First seizure…

Dr. Eduard Bercovici

1) Epileptologist / Adult Epilepsy Diet Clinic– UHN - Toronto Western Hospital
2) Neurologist / Epileptologist – Trillium Health Partners
3) Lecturer, Faculty of Medicine, University of Toronto

Disclosure

- Received grants / research support from Eisai and UCB
- Received honoraria from Eisai and UCB

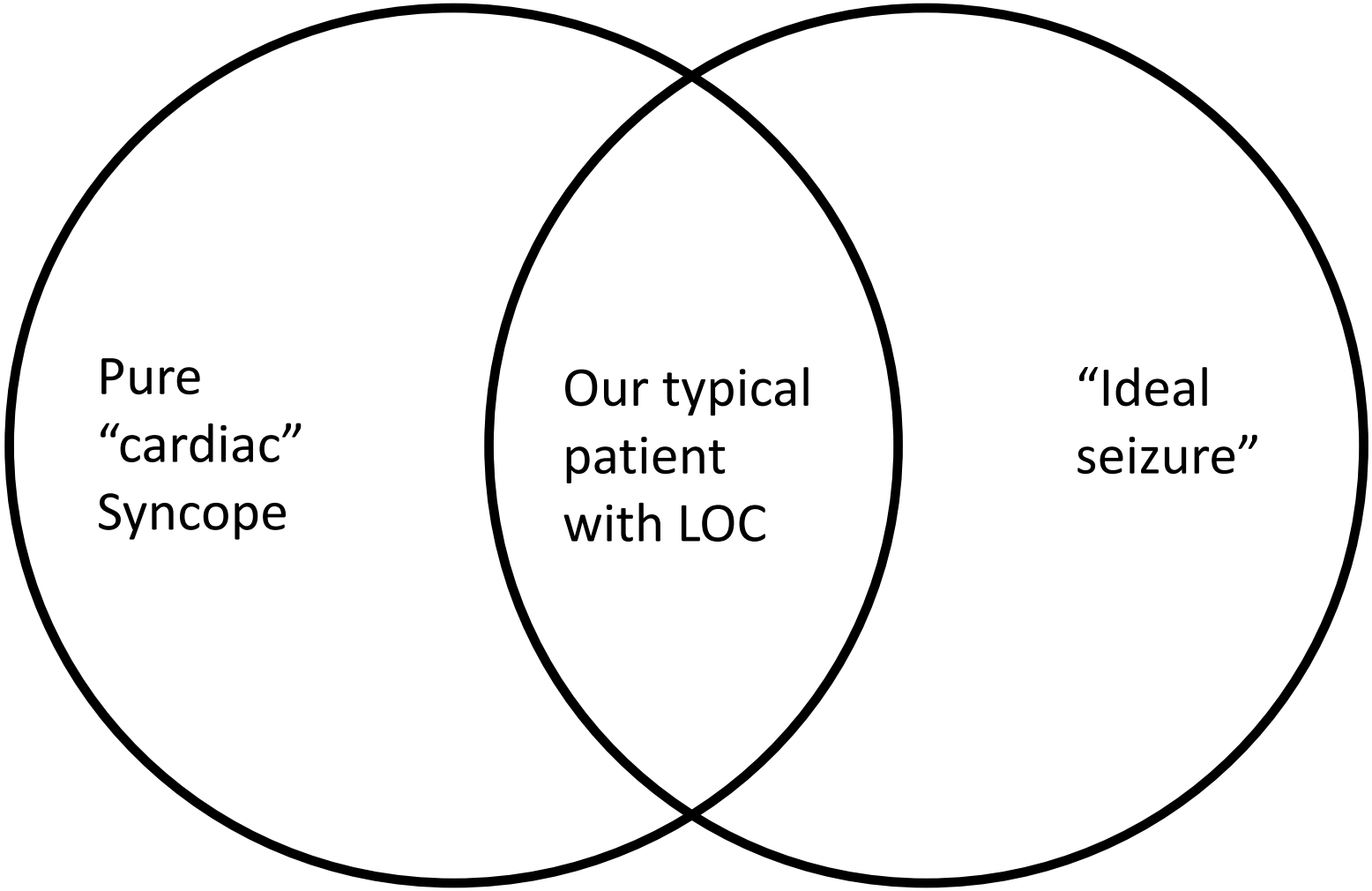
Objective

- Review seizures and other differential diagnosis
- Discuss AAN guidelines on investigations and management in adults presenting with first unprovoked seizure
- Highlight evidence based studies on AED use in adults with seizures.

Differential Diagnosis (top)

- Syncope (all causes)
- TIA
- Migraine
- Transient global amnesia
- Sleep disorder
- Movement disorder
- Psychiatric (anxiety, panic etc)
- Psychogenic non epileptic events – ex conversion, dissociative etc.

A Venn diagram example

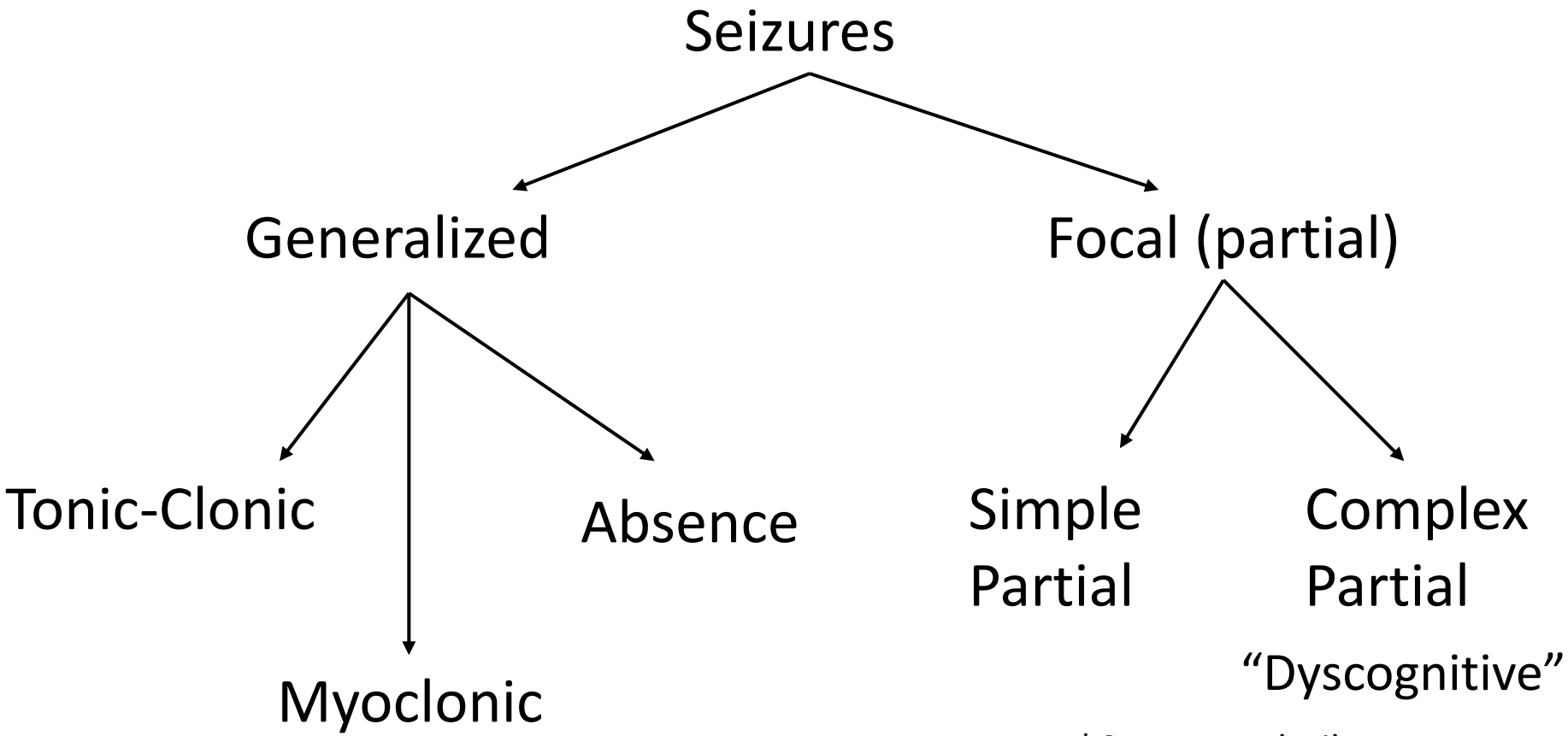


Definitions

- Seizure – sudden discharge of neuronal activity in synchrony producing electrical or clinical manifestations

- Epilepsy – chronic disease marked by recurrent unprovoked seizures*
  - Can be defined based on >2 seizures or > 1 seizure with > 60% risk of having subsequent seizure

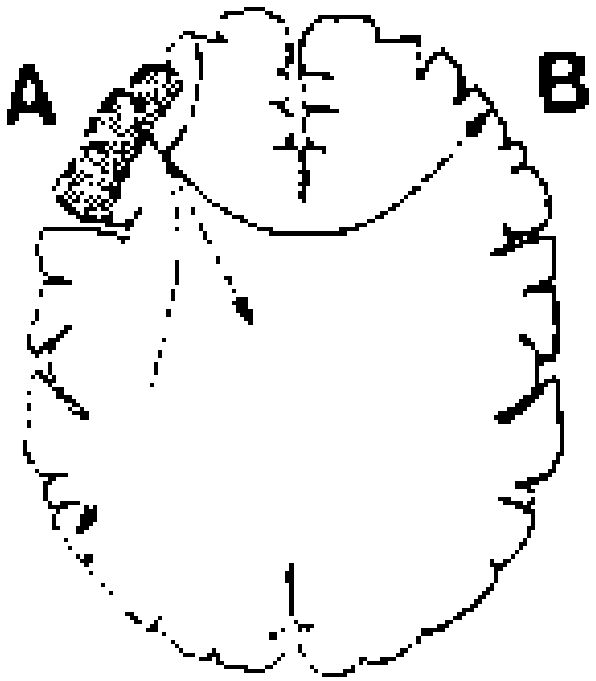
Classification of Seizures



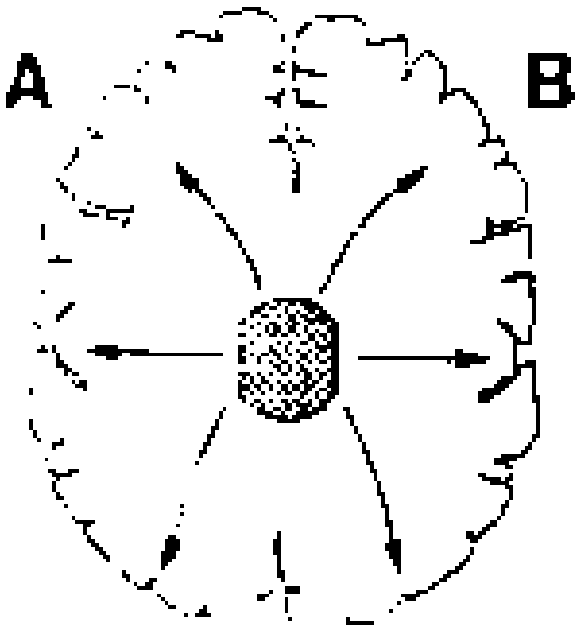
*Can secondarily generalize

ILAE 2010

Focal Seizure



Primary Generalized Seizure



Seizure types - typical

- Stereotyped semiology, last approx 1-2 minutes
- Focal
  - Simple partial – aura, motor, sensory – preserved awareness
  - Complex partial “dyscognitive”– loss of awareness, automatism, unresponsive, “glossy eye”
- Generalized
  - Can be preceded by focal seizure
  - Stiffening (tonic) +/- clonic
- Ictal tongue biting / incontinence
- Post ictal sleepiness / confusion

Seizures – atypical features

- Seizure semiology – bizarre behaviours, hypermotor, hallucinations, spitting/laughing
- Jacksonian march
- Todd's paresis – "stroke like" post seizure
- Status epilepticus – seizure > 5-15 minutes
  - Generalized
  - Focal - epilepsia partialis continua (EPC) w/ awareness or complex partial status

Seizure as a symptom…

- Structural
  - Tumor, Ischemia / hemorrhage
- Drug induced toxic/metabolic encephalopathy
  - Illicit drug use
  - Alcohol / Benzo withdrawal
  - Rarely other medication
- Metabolic – hypo/ hyperglycemia, electrolyte (Na, Mg, Ca, Phosphate)
- Infection: Abscess; meningoencephalitis

Avila & Graber, 2010

Seizures and Epilepsy

- Seizures are common – incidence approximately 8% of single seizure
  - Cause variable
- Epilepsy defined as >2 unprovoked seizures
  - Affects approximately 1% of population
  - 47% can become seizure free on single antiepileptic (AED); 14% after 2nd or 3rd , 3% after taking >2 AED
- Refractory – failure of properly chosen 2 AEDs
- Approx 1/3 of patients diagnosed with epilepsy will be refractory to medical treatment

Potschka and Brodie 2012, Wiebe and Jette 2012

AAN Guideline for Evaluating first Seizure

1. EEG

Good evidence supports

- An EEG should be considered as part of the routine neurodiagnostic evaluation of the adult with an apparent unprovoked first seizure **(Level B).***
- An EEG should be considered as part of the routine neurodiagnostic evaluation of the adult with an apparent unprovoked first seizure because it has value in determining the risk for seizure recurrence **(Level B).***

2. Imaging

Good evidence supports

- Brain imaging using CT or MRI should be considered as part of the routine neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure **(Level B).***

3. Lab

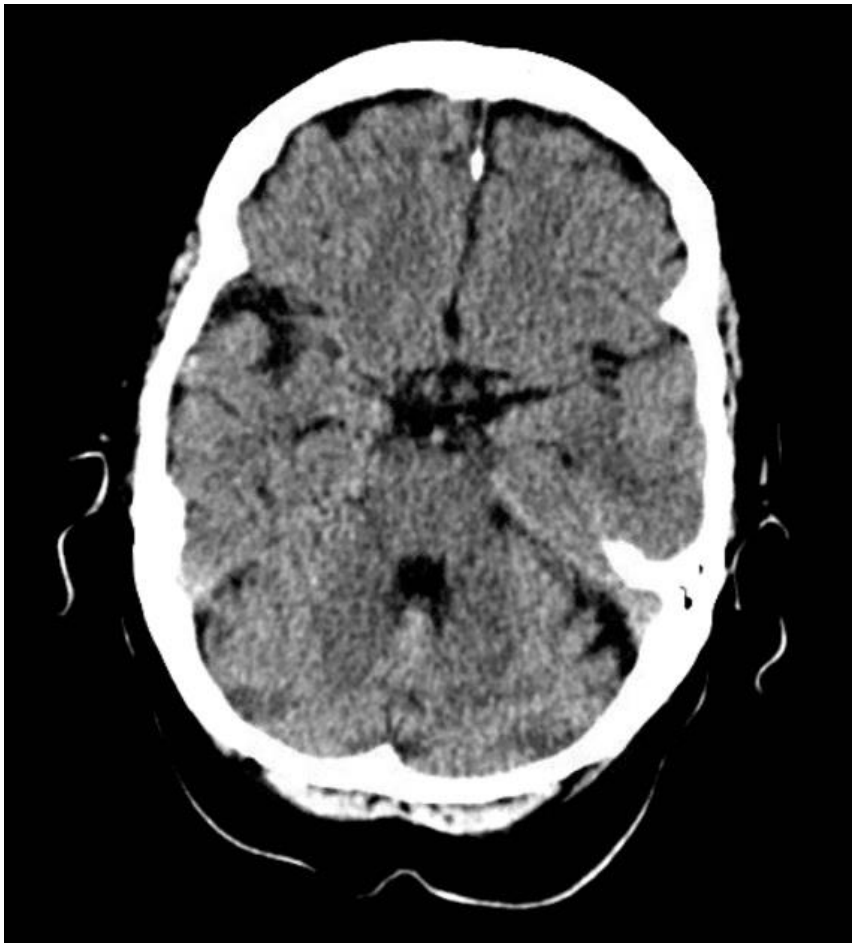
Inadequate evidence to support or refute

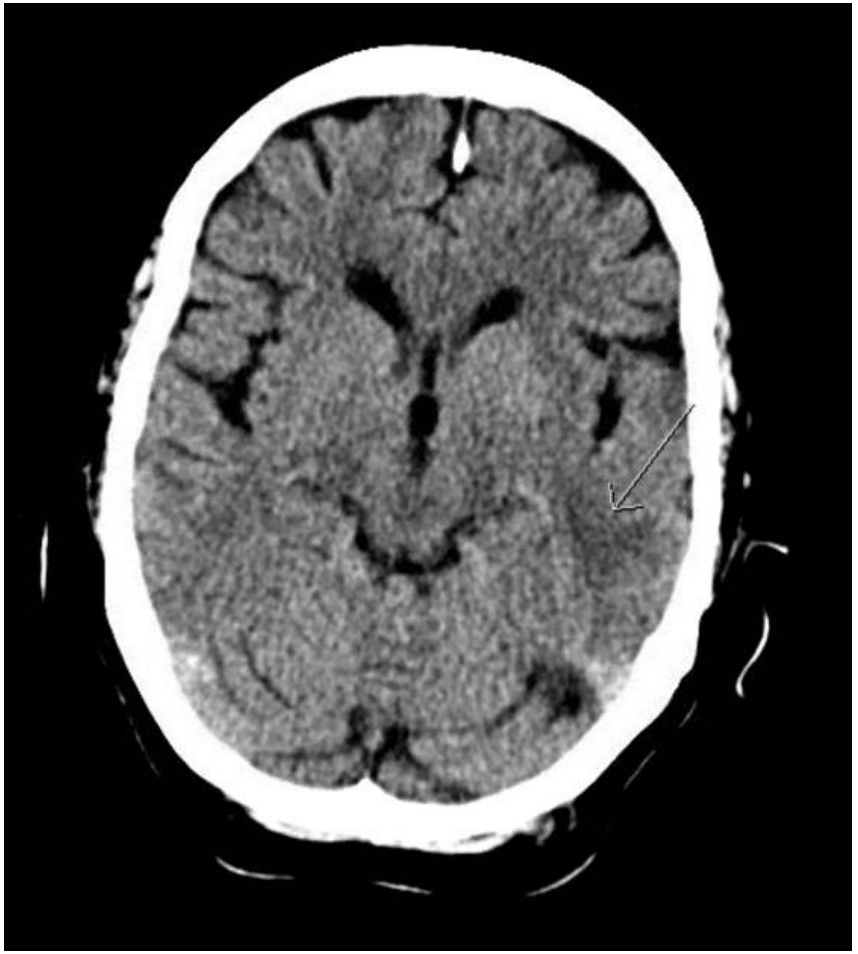
- In the adult initially presenting with an apparent unprovoked first seizure, blood glucose, blood counts, and electrolyte panels (particularly sodium) may be helpful in specific clinical circumstances, but there are insufficient data to support or refute routine recommendation of any of these laboratory tests **(Level U).***

Krumholz et al., Neurology 2007

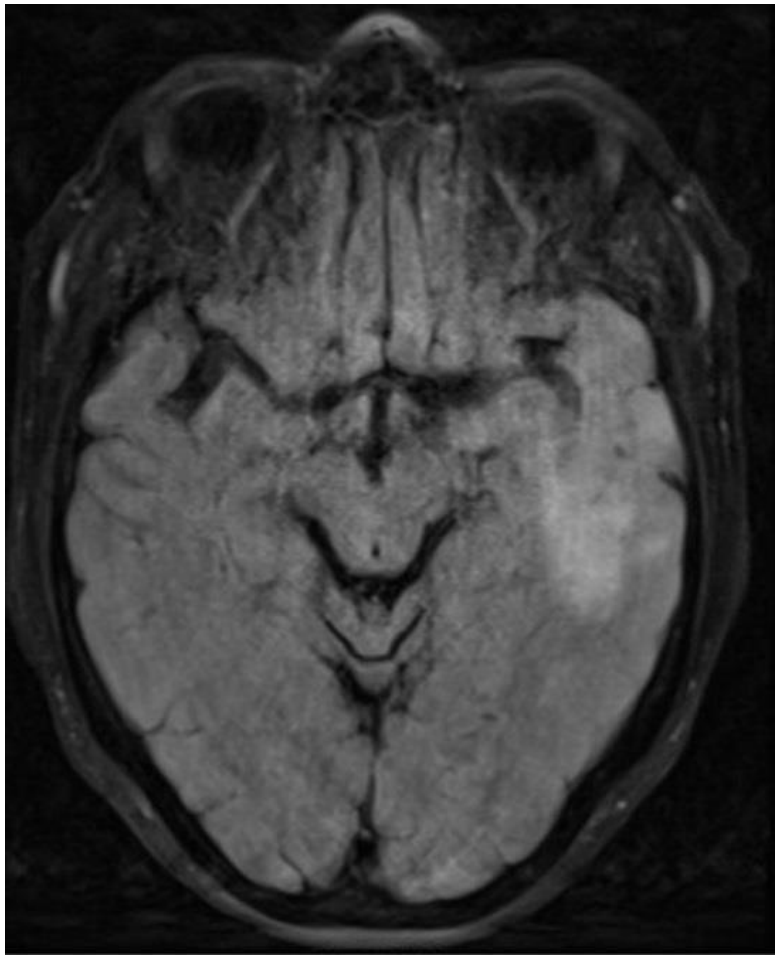
What’s better a CT or MRI?

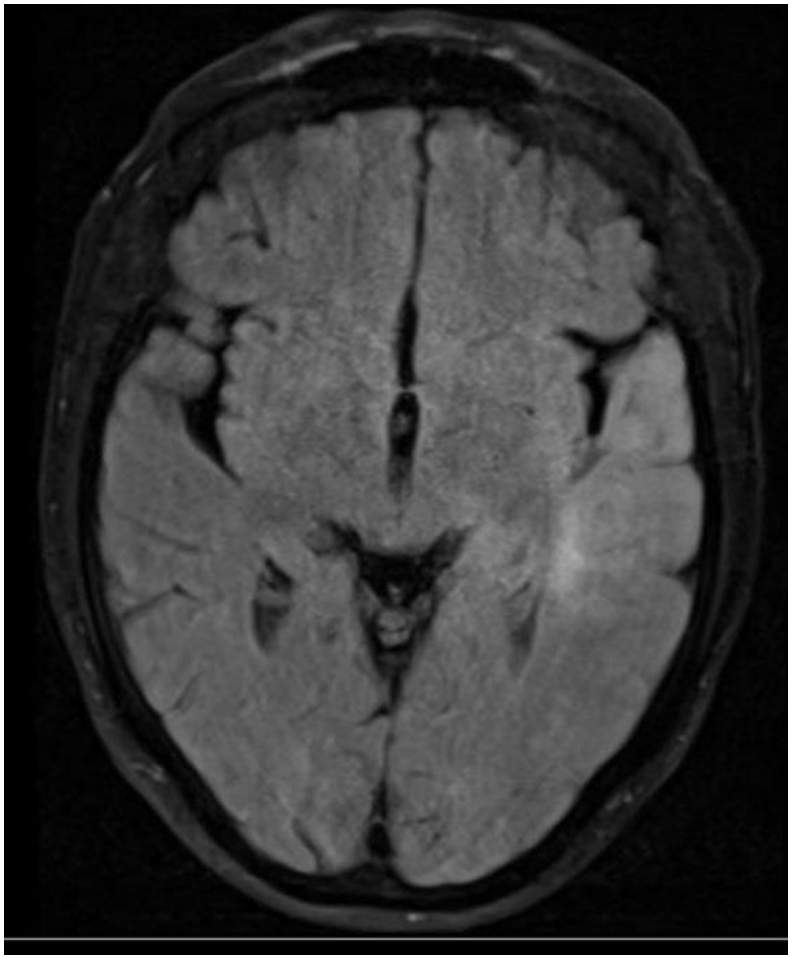
CT initially reported as normal





Urgent MRI requested…





Pathology…

- Part of lesion was Grade I glioma
- However, second biopsy sample was Grade III anaplastic astrocytoma

Does a normal EEG “rule out” epilepsy or seizures?

EEG

- A test that assesses brain electrical activity at that point in time over ~ 30 minutes
- Should be used as a risk stratifying tool and supportive
- Not commonly “diagnostic” – unless patterns (ex. infantile spasms) or ictal events are captured
  - Assesses for interictal epileptiform discharges (IED)
- Highest yield within 24 hours (51 vs 34%) to capture IED
- Range of IED is 12-27%
- Sleep deprivation increases yield to 23-50%

- Yield seems to be higher in patients < 16 yo (59 vs 39%)

Pohlmann-Eden and Newton, Epilepsia 2008

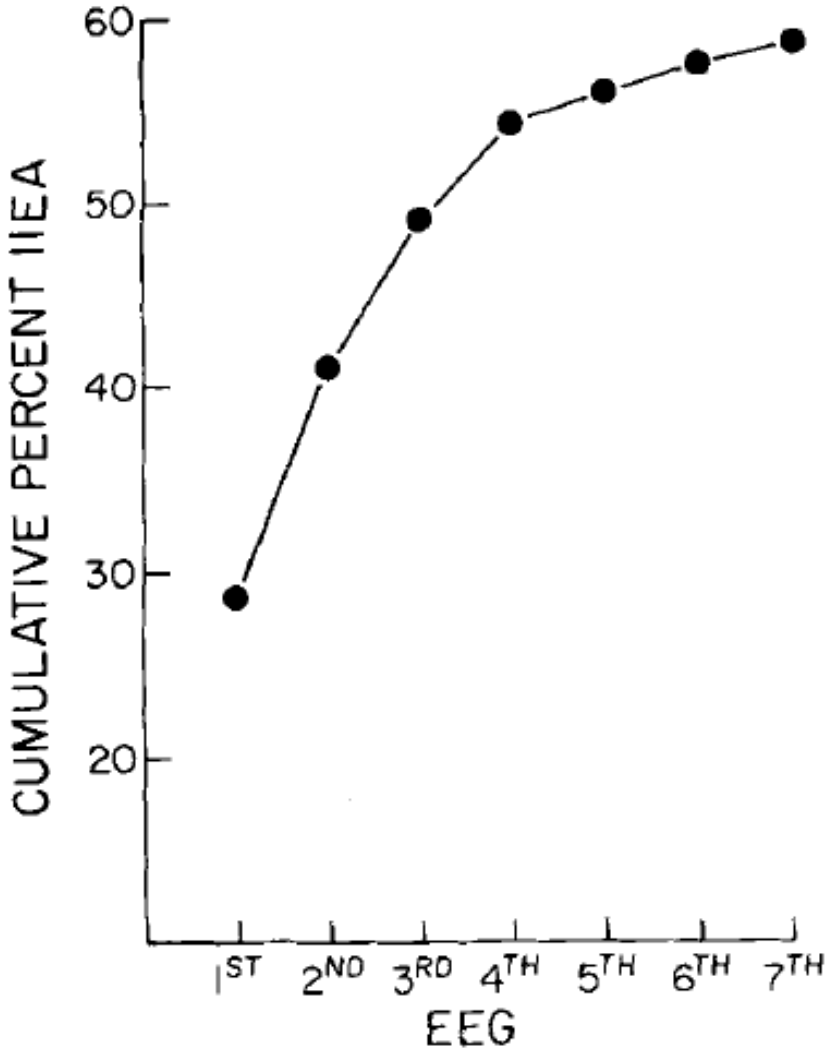


FIG. 2. Operational curve for new interictal epileptiform activity (IIEA) detection by serial EEGs. Points are based on percentage of yield of new IIEA for each EEG, applied to the group undergoing EEG (corrected for patient attrition). A full explanation is given in the text.

Salinsky et al.,
Epilepsia 1987

AAN Guideline

- What is the risk of recurrence?

Strong Evidence

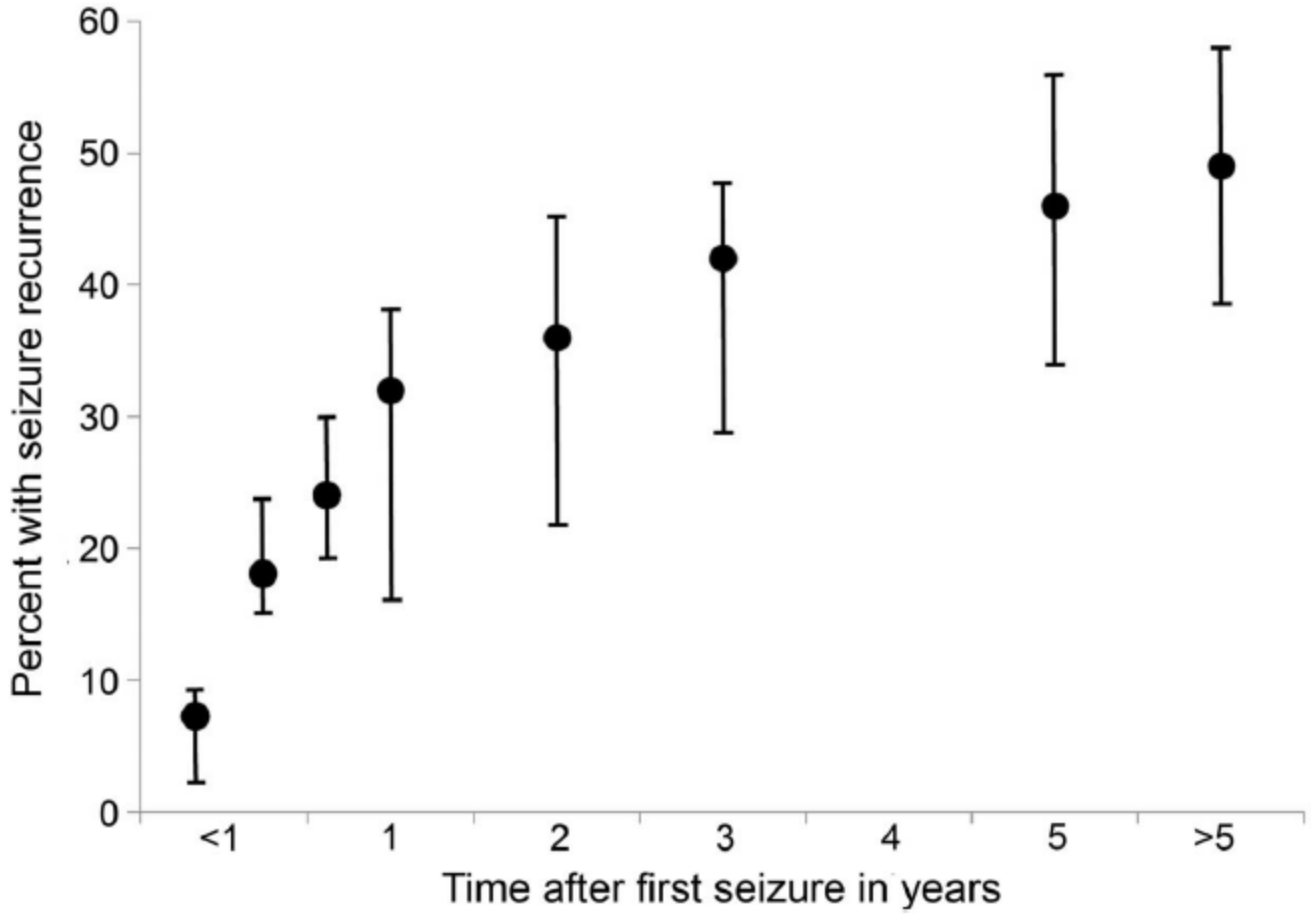
Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first two years after a first seizure (21 percent to 45 percent) (**Level A**).
Clinicians should also advise such patients that clinical factors associated with an increased risk for seizure recurrence include a prior brain insult such as a stroke or trauma (**Level A**) and an EEG with epileptiform abnormalities (**Level A**).

Moderate Evidence

Clinicians should also advise such patients that clinical factors associated with an increased risk for seizure recurrence include a significant brain-imaging abnormality (**Level B**) and a nocturnal seizure (**Level B**).

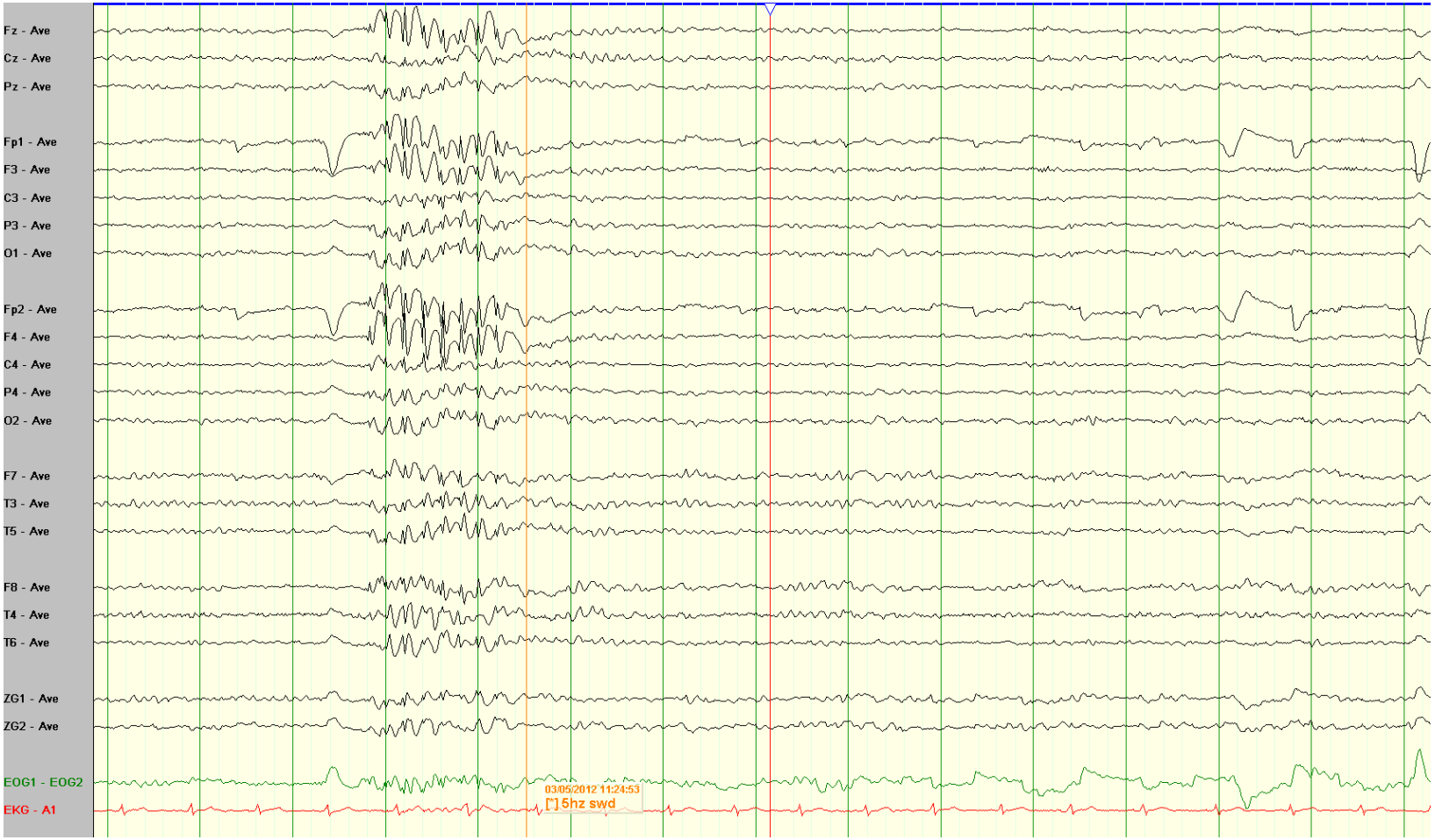
Krumholz et al., Neurology 2015

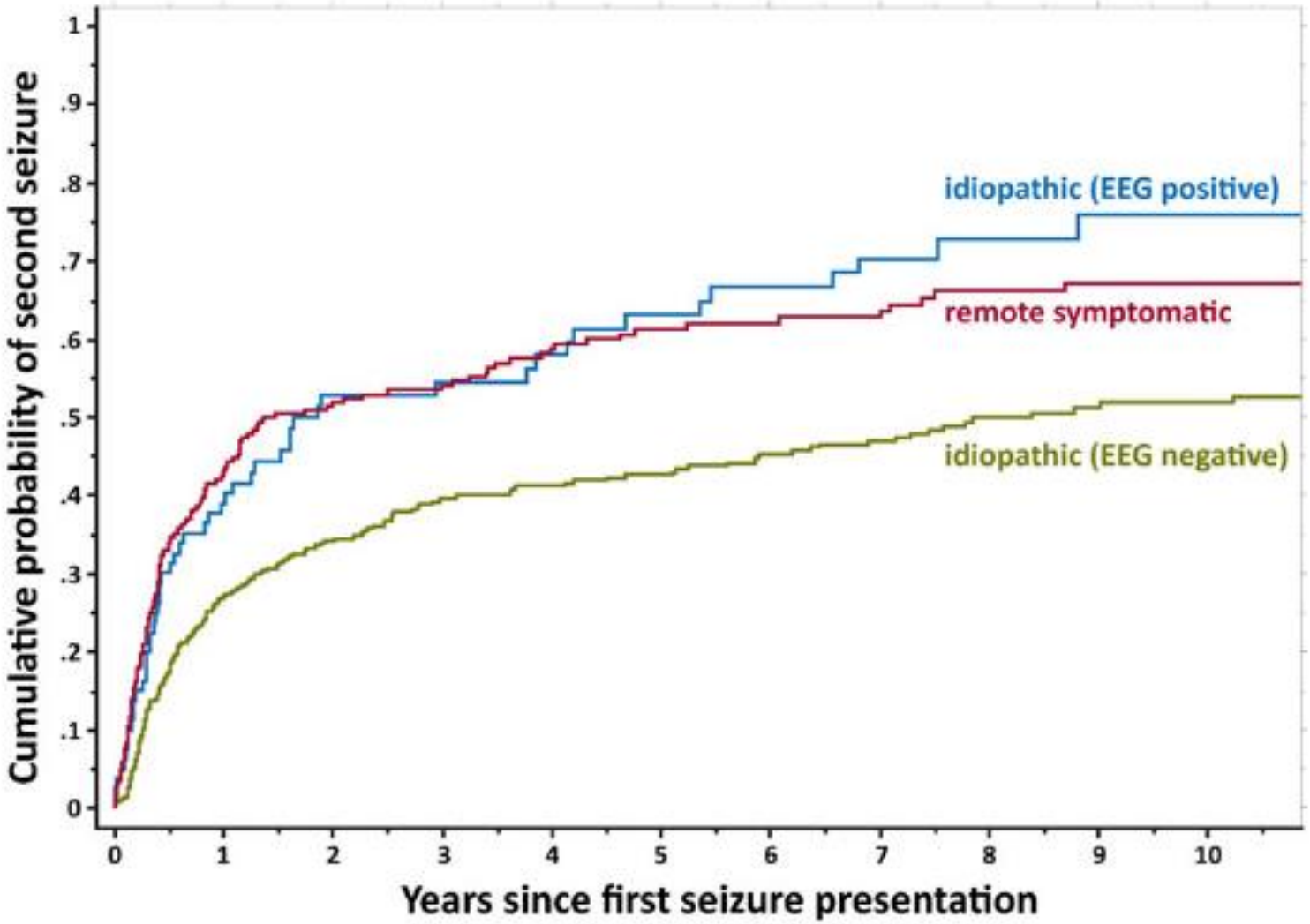
Figure 1 Percentages of patients with first seizure experiencing a recurrent seizure over time



Krumholz et al., Neurology 2015

Patient with Juvenile Myoclonic Epilepsy





Patients at risk:											
idiopathic (EEG positive)	80	47	31	29	24	21	18	15	10	7	6
remote symptomatic	253	137	102	82	6	56	49	47	34	29	21
idiopathic (EEG negative)	461	318	237	192	171	154	139	118	96	73	55

Lawn et al., 2015

AAN Guideline

Moderate Evidence

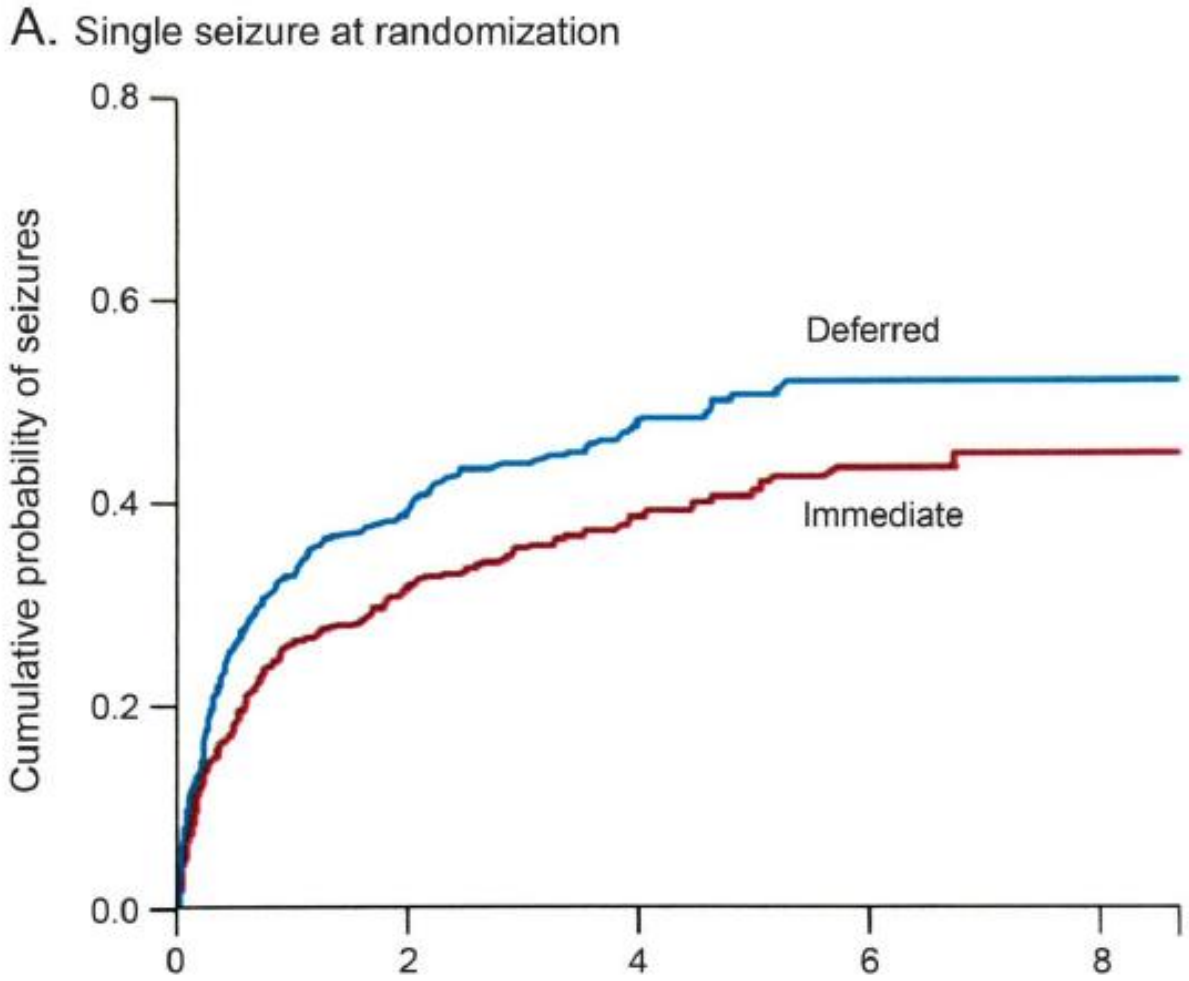
Clinicians should advise patients that immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk for a seizure recurrence in the two years subsequent to a first seizure (**Level B**).

Moderate Evidence

Clinicians should advise patients that over the longer term (> 3 years) immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission (**Level B**).

Krumholz et al., Neurology 2015

Figure 2 **Cumulative proportion of patients experiencing a seizure recurrence after randomization, comparing immediate vs deferred treatment**



Immediate treatment of seizures reduces chance to second seizure so early remission (~2 years), but at 5 years both have same rate of seizure freedom

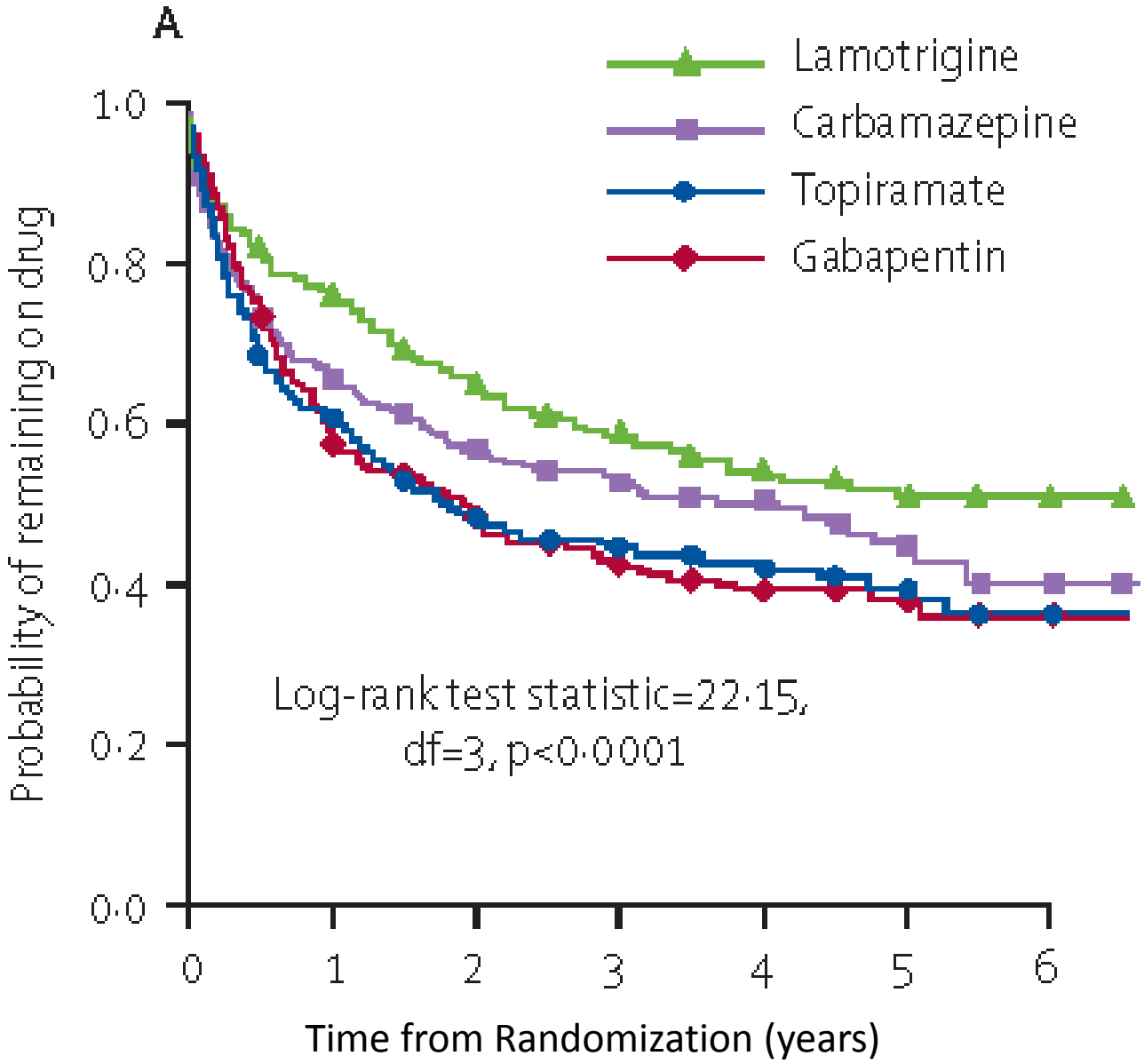
Krumholz et al., Neurology 2015

What’s the perfect drug?

….the one that works!

Show me the evidence…

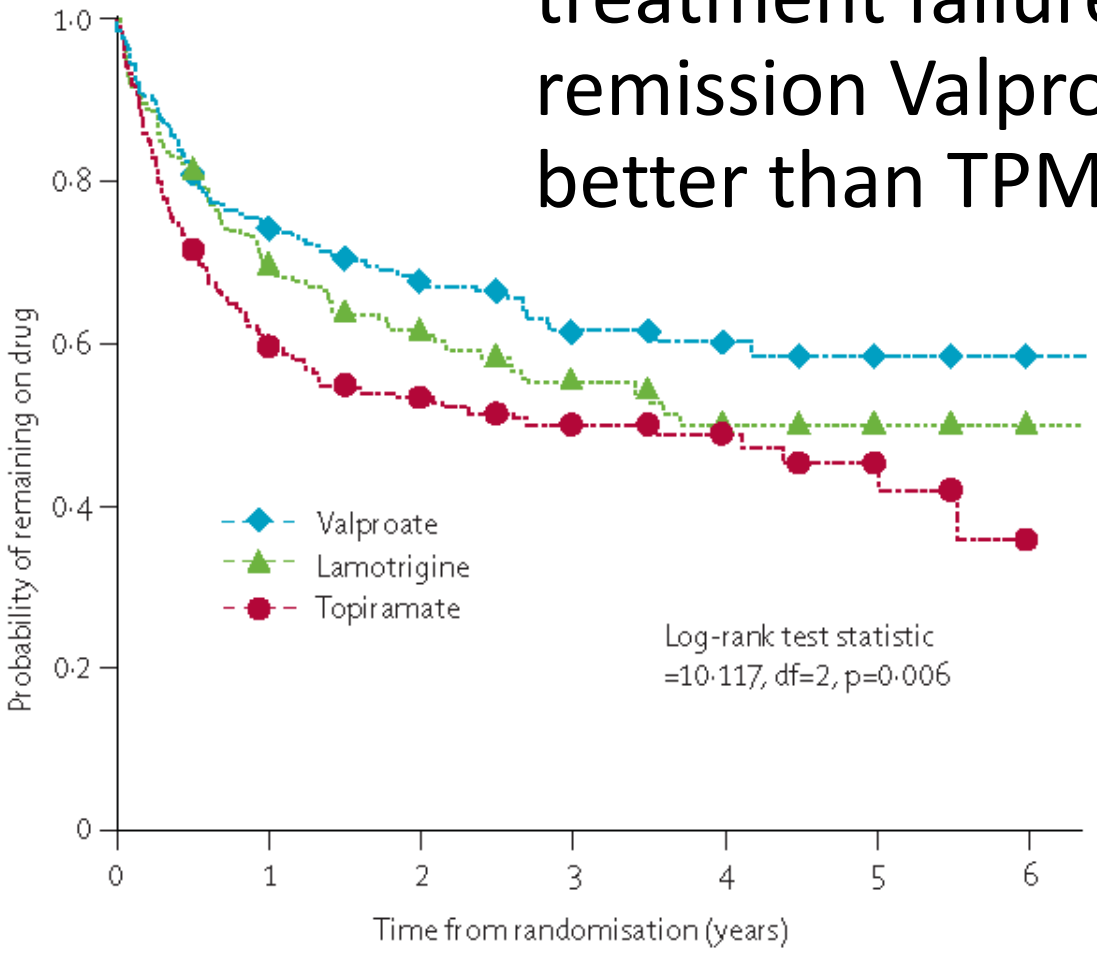
- Standard and New Antiepileptic Drug-trial (SANAD) – compared lamotrigine (LTG), carbamazepine (CBZ), Oxcarbazepine (OXC), Gabapentin (GBP), Topiramate (TPM)
  - Unblinded study over 12 mths – LTG had lowest incidence of treatment failure compared to all except OXC (started later in study)
- LaLimo trial – LTG vs Levetiracetam (LEV) – superiority trial (26 weeks)
  - Partial and generalized epilepsy
  - No difference in seizure freedom between two



Marson et al., Lancet 2007

Primary generalized epilepsy

- SANAD Trial #2 – Time to treatment failure and to 12 month remission Valproic acid (VPA) was better than TPM and to LTG



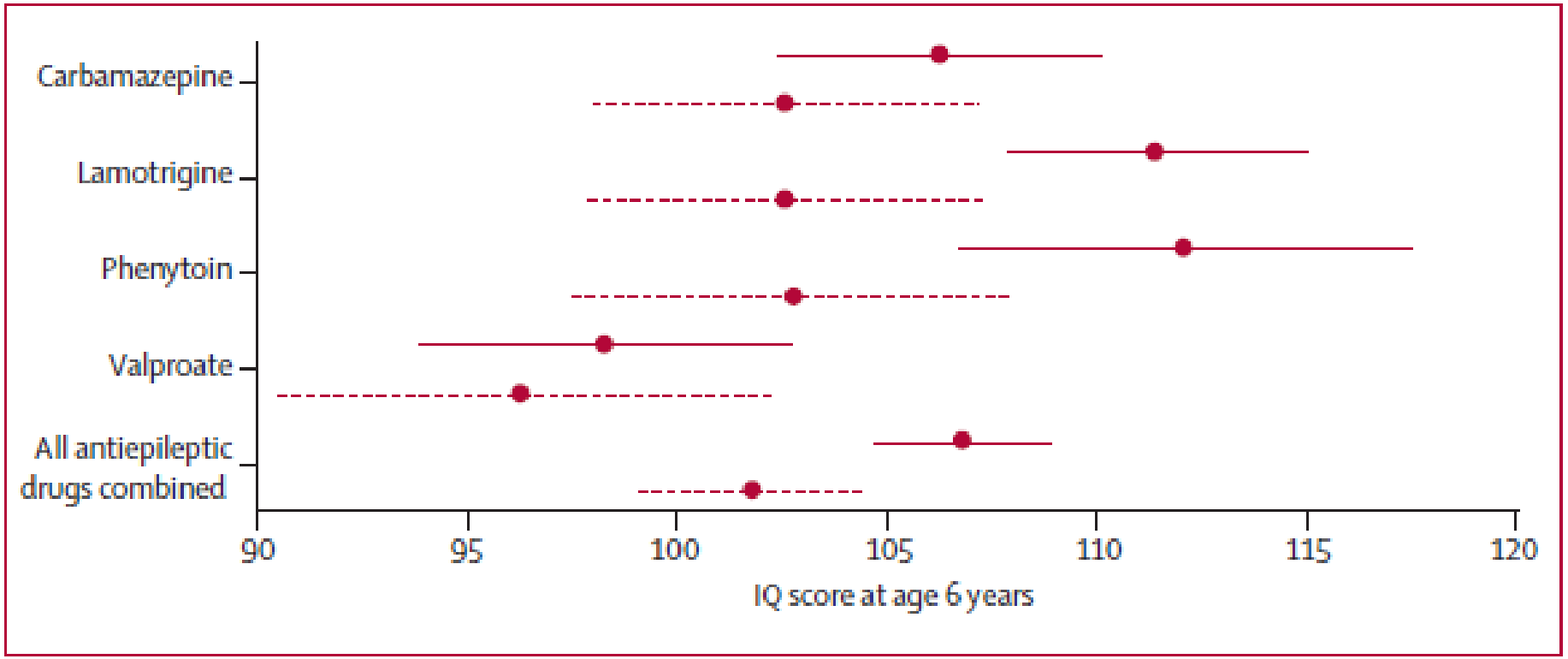
- Avoid Carbamazepine, Oxcarbazepine, Dilantin, Gabapentin

Marson et al., Lancet 2007

But…

- Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study (2013)
  - Largest prospective study examining IQ and other cognitive domains after exposure to AED
- At 6 yo IQ of children exposed to VPA was lower (~-8-12 pts) compared to CBZ, LTG, and PHT on verbal and non verbal tests
- This was a dose dependent effect and was improved if mothers were given pre-conceptual folate

NEAD Study (2013)



Dashed lines (no folate); solid lines (with folate)

Meador et al., Lancet Neuro 2013

<sigh>…Driving…

Driving

- As drivers we are bound by Ontario highway Traffic Act to obey laws
- Driving is a privilege not a right
- As physicians we are bound by law to report patients >16 yo who we feel is “suffering from a condition that may make it dangerous for the person to operate a motor vehicle.”
- Mandatory reporting: MD, Optometrist, Police
- Nurse practitioner: no definite legislation yet but can complete forms for reinstatement

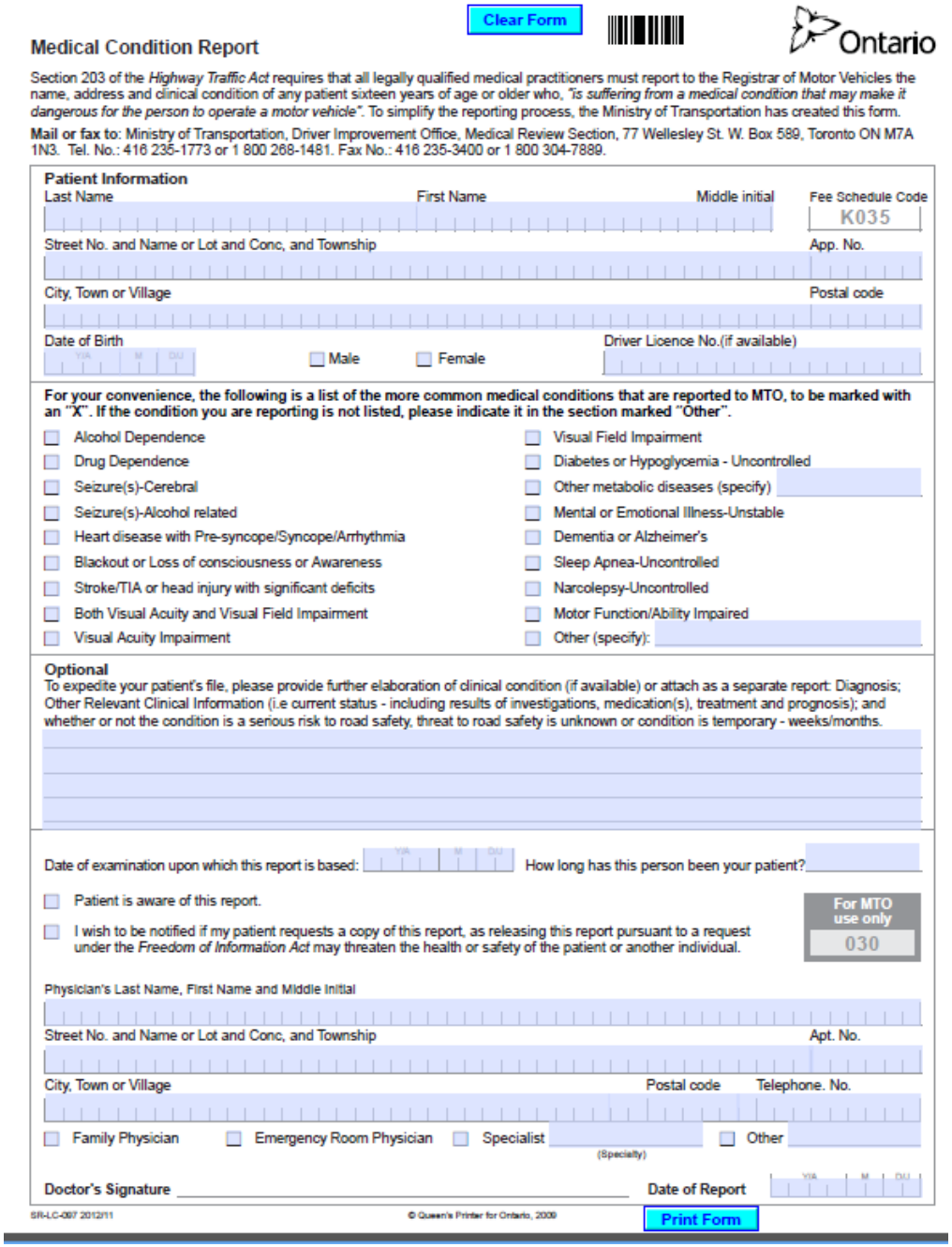
Risk of seizures and driving

- Seizures are unpredictable, unprovoked*
  - Increased risk with sleep deprivation, alcohol
- risk is assumed to be frontloaded - length of time being seizure free correlates to reduced accidents
- One study suggests 85% reduced chance of accident after 6 months and 93% after 12 months seizure free (but this is self reported)
  - no good pooled data

Naik et al., Epilepsy Behav 2015

Why report? Are all seizure same?

- Overall seizure with LOA / LOC risk of accident
  - Generalized tonic clonic; Absence; Complex partial / “dyscognitive”
- Nocturnal – less risk in itself, but some patients convert to diurnal so need period of stability
- Aura – some patients quickly turn to CPS
  - Need to see stability because auras are seizures
  - No auras of forced head / eye deviation



Clear Form

Medical Condition Report

Ontario

Section 203 of the *Highway Traffic Act* requires that all legally qualified medical practitioners must report to the Registrar of Motor Vehicles the name, address and clinical condition of any patient sixteen years of age or older who, *"is suffering from a medical condition that may make it dangerous for the person to operate a motor vehicle"*. To simplify the reporting process, the Ministry of Transportation has created this form.

Mail or fax to: Ministry of Transportation, Driver Improvement Office, Medical Review Section, 77 Wellesley St. W. Box 589, Toronto ON M7A 1N3. Tel. No.: 416 235-1773 or 1 800 268-1481. Fax No.: 416 235-3400 or 1 800 304-7889.

Patient Information

Last Name | First Name | Middle initial | Fee Schedule Code K035

Street No. and Name or Lot and Conc, and Township | App. No.

City, Town or Village | Postal code

Date of Birth (YIA M DU) ☐ Male ☐ Female | Driver Licence No.(if available)

For your convenience, the following is a list of the more common medical conditions that are reported to MTO, to be marked with an "X". If the condition you are reporting is not listed, please indicate it in the section marked "Other".

- ☐ Alcohol Dependence
- ☐ Drug Dependence
- ☐ Seizure(s)-Cerebral
- ☐ Seizure(s)-Alcohol related
- ☐ Heart disease with Pre-syncope/Syncope/Arrhythmia
- ☐ Blackout or Loss of consciousness or Awareness
- ☐ Stroke/TIA or head injury with significant deficits
- ☐ Both Visual Acuity and Visual Field Impairment
- ☐ Visual Acuity Impairment
- ☐ Visual Field Impairment
- ☐ Diabetes or Hypoglycemia - Uncontrolled
- ☐ Other metabolic diseases (specify)
- ☐ Mental or Emotional Illness-Unstable
- ☐ Dementia or Alzheimer's
- ☐ Sleep Apnea-Uncontrolled
- ☐ Narcolepsy-Uncontrolled
- ☐ Motor Function/Ability Impaired
- ☐ Other (specify):

Optional

To expedite your patient's file, please provide further elaboration of clinical condition (if available) or attach as a separate report: Diagnosis; Other Relevant Clinical Information (i.e current status - including results of investigations, medication(s), treatment and prognosis); and whether or not the condition is a serious risk to road safety, threat to road safety is unknown or condition is temporary - weeks/months.

Date of examination upon which this report is based: (YIA M DU) | How long has this person been your patient?

☐ Patient is aware of this report.

☐ I wish to be notified if my patient requests a copy of this report, as releasing this report pursuant to a request under the *Freedom of Information Act* may threaten the health or safety of the patient or another individual.

For MTO use only 030

Physician's Last Name, First Name and Middle Initial

Street No. and Name or Lot and Conc, and Township | Apt. No.

City, Town or Village | Postal code | Telephone. No.

☐ Family Physician ☐ Emergency Room Physician ☐ Specialist (Specialty) ☐ Other

Doctor's Signature _____ **Date of Report** (YIA M DU)

SR-LC-007 2012/11 © Queen's Printer for Ontario, 2009

Print Form

Billing code - $36.25 – allowed at 1 per 12 months PER physician

CMPA and the Law / Colleges

- CMPA reviewed 67 cases from 2005-2009 and described three main themes
  - Allegations of physicians who failed to report
    - Need to discuss with patient duty to report and explain the process
  - Complaints that a report was made
    - Ontario legislation protects against legal action
    - College supports physician if report was made in “good faith.”
  - Complaints relating to refuse application to restore driving privilege

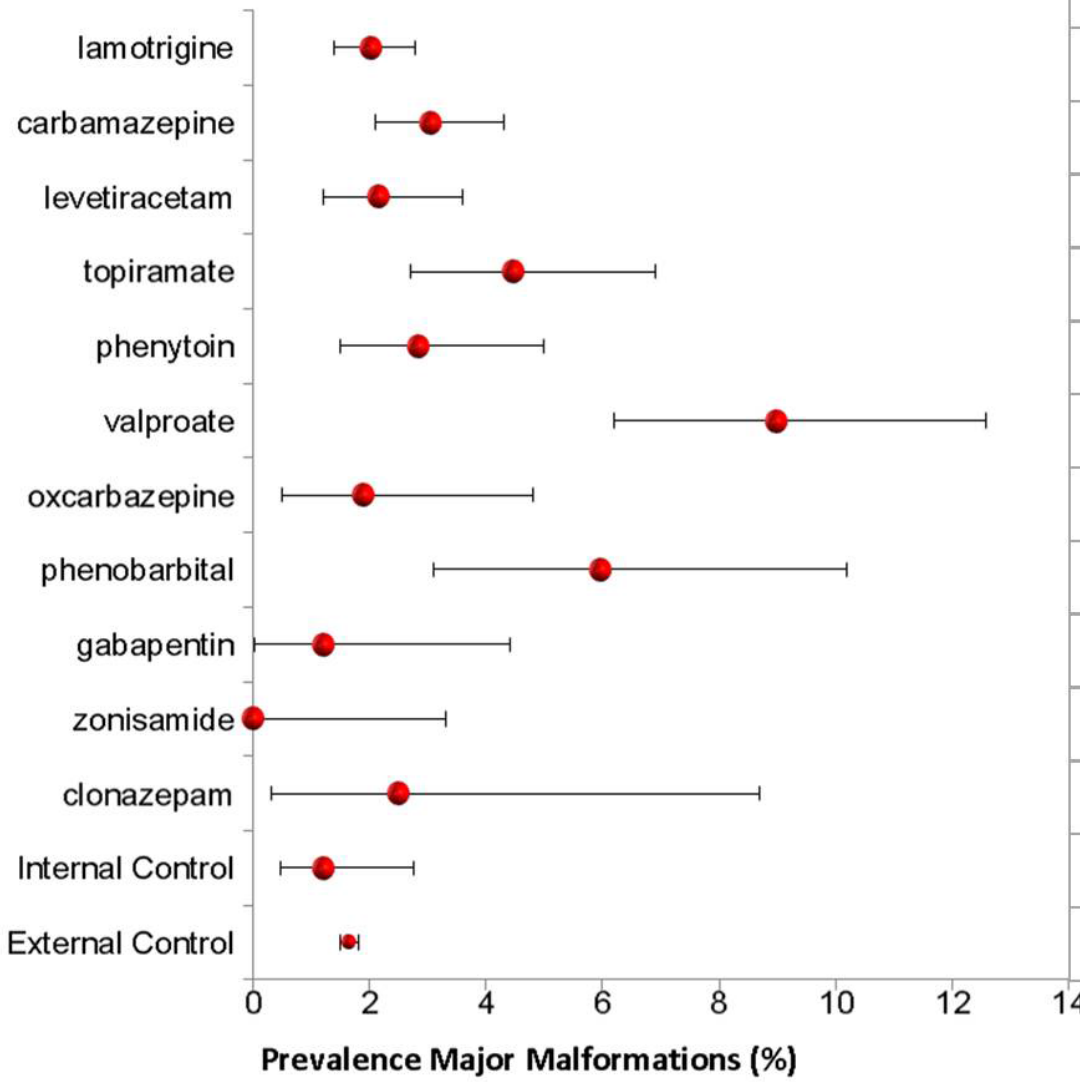
Driving pearls…

- Don’t assume someone else sent MTO form
- 1st seizure generally 3 months with
  - Assessment, imaging, EEG
- Epilepsy > 2 sz - 6 months no driving
- Commercial drivers (A/Z) usually stricter
- Be careful of just “CC” to the MTO of your letter
- Structural lesion ~ 6 mth
- Alcohol withdrawal seizure – still need EEG to r/o epileptiform discharges
  - Need proof of enrolment in program ~ 6 vs 12 mths

Summary

- Everyone who had a first seizure should be investigated with imaging and EEG (routine or sleep deprived)
- If suspicion of mimick, other investigations needed
- Careful discussion of driving
- Many choices for antiepileptic drugs; but the choice depends also on situation

Mass General Epilepsy Registry



N	%	95% CI
1812	2.0	(1.4 to 2.8)
1078	3.1	(2.1 to 4.3)
648	2.2	(1.2 to 3.6)
425	4.5	(2.7 to 6.9)
420	2.9	(1.5 to 5.0)
333	9.0	(6.2 to 12.6)
211	1.9	(0.5 to 4.8)
201	6.0	(3.1 to 10.2)
163	1.2	(0.02 to 4.4)
119	0.0	(0.0 to 3.3)
80	2.5	(0.3 to 8.7)
495	1.2	(0.46 to 2.7)
69277	1.6	(1.5 to 1.7)