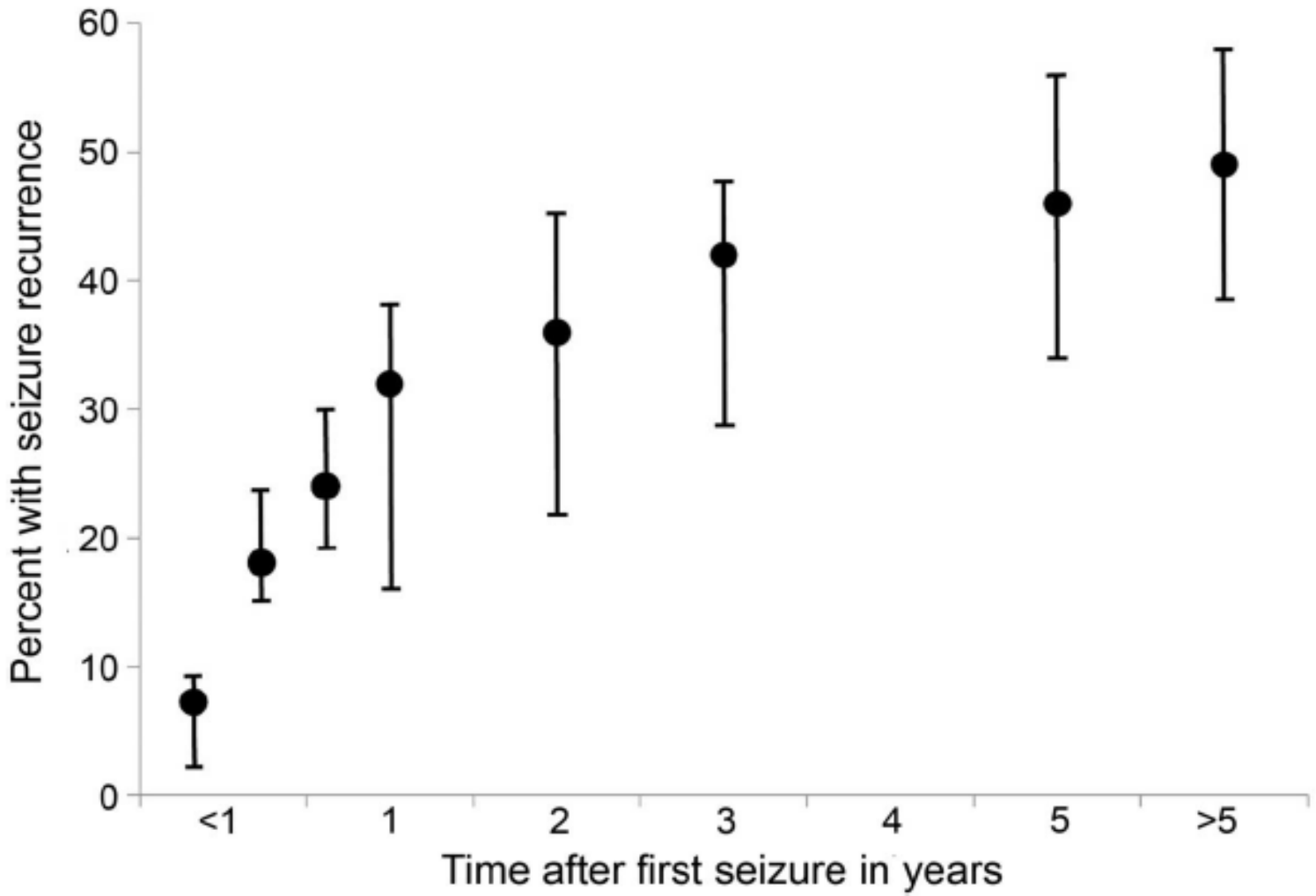
- Epilepsy classification update
- Women with epilepsy
- AED level monitoring
- Other stuff
- Seizure mimics

Diagnosis

- Historically required “2 unprovoked seizures”
- <50% of patients with a single seizure will have a second event
  - “How long do I have to wait to find out?”
- Updated so that epilepsy can be diagnosed* after a single seizure if:
  - There if is an ongoing increased risk of recurrent unprovoked seizure
  - Epileptiform pattern on EEG
  - Structural abnormality on imaging
- Provides guidance on starting management (not having to wait)
  - Challenges to notion of not treating after a single seizure

Fisher et al. A practical clinical definition of epilepsy. Epilepsia, 55(4):475–482, 2014

Figure 1 Percentages of patients with first seizure experiencing a recurrent seizure over time

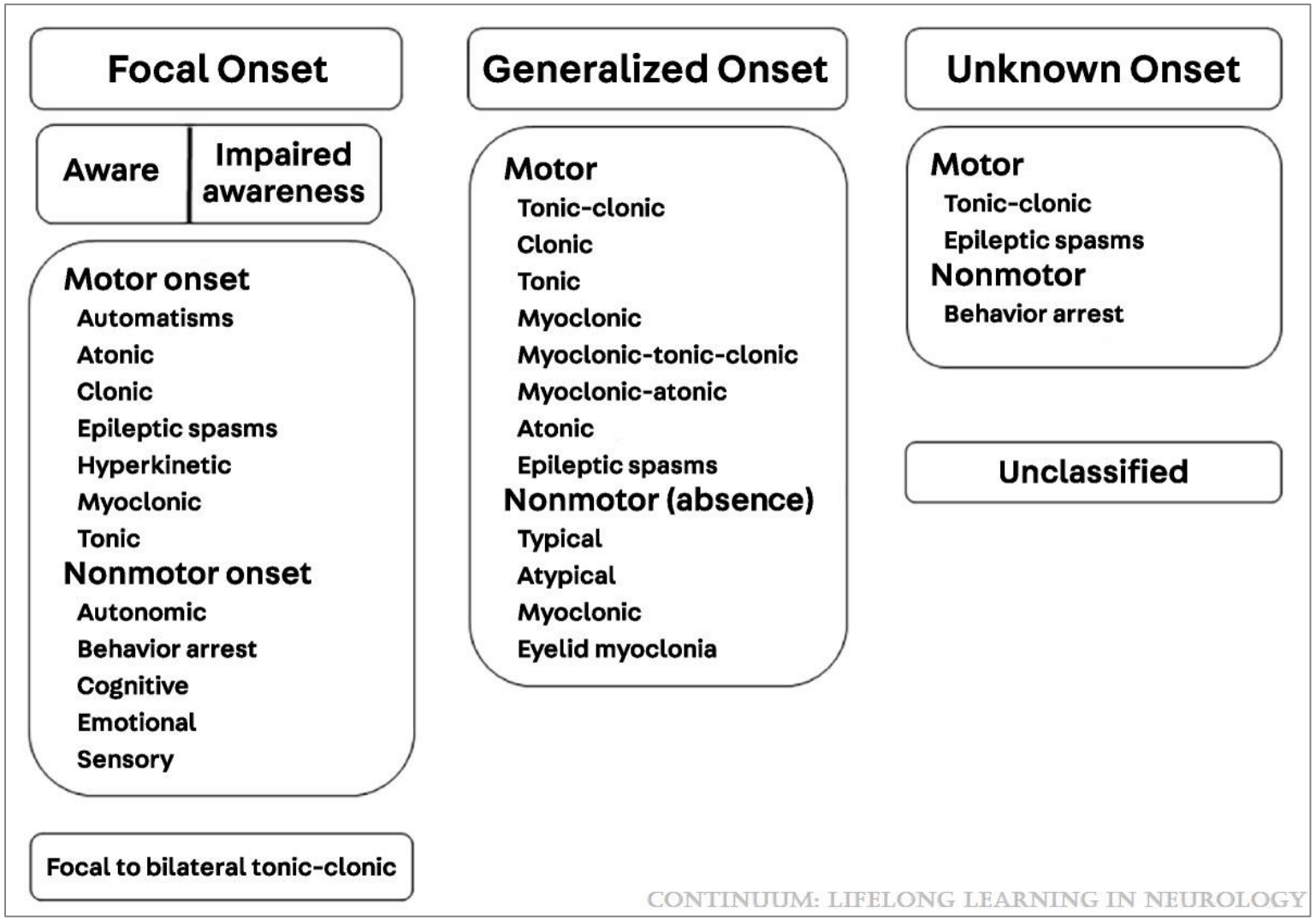


AAN Guideline 2015

Classification

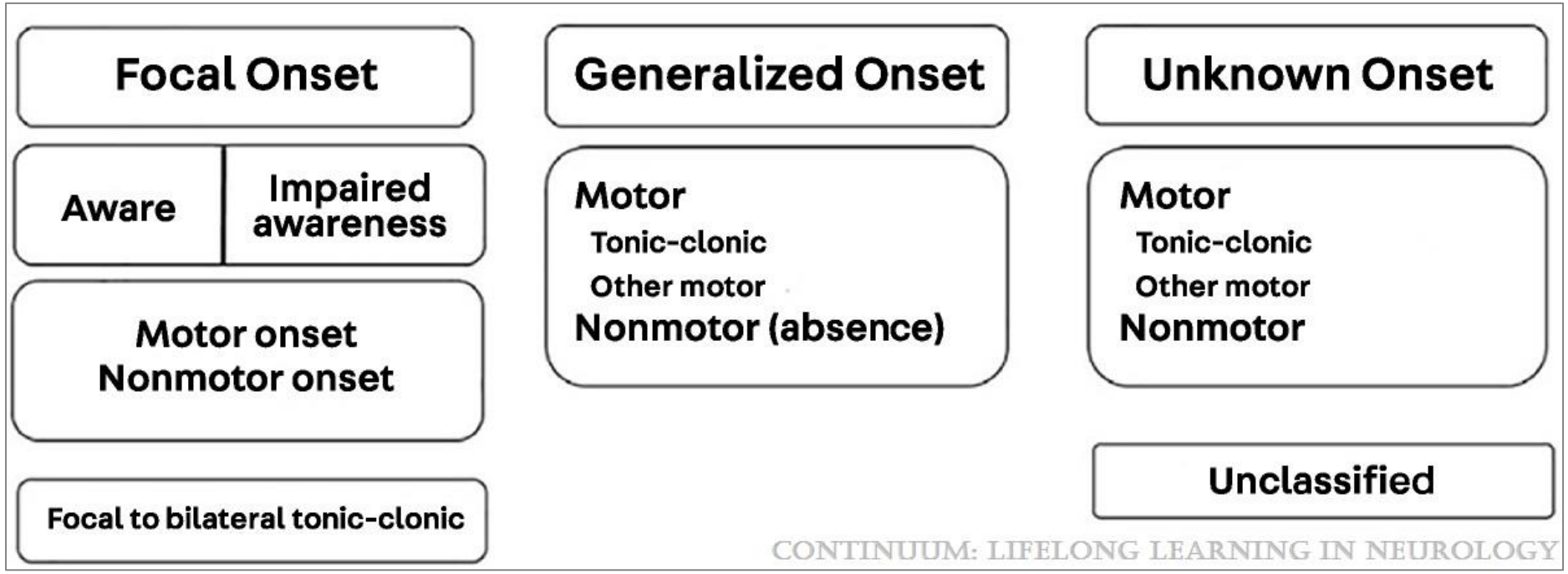
- Updated 2017
- Aim to use less confusing language
  - ”complex partial”
- Emphasizing onset and the distinction between
  - Focal
  - Generalised
  - Uncertain

Epilepsy Overview and Revised Classification of Seizures and Epilepsies



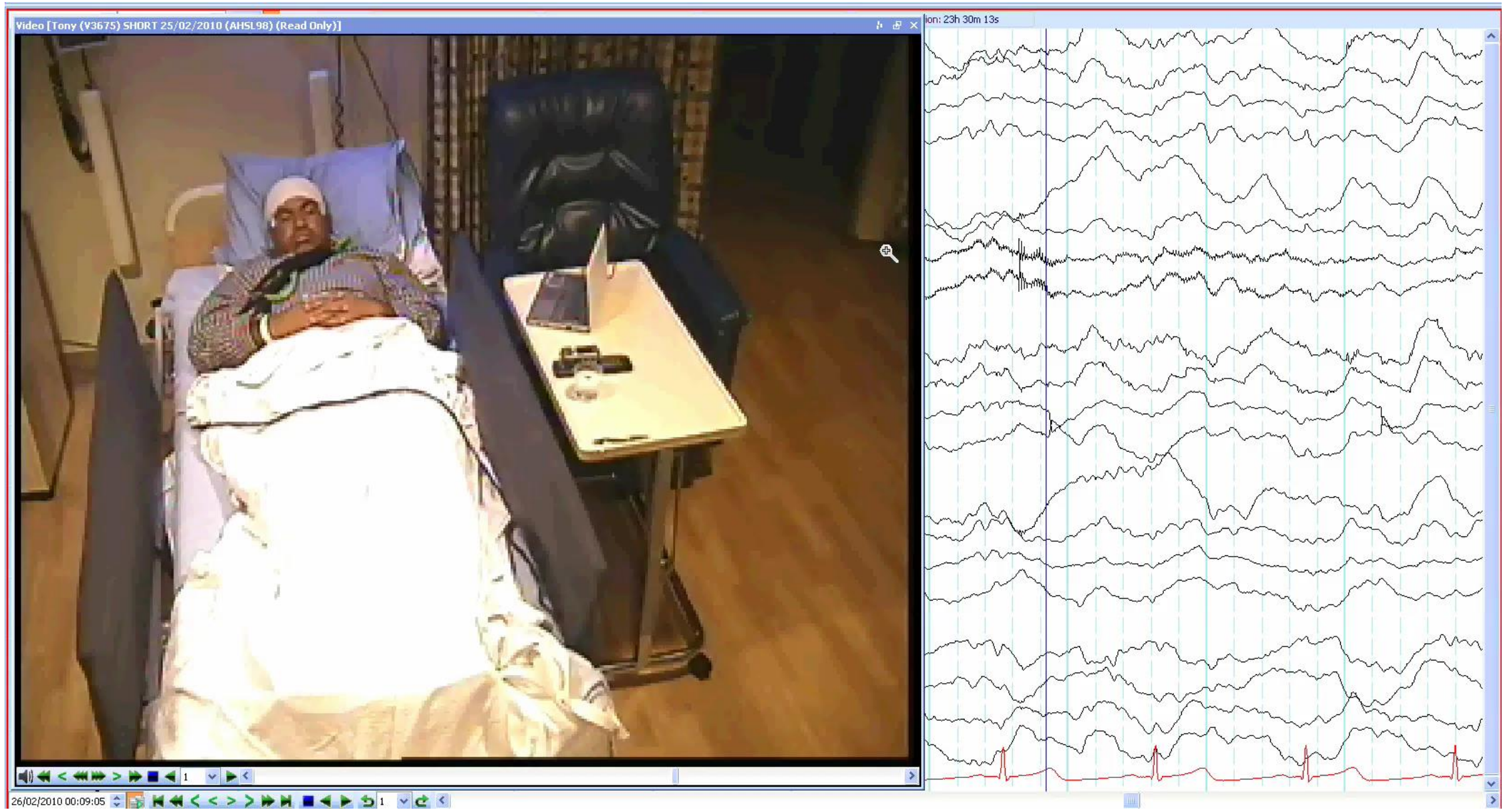
Pack, Alison M. CONTINUUM: Lifelong Learning in Neurology25(2):306-321, April 2019.

Epilepsy Overview and Revised Classification of Seizures and Epilepsies



Why is onset important? → Guides investigation and treatment choices

Pack, Alison M. CONTINUUM: Lifelong Learning in Neurology25(2):306-321, April 2019.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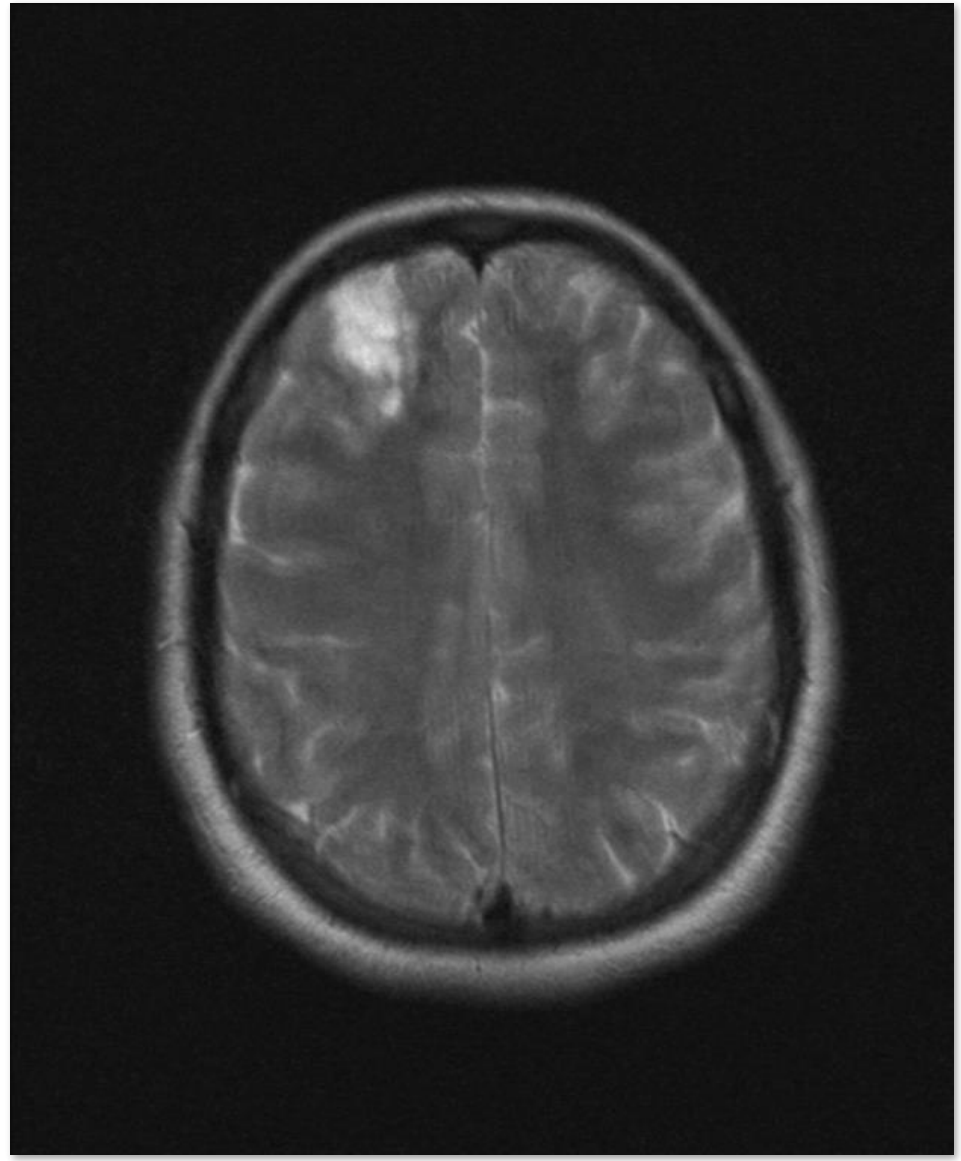

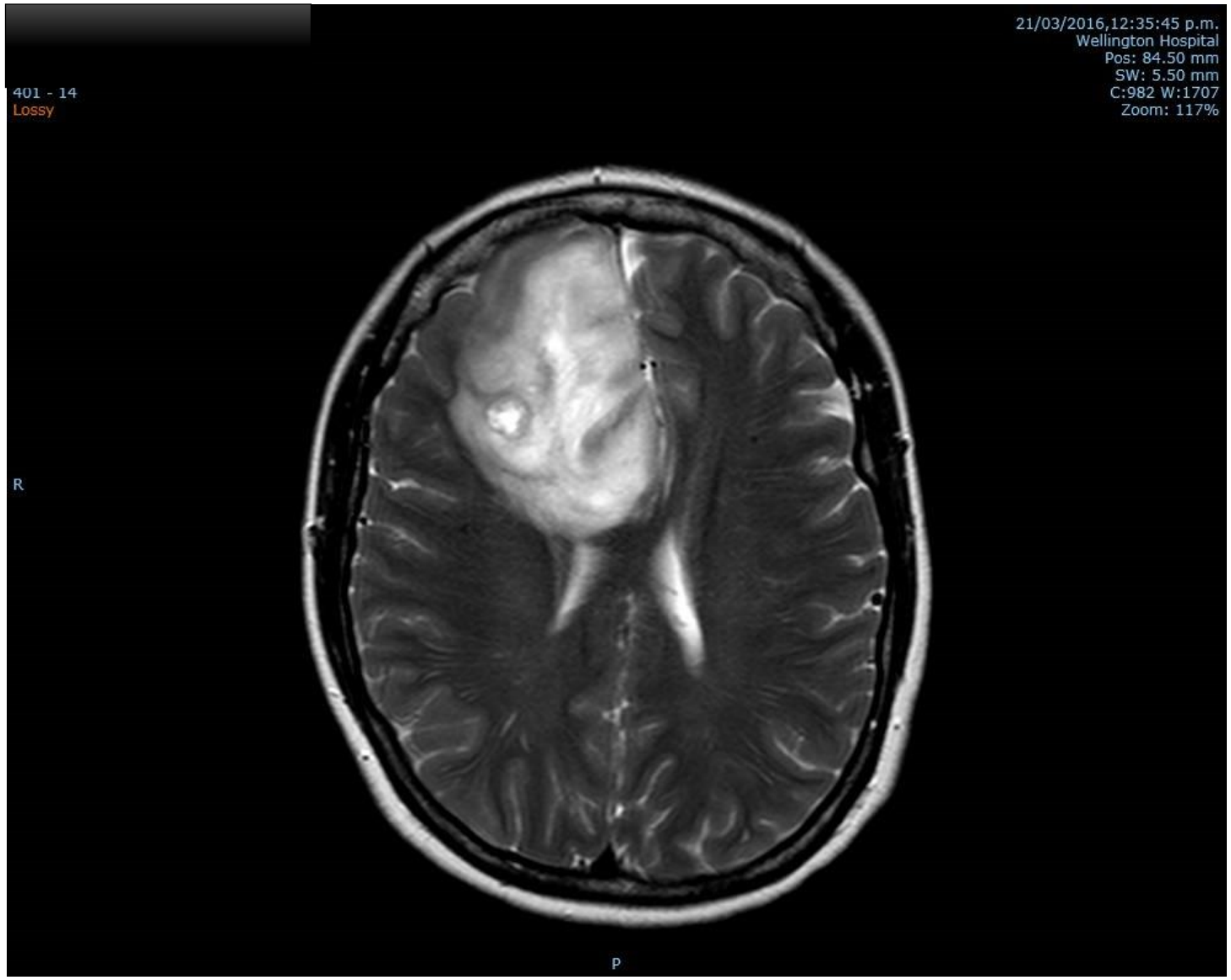
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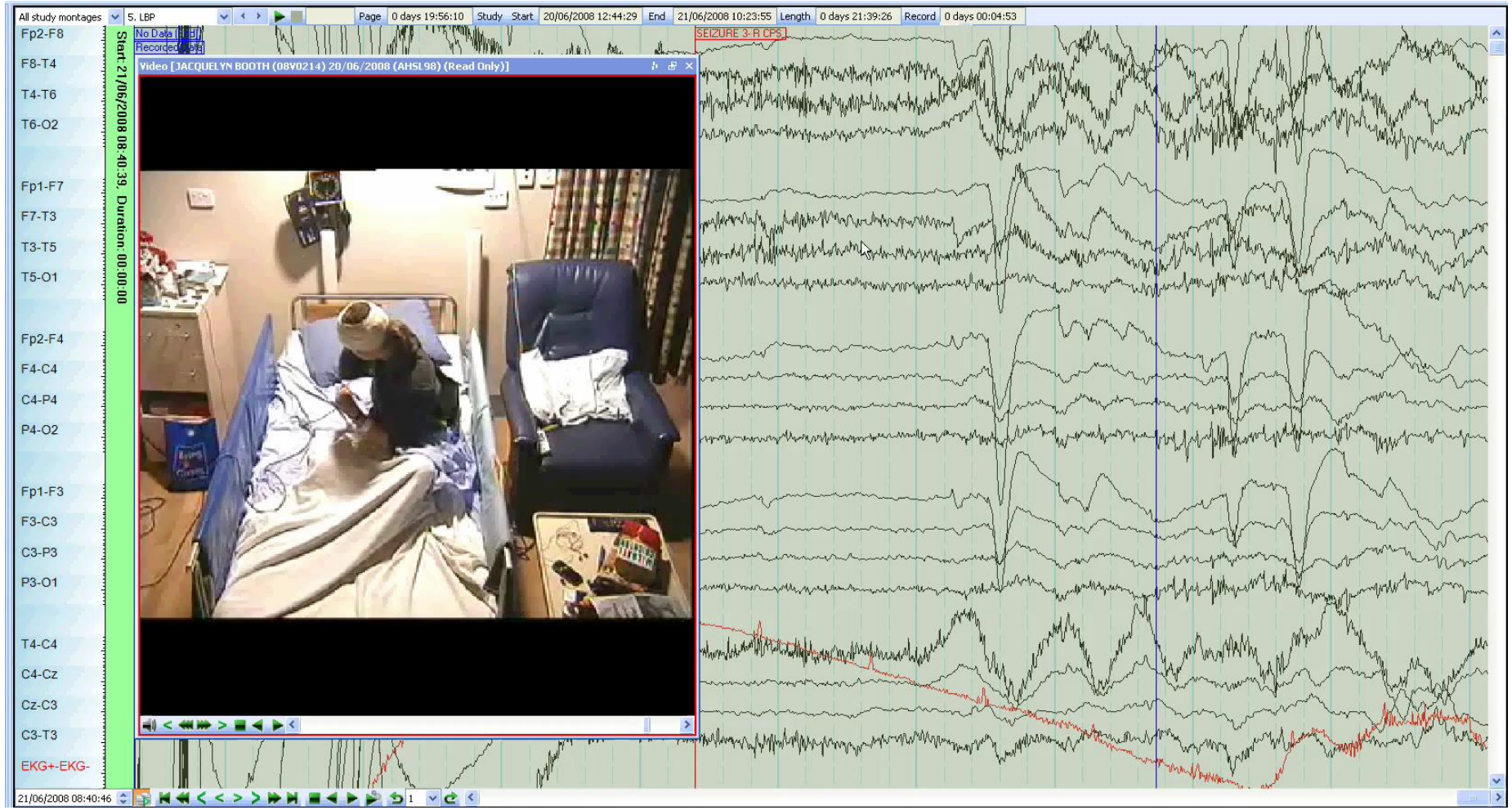
MedLink Neurology • www.medlink.com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P4-O2
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Comments

- Complicated syncope
  - Common seizure mimic
  - Does not predict a future diagnosis of epilepsy
- Ictal bradyarrhythmia (asystole)
  - Secondary to temporal lobe seizure

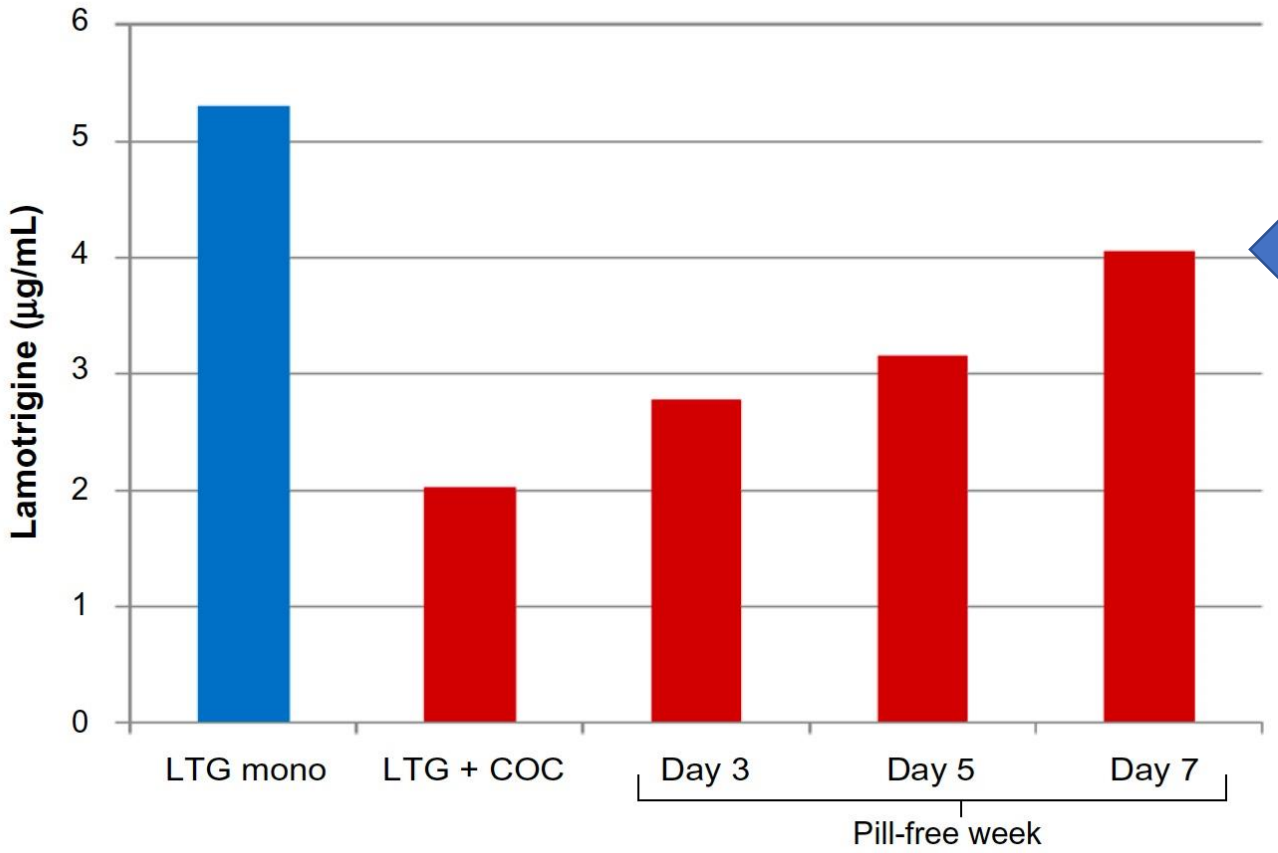
Women with Epilepsy

- Hormonal triggers for various relapsing neurological disorders
  - Migraine, epilepsy, multiple sclerosis
- Hormonal changes influence AED levels
- AED’s can affect hormonal (oestrogen) contraception
- Particular issues in pregnancy

Lamotrigine

- Metabolism enhanced by oestrogen
  - Combined oral contraceptive
  - Pregnancy
- Increased likelihood of breakthrough seizures
- Expect to double dose of LTG in 2nd trimester
  - And reduce after delivery

Lamotrigine and the pill



Risk of transient toxicity

Contraception for women with epilepsy: counselling, choices, and concerns

Antiepileptic Drugs and Contraceptive Failure

Antiepileptic Drugs Causing Contraceptive Failure

- Carbamazepine
- Clobazam
- Eslicarbazepine acetate
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Primidone
- Rufinamide

Antiepileptic Drugs Causing Contraceptive Failure at Higher Doses

- Felbamate
- Perampanel
- Topiramate

Antiepileptic Drugs With No Known Effect on Contraceptive Failure

- Clonazepam
- Ethosuximide
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam[a]
- Retigabine/ezogabine
- Tiagabine
- Valproate[b]
- Vigabatrin
- Zonisamide

[a] Increased testosterone concentrations reported in men on levetiracetam.
[b] Decreased free testosterone concentrations in men and increased androgen concentrations in women taking valproate.

CONTINUUM:408-430, April 2019.

Pregnancy

- Main concerns are
  - Risk of major congenital malformation
  - Risk of cognitive damage
  - Maternal risks during pregnancy
- Maternal risk
  - Some improve, some stay the same, some get worse
  - Concern regarding risk of status epilepticus

MCM risk (Registry data)

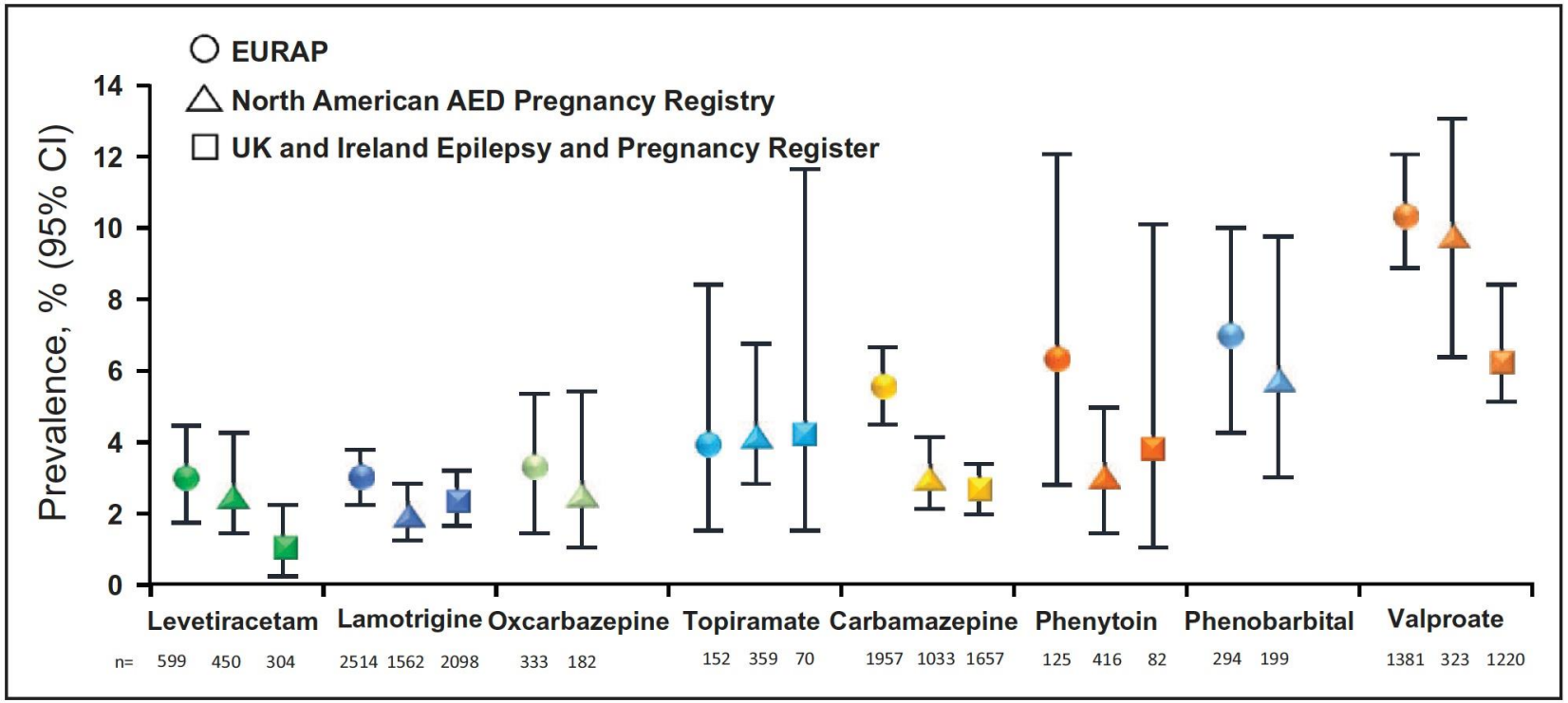


FIGURE 1. Prevalence (%; and 95% confidence intervals, CI) of major congenital malformations with eight different antiepileptic drug monotherapies based on data from three prospective registries [2,4,5▪▪].

Dose dependent effects

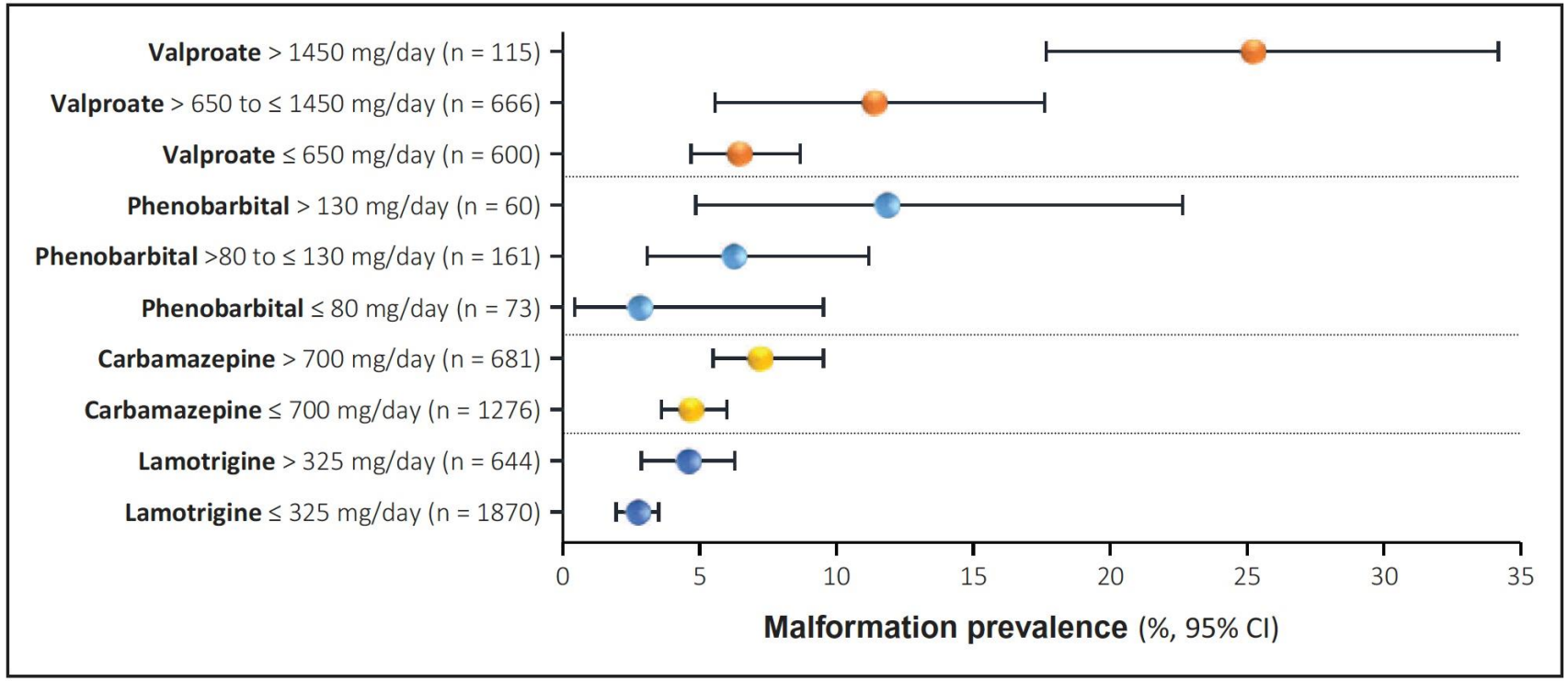


FIGURE 2. Dose dependency of major congenital malformations (%; and 95% confidence intervals) with four antiepileptic drug monotherapies. Based on Data from [5▪▪].

Sodium Valproate and IQ

- "*prenatal exposure to valproate is associated with reduced IQ in children of a magnitude sufficient to affect education and occupational outcomes in later life*"
- Neurodevelopmental Effects of Antiepileptic Drugs (NEAD study)
  - Early pregnancy on monotherapy with CBZ, LTG, PHT and VAL.
  - Primary outcome was child's IQ at 6 years
  - IQ was lower after exposure to valproate (mean score 97; 95% CI, 94–101)
  - The difference only significant for those exposed to doses of >1000 mg/day.
  - Verbal performance was the function most affected by valproate exposure
  - Most differences were observed by 3 years of age

Curr Opin Neurol 2019, 32:246–252

Cognitive function at 3 years of age after foetal exposure to antiepileptic drugs. (Meador et al.)

- Poorer outcomes associated with valproate exposure.
  - adjusted mean IQ 9.7 points lower (95% CI, 4.9–14.6) for children exposed prenatally to more than 800mg/day.
- Although IQ was not reduced in children exposed to less than 800 mg/day, there was evidence of impaired verbal abilities and increased educational needs at the lower doses.

Dose dependent congenital malformation risk and cognitive risk
No safe lower level
Some women still require VAL treatment during pregnancy

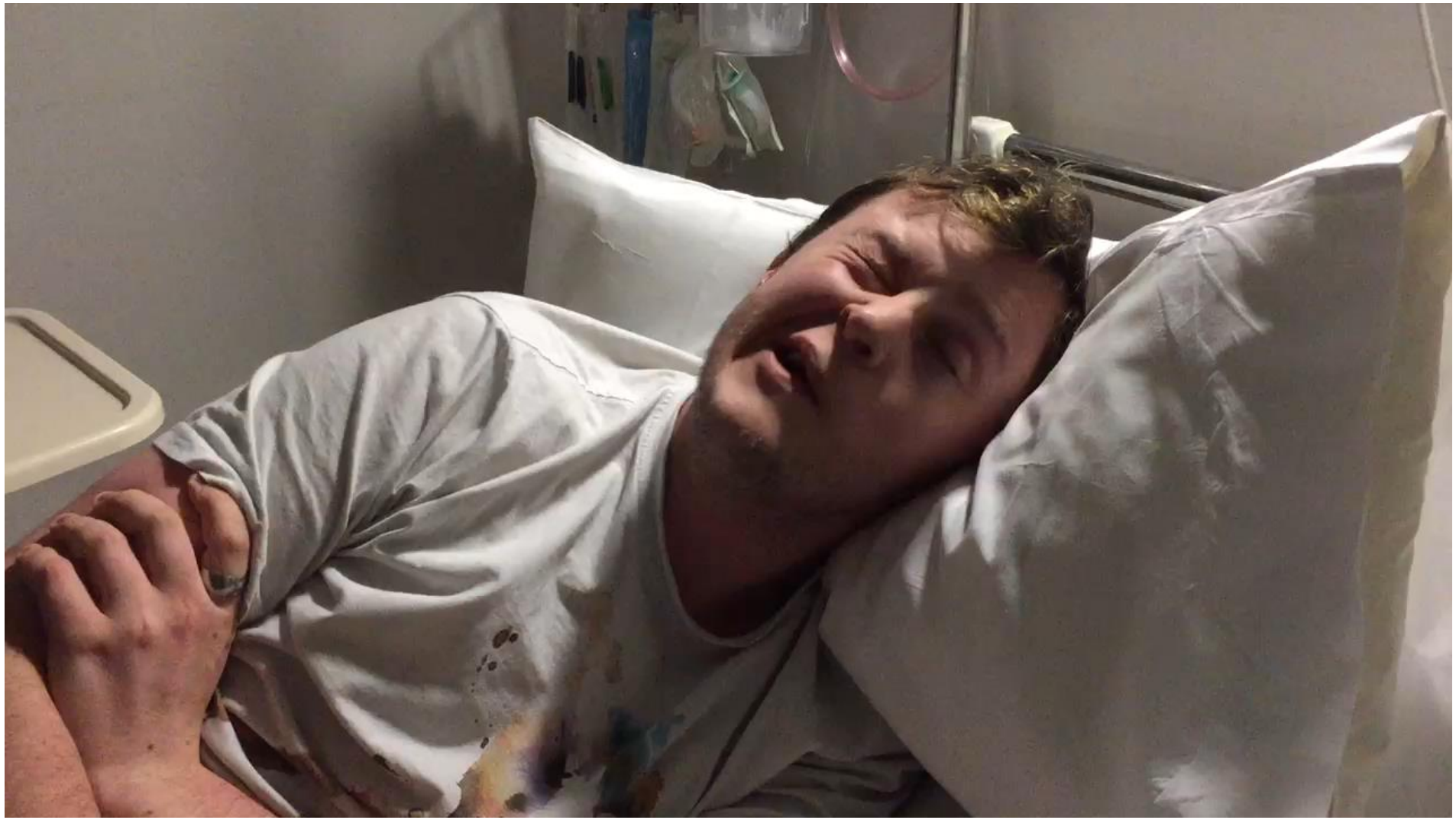
N Engl J Med 2009; 360:1597–1605.

AED Level Monitoring

- No need for routine checking
  - Except lamotrigine in pregnancy
- Once established on dose, can check baseline level (PHT)
- Useful in certain situations
  - Pregnancy
  - Rapidly growing youth
- Can be harmful
  - “therapeutic range” does not necessarily equate to efficacy
  - Unnecessary alteration of AED doses to get in “normal range” can cause toxicity

Case

- 25 year old male
- 5 days intermittent dysphasia
- 4 days of right arm and face twitching
- 1 probable generalised convulsion
- PMHx unremarkable
- No drug or alcohol issues



Tests

Test	Result
CT head	normal
CSF WCC	normal
CSF protein	normal

CSF glucose	**13.3 mmol/L**
Serum glucose	19.1 mmol/L

GAD Ab	**82 (0 – 10)**

Wellness in epilepsy

- Usual focus is on decreasing seizure frequency
- Quality of life for people living with epilepsy is determined by many factors beyond seizure control
- Comprehensive epilepsy care addresses the impact of the diagnosis on other areas of daily living including
  - Mood, AED adverse effects, safety, driving, education, employment, independence
- Addressing wellness and the risks associated with epilepsy is not a “one size fits all”
- Role of specialist epilepsy nurses

Emotional Health - Mood disorders

- Increased risk of depression, anxiety and attention deficit disorder.
  - pooled lifetime prevalence of 23% of depression and 20% for anxiety in people with epilepsy,
  - representing a twofold to threefold increased lifetime risk.
  - Rates higher in people with intractable epilepsy.
- People with epilepsy are twice as likely to report suicidal thoughts and up to 3 times more likely to die of suicide compared to the general population.
- Comment of levetiracetam

Continuum. April 2019, Vol.25, No.2

Relationships

- >1000 people with epilepsy living in the community, an epilepsy diagnosis was reported to:
  - negatively affect relationships with others in 32%,
  - relationship with spouses or partners in 28%,
  - relationship between patients and their children in 25%

Driving

- Driving rated as the number one concern impacting quality of life
- Ability to drive influences ability to work, maintain relationships, and to live independently
- Driving is highly regulated for people with epilepsy compared to other medical conditions that could impact driving
  - Epilepsy may not represent the condition of greatest threat to on-the-road safety.
  - A study of fatal US car crashes found that 0.2% were related to epilepsy as compared to 4% related to cardiovascular disease and 30% related to alcohol.

Continuum. April 2019, Vol.25, No.2

Epilepsy and Driving

Ordinary licence

- Seizure or unexplained blackout
- Can’t drive for one year unless special circumstances apply
- Can apply to LTSA after 6 months seizure free on treatment

Heavy vehicle or passenger endorsement

- Can’t drive ever unless very special circumstances

Please do not leave the person with the impression that this ban may last only until they see a specialist - this creates very unpleasant interactions in outpatients


Sky Dive
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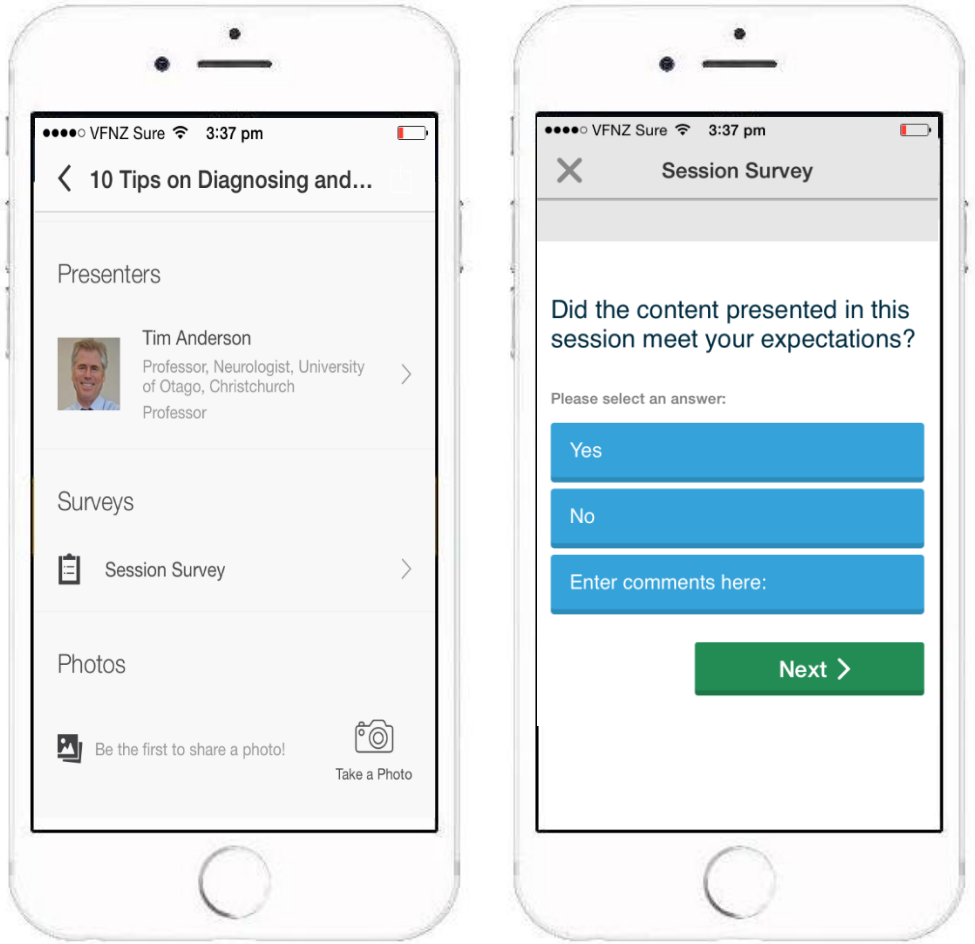
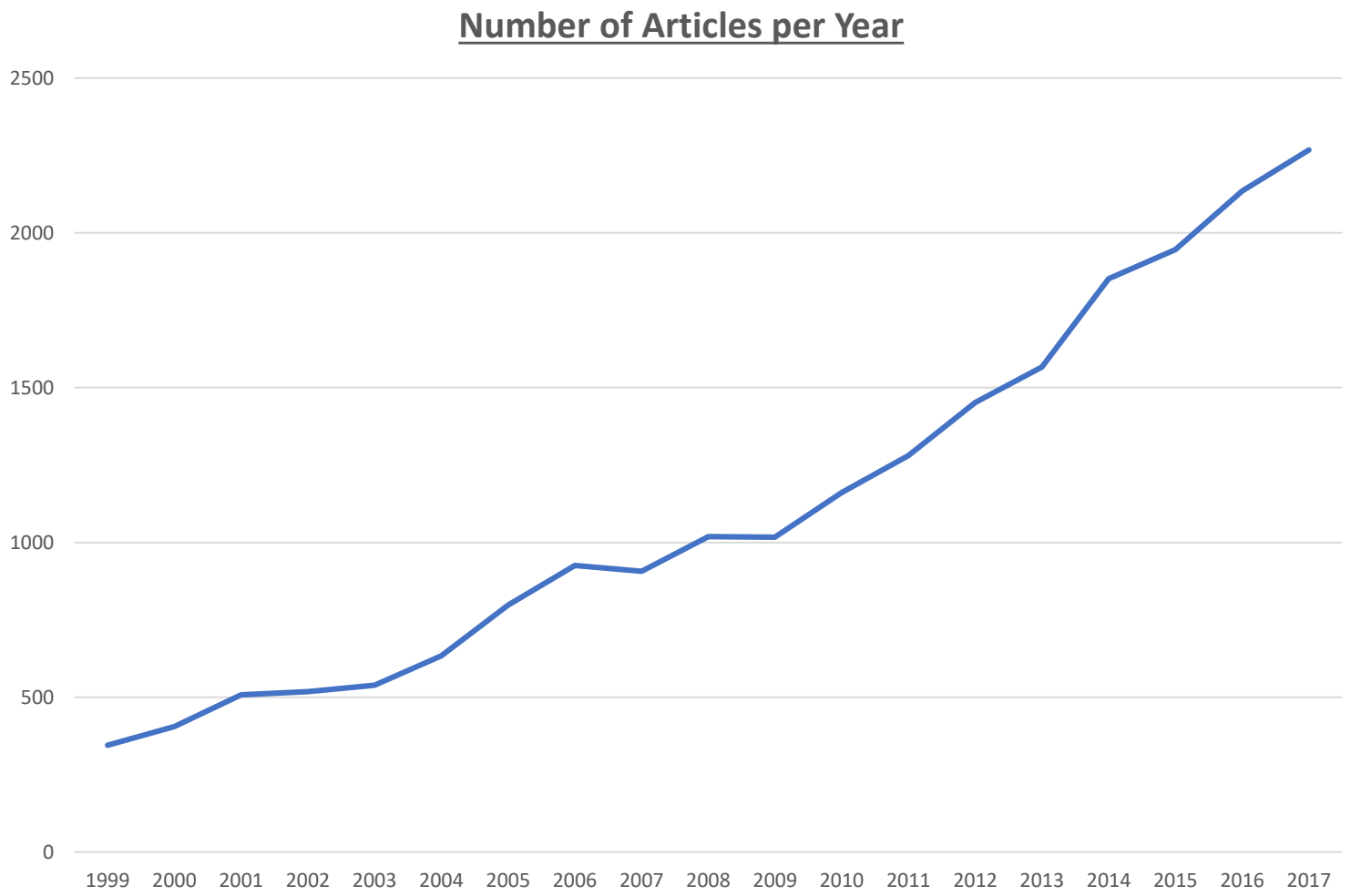
Goes wrong

Don't forget to take the session survey!

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Randomised Controlled Trials

Author	Year	Placebo arm	Treatment arm	
Mechoulam et al	1978	5	4	Partial benefit
Cunha et al	1980	7	8	Partial benefit
Ames et al	1986	6	6	No difference
Trembley et al	1990	10 (cross over)		No change
Devinsky et al	2016			Decreased motor seizures
Devinsky et al	2017	59	61	43% decrease frequency 5% were seizure free
STAR1	2018			

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

- 120 children and young adults with the Dravet syndrome and drug-resistant seizures
- CBD oral solution (20 mg per kg/day) or placebo, in addition to standard antiepileptic treatment.
- Decrease median frequency of convulsive seizures/month
  - **Cannabidiol** group **12.4 to 5.9**
  - **Placebo** group 14.9 to 14.1
- 50% reduction in convulsive- seizure frequency
  - **Cannabidiol** 43%
  - **Placebo** 27% (OR 2.0)
- Seizure freedom 5% with cannabidiol and 0% with placebo (P = 0.08)

NEJM 376;21 nejm.org May 25, 2017

Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence

- Plant based and pharmaceutical cannabinoids to prevent or treat epilepsy and epileptic seizures in participants of any age, with any type of epilepsy or seizure.
  - Variety of epilepsy syndromes but mostly Lennox Gastaut and Dravet's
- Variety of study types
  - Few RCT's
- CBD range of 2.5–20 mg/kg/day across a mean treatment length of 14 weeks.

Stockings E, et al. J Neurol Neurosurg Psychiatry 2018;0:1–13.

Table 4 An overview of the research evidence on cannabis and cannabinoids in the treatment of epilepsy

	50% reduction in seizures n=19 studies (2 RCTs)	Complete seizure freedom n=17 studies (3 RCTs)	Quality of life n=14 studies (2 RCTs)	Withdrawals n=12 studies (4 RCTs)	Adverse events n=16 studies (4 RCTs)
Cannabis sativa/extract	Two studies (no RCT)	No studies	Two studies (no RCT)|	No studies	Two studies (no RCT)
Findings	Positive effect		Positive effect		AEs reported by 13%
Evidence GRADE	⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk		Critical risk		Critical risk
Conclusion	Insufficient evidence		Insufficient evidence		Insufficient evidence
CBD	11 studies (2 RCT)	13 studies (3 RCT)	9 studies (2 RCT)	8 studies (3 RCT)	11 studies (4 RCT)
Findings	Small effect	Positive effect	Positive effect	Patients more likely to withdraw from CBD	AEs reported by 11%–100%
Evidence GRADE	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW
Risk of bias	Low to serious risk	Low to critical risk	Low to critical risk	Low to critical risk	Low to critical risk
Conclusion	Some evidence of effect	Some evidence of effect	Some evidence of effect	Greater likelihood of withdrawal	Mild-to-moderate AEs likely
Oral THC	No studies	No studies	No studies	No studies	One study (no RCT)
Findings					AEs reported by 12.5%
Evidence GRADE					⊕◯◯◯ VERY LOW
Risk of bias					No information
Conclusion					Insufficient evidence
CBD:THC	Five studies (no RCTs)	Three studies (no RCTs)	Two studies (no RCT)	Two studies (no RCT)	Two studies (no RCT)
Findings	Positive effect	Small effect	Positive effect	Withdrawal rate 14%	AEs reported by 42%
Evidence GRADE	⊕⊕◯◯ LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk	Serious to critical risk	Serious risk	Serious risk	Serious to critical risk
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence
Oral cannabis extracts	One study (no RCT)	One study (no RCT)	One study (no RCT)	One study (no RCT)	No studies
Findings	Positive effect	Small effect	Positive effect	Withdrawal rate 15%	
Evidence GRADE	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	
Risk of bias	Critical risk	Serious risk	Serious risk	Serious risk	
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	

Risk of bias=low to high in randomised trials; low to critical risk in non-randomised studies, no information where information not available.

Table 4 An overview of the research evidence on cannabis and cannabinoids in the treatment of epilepsy

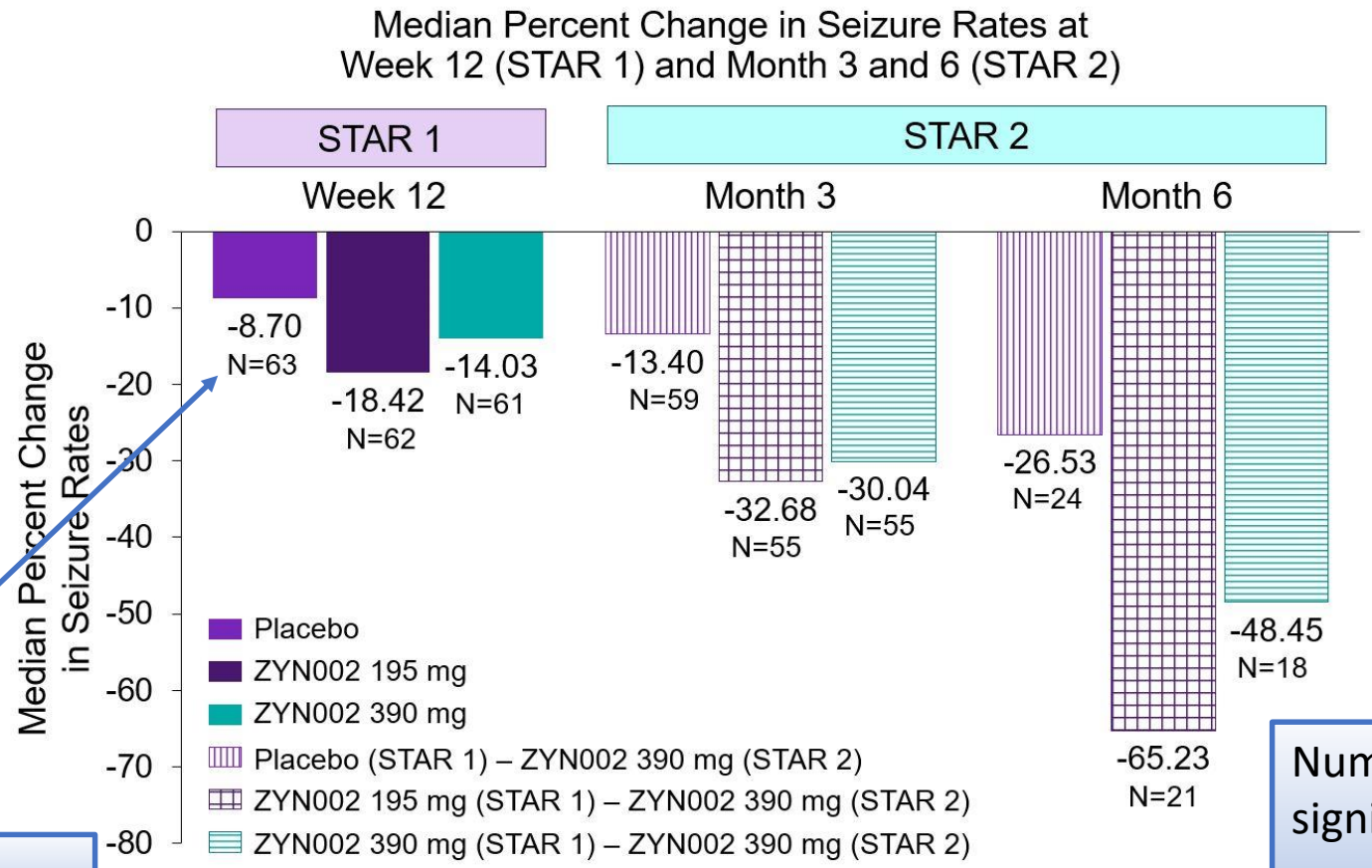
	50% reduction in seizures n=19 studies (2 RCTs)	Complete seizure freedom n=17 studies (3 RCTs)	Quality of life n=14 studies (2 RCTs)	Withdrawals n=12 studies (4 RCTs)	Adverse events n=16 studies (4 RCTs)
Cannabis sativa/extract	Two studies (no RCT)	No studies	Two studies (no RCT)	No studies	Two studies (no RCT)
Findings	Positive effect		Positive effect		AEs reported by 13%
Evidence GRADE	⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk		Critical risk		Critical risk
Conclusion	Insufficient evidence		Insufficient evidence		Insufficient evidence
CBD	11 studies (2 RCT)	13 studies (3 RCT)	9 studies (2 RCT)	8 studies (3 RCT)	11 studies (4 RCT)
Findings	Small effect	Positive effect	Positive effect	Patients more likely to withdraw from CBD	AEs reported by 11%–100%
Evidence GRADE	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW
Risk of bias	Low to serious risk	Low to critical risk	Low to critical risk	Low to critical risk	Low to critical risk
Conclusion	Some evidence of effect	Some evidence of effect	Some evidence of effect	Greater likelihood of withdrawal	Mild-to-moderate AEs likely

STAR1 – topical CDB gel

Product	N=	Median reduction in sz
195 mg daily	63	18.4%
390 mg daily	62	14%
Placebo	63	8.7%

Results not statistically significant

Results



STAR 2 results based on data collected through mid-August 2017 and in patients who reported seizure frequency data during the respective time period.

High rate of seizure reduction in placebo group

Numerical but not statistically significant reduction in seizures

STAR2 “clinically meaningful” reduction in seizures

Paediatric study underway

- Prof Mike Barnes (UK based neurologist)
  - Radio NZ interview (16 July 2019)
- Interviewer:
  - “is there a precedent for not waiting for the clinical trials ……. for learning as we go?”
- Prof Barnes :
  - ” … in epilepsy … we have to accept a slightly different view of the evidence at the moment and accept case studies and a whole range of observational trials and not be too obsessed with the standard medical randomized placebo controlled studies.”

Nine to Noon, Radio NZ, 16 July 2019

Conclusion

- I disagree
- Epilepsy is a significant disorder
- Cannabis products are held to a different standard
- Need to be honest about where cannabis products are placed in treatment regimen
- No RCT data to support CBD, marijuana, cannabis for the treatment of adult epilepsies
- Some RCT evidence in specific paediatric epilepsy syndromes