When to start anti-seizure medications, and which ones?

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Disclosures

- No disclosures

When to start anti-seizure medications?

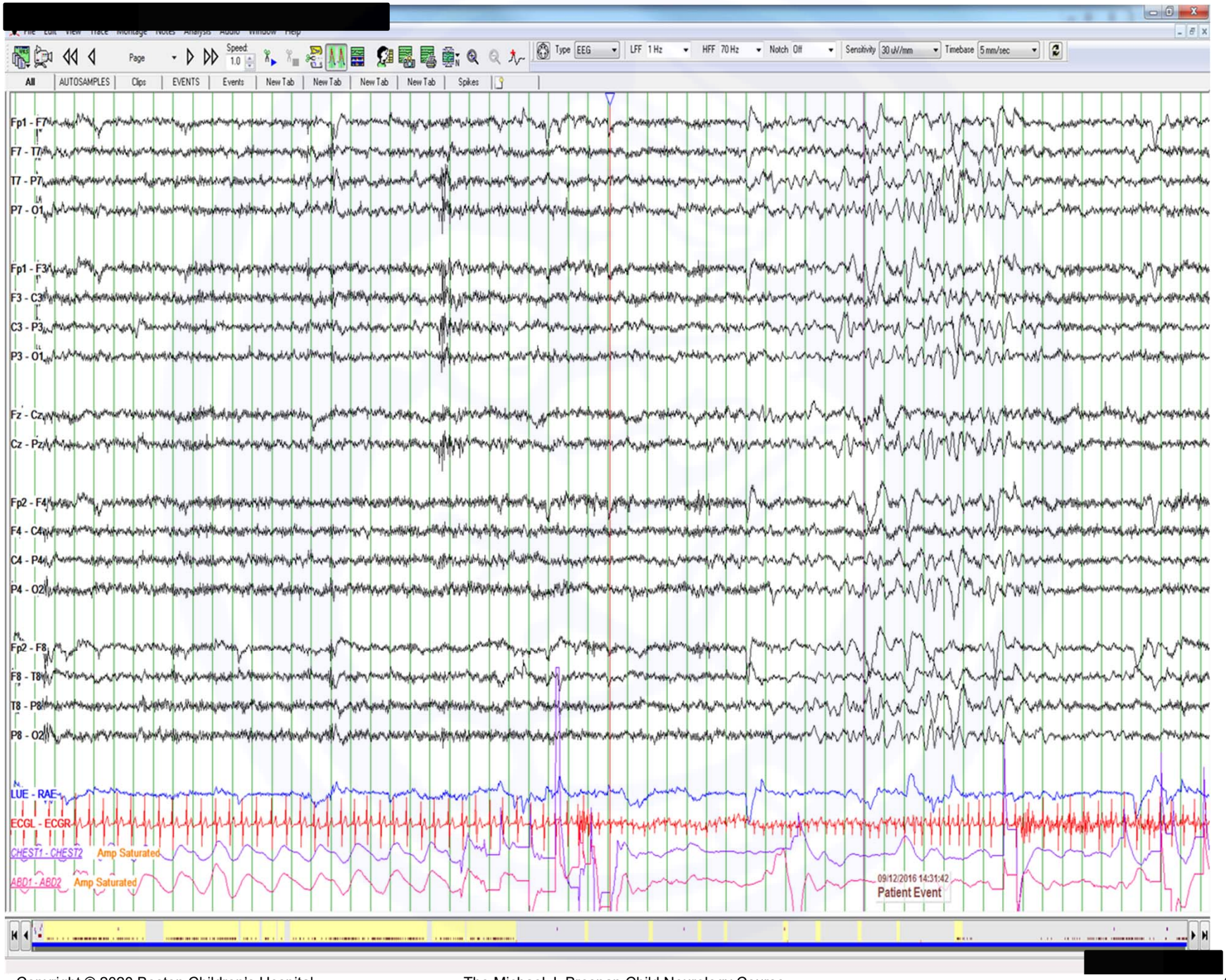
- different types of seizures, different etiologies, different prognoses
- self-limited epilepsy syndromes in children
- occur only in the course of an acute medical or neurologic illness or febrile seizures
- different implications for different situations and for individual patients

When to start anti-seizure medications?

- accurate differentiation of a seizure from a nonepileptic event is important
- confirming or refuting the epileptic origin may be quite difficult
- Diagnostic inaccuracies are common in children

Seizure- differential

- 7 yr old with autism, hyperventilation and epilepsy presenting to ED with vomiting and seizures (new type)
- turning her head to side (looking for mom) subsequently falling backwards, some eye fluttering for 2 seconds and being back at her baseline.
- With one such event “stood up to go to the bathroom and her knees buckled. She slumped over and had shaking and face twitching”



Seizure versus syncope

- Patient T had diarrhea 1 day prior to the episode of altered responsiveness. The next morning he woke up early, had a Gatorade only for breakfast and dressed to go skiing. He was walking to meet his friends. The next thing he remembers is waking up lying on the ground with EMT personnel around. His friends noted that he had brief twitching. He was confused and had vomited after coming to consciousness. Vasovagal syncope was diagnosed.

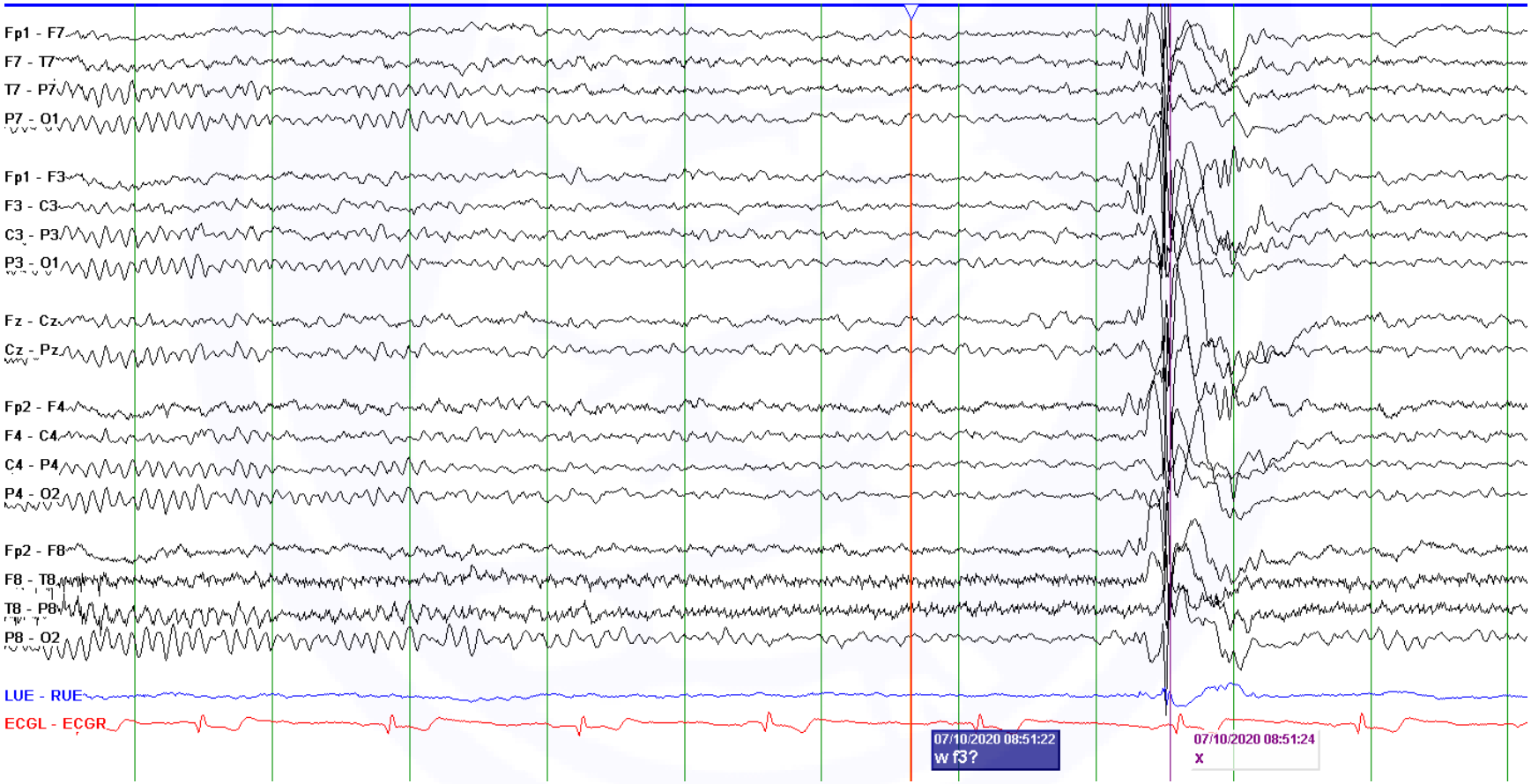
Seizure versus syncope

- 2nd episode of altered consciousness. “Today he smoked marijuana. About 30 minutes after he smoked, his sister heard heavy snoring in his room. Mom noted that he was asleep but with his eyes partially open. While attempting to wake him his speech was noted to be slurred and kept asking "what" over and over. He vomited, looked pale. It took him about 5 minutes to become coherent. He didn’t remember any of these”.
- He had 1 SBP of 81 just after vomiting. His mental status was normal as per EMS

Seizure versus syncope

- Is this a seizure or a non-epileptic event or unclassified event?

EEG



When to start anti-seizure medications?

First step-diagnose epileptic seizure

Diagnosing seizure/epilepsy

- description, made by an eye witness to the events, Video documentation etc, clinical examination
- EEG - support a diagnosis of epilepsy/seizure but unlikely to be diagnostic unless an event occurs during the recording
- EEG should not be used in isolation to make a diagnosis of epilepsy

Diagnosing seizure/epilepsy

Prospective- 127 children in First Seizure clinic
(52 ± 18 days after their "first seizure")

- 31 (24%) of events "nonepileptic"
- 38% (36/94 pts) had at least one prior event (> half had partial complex seizures)
- Focal seizures, absences, myoclonus- identified after multiple attacks

("First Seizure": Role for a First Seizure Clinic. Hamikawa, Epilepsia, 48(6):1062–1066, 2007)

EEG

- EEG was obtained in 30/31 (97%) children with a “nonepileptic” event
- Six had abnormal EEGs :

rolandic sharp waves (3), occipital sharp waves (1), slow background activity for age (2), and multifocal discharges (1)

- clinical history of the episodes was not consistent with EEG

(“First Seizure”: Role for a First Seizure Clinic. Hamikawa, Epilepsia, 48(6):1062–1066, 2007)

The next step

To determine if the patient has presented with unprovoked first seizure

or

Has had more than 1 unprovoked seizure at the time of presentation (epilepsy)

ILAE definition of epilepsy 2014

- At least two unprovoked (or reflex) seizures occurring >24 h apart;

  Diagnosing epilepsy after a single unprovoked seizure

- 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

  Or

- diagnosis of an epilepsy syndrome

(Fisher RS, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. Epilepsia 2014;55:475–482)

When to start anti-seizure medications?

- Diagnosis of epilepsy does not necessarily require treatment

- Decision for treatment does not necessarily equate to a diagnosis of epilepsy

- What is the impact of anti-seizure treatment in epilepsy

When to start anti-seizure medications? natural course of epilepsy

spontaneous remission

- 20–44% of patients with untreated or undertreated epilepsy become seizure-free without or with minimal drug treatment

Inconsistent course of epilepsy

- 20% of patients with early refractory epilepsy will enter late remission
- 15% of those with early remission will become refractory

(*Evidence-based review on the natural history of the epilepsies, Schmidt, Curr Opin Neurol 2012, 25:159–163*)

natural course of epilepsy-children

Complete remission at last contact (60%)

- early sustained remission- 33%
- later but sustained remission-10%
- fluctuating course of epilepsy-remission/relapses -17%

No complete remission at last contact- 35%

Never experienced 1-year remission- 5%

(The course of childhood-onset epilepsy over the first two decades: A prospective, longitudinal study, Berg, Epilepsia, 56(1):40–48, 2015)

When to start anti-seizure medications?
epilepsy course and treatment strategies
Epidemiological data

- Variable epilepsy course
- Improvement/deterioration may occur years after onset
- Discontinuation of antiseizure medications leads to relapse in more than one third
- reinstitution of the therapy does not result in remission in all
- drug-resistance need not be irreversible

(Long-term outcome of medically treated epilepsy, Sillanpaa, Seizure Volume 44, January 2017, Pages 211-216)

When to start anti-seizure medications? Anti-seizure medications

- Anti-seizure medications probably do not influence epilepsy course; merely suppress seizures

(Course and outcome of childhood epilepsy: A 15-year follow-up of the Dutch Study of Epilepsy in Childhood, Geerts, Epilepsia, 51(7):1189–1197, 2010)

- Impact of anti-seizure treatment after first unprovoked seizure

When to start anti-seizure medications? first unprovoked seizure- impact of anti-seizure medication randomized trials

- FIRST seizure trial- randomized to immediate treatment or treatment after another seizure

probability of recurrence by 2 years

- 26% - immediate treatment group
- 45% - delayed treatment group

overall hazards ratio for immediate versus deferred treatment- 0.4

(Musicco M,et al Treatment of first tonic clonic seizure does not improve the prognosis of epilepsy. First Seizure Trial Group (FIRST Group). Neurology 1997;49:991–8) Treatment of the first tonic-clonic seizure does not affect long-term,remission of epilepsy, Leone, Neurology 2006)

- Multicenter Trial for Early Epilepsy and Single Seizures (MESS trial)

Cumulative % Seizure recurrence by 2 Years

- 32%- immediate treatment group
- 39%- delayed treatment group

overall hazards ratio for untreated versus treated arms- 1.4

(Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D; Medical Research Council MESS Study Group. (2005) Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet 365:2007–2013)

reduce absolute risk by about 35% for a seizure recurrence within the subsequent 2 years (Meta analysis)

When to start anti-seizure medications? Remission long term

FIRST trail

Probability of 2-year remission at 3 years

84% -immediate treatment group

79% -delayed treatment group

MESS trial

2-year remission at 3 years

74% - immediate treatment group

71% -delayed treatment group

	Proportion with 2-year remission		
	Immediate treatment, %	Deferred treatment , %	Difference, % (95% CI)
2 years			
All participants	64	52	12 (6.3–17.4)
Single seizure	69	61	
Multiple seizure	57	39	
5 years			
All participants	92	90	2 (−1.2 to 6.1)
Single seizure	92	92	
Multiple seizure	91	87	
8 years			
All participants	95	96	1 (−2.5 to 3.9)
Single seizure	95	96	
Multiple seizure	94	95	

When to start antiepileptic drug treatment and with what evidence? Anthony G.Marson, Epilepsia, 49(Suppl. 9):3–6, 2008

When to start anti-seizure medications? first unprovoked seizure- impact of anti-seizure medication randomized trials

- immediate treatment group-risk of recurrence lower (~50%) at 2 years
- long-term outcomes not different

When to start anti-seizure medications? child with first unprovoked seizure-treatment

- 31 children randomized to CBZ (n = 14) or no treatment (n = 17)
- rate of 2-year terminal remission (15 year FU) - 80% - Treated group
  - 88% - Untreated group

Evidence of treatment impact from pediatric studies alone is weak

(Hirtz D, Berg A, Bettis D, et al. Practice parameter: Treatment of the child with a first unprovoked seizure: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology, 2003;60:166–175)

When to start anti-seizure medications?

perceived risk of anti-seizure medication

versus

benefit of reducing risk for further seizures in the first 2–3 years after diagnosis

However, not all patients have similar risk for seizure recurrence

- How likely is a seizure recurrence and what are the factors affecting the recurrence

When to start anti-seizure medications? first unprovoked seizure-Risk of recurrence

- Prospective study 407 children (FU- 6.3 years)
- cumulative risk of seizure recurrence with a first unprovoked seizure
  1yr-29%
  2yr-37%
  5 yr-42%

Meta-analysis

prospective studies - 40% at 2 years

Retrospective studies -51 to 52% at 2 years

(Shinnar S, Berg AT, Moshe SL, et al. The risk of seizure recurrence following a first unprovoked afebrile seizure in childhood: an extended follow-up. Pediatrics 1996;98:216–225, Wiebe S. An evidence-based approach to the first unprovoked seizure. Can J Neurol Sci 2002;29:120–124)

When to start anti-seizure medications? Factors that increase recurrence risk

- underlying etiology
- EEG abnormality
- A second recurrence
- initial seizure during asleep state (?)

When to start anti-seizure medications? decision-making on the basis of risk factors-MESS trial data

- Regression modeling Prognostic index stratified- low, medium, or high risk of seizure recurrence

No significant difference between treatments for low-risk (p=0·2)

improvement with immediate treatment for medium/high-risk (p=0·008; p<0·0005, respectively)

	Prognostic index
Starting score	
Single seizure	0
Two or three seizures	1
Four or more seizures	2
Add if present	
Neurologic disorder of deficit	1
Abnormal EEG	1
Risk classification group	Final score
Low risk	0
Medium risk	1
High risk	2–4

	Treatment policy	1 year recurrence risk (%)	3 year recurrence risk (%)	5 year recurrence risk (%)
Low risk	Start	26	35	39
	Delay	19	28	30
Medium risk	Start	24	35	39
	Delay	35	50	56
High risk	Start	36	46	50
	Delay	59	67	73

Kim LG, Johnson TL, Marson AG, Chadwick DW, MRC MESS Study group. (2006) Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the mess trial. Erratum appears in lancet neurol. Lancet Neurol 5:317–322.

When to start anti-seizure medications? statistical model to predict long-term outcome in children

- Across all studies, childhood epilepsy remits in ~60%
- Combined two large prospective cohort studies of childhood epilepsy (Nova Scotia and the Netherlands)- clinical and EEG variables to predict outcome
- positive predictive value for a good outcome ~ 0.7
- Predicting the outcome of childhood epilepsy appears to be incorrect in about 1 in 3 patients

(The Accuracy of Outcome Prediction Models for Childhood-onset Epilepsy, Geelhoed, Epilepsia, 46(9):1526–1532, 2005)

When to start anti-seizure medications? recurrence risk-ILAE report

- No formula can be applied for additive risks, since data are lacking on how such risks combine
- Decided by individualized considerations

When to start anti-seizure medications? Recurrence -Convulsive status epilepticus at presentation

- risk of subsequent epilepsy- 5% to 36%
- risk of recurrent Status epilepticus-10% - 56%
- Recurrent SE- associated with remote symptomatic/progressive etiology

(Long-term outcomes of status epilepticus: A critical assessment, Claudine Sculier, Marina Gaínza-Lein, Iván Sánchez Fernández,Tobias Loddenkemper, Epilepsia. 2018;59(S2):155–169)

Potential risks of

1. pharmacological treatment
2. second seizure

When to start anti-seizure medications? Risks of anti-seizure medications

- potential serious pharmacologic and psychosocial side effects
- one in 10 children stop treatment due to toxicity
- behavioral problems (12%), somnolence/sleep problems (10%)

(Anderson M, et al. A prospective study of adverse drug reactions to antiepileptic drugs in children. BMJ Open 2015;5(6):e008298)

When to start anti-seizure medications? Risks of mortality and injuries

- Starting anti-seizure treatment after the first generalized tonic-clonic seizure or only after seizure recurrence did not affect survival over the following 20 years
- MESS trial, injuries occurred more frequently in the immediately treated than in the deferred group

- Treatment after first unprovoked seizure

When to start anti-seizure medications? AAN practice parameter treatment of the child with a first unprovoked seizure

- Treatment with Anti-seizure medication may be considered

benefits outweigh the risks of side effects (pharmacological/psychosocial)

but

not for prevention of development of epilepsy

(Hirtz D, Berg A, Bettis D, et al. Practice parameter: treatment of the child with a first unprovoked seizure: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2003;60:166–175)

- Management after 2nd unprovoked seizure

When to start anti-seizure medications?- Adults with second unprovoked seizure

After 2 or more seizures, risk high for additional seizures

57% -1 year

73% - 4 years

-risk increasing proportionally as time interval between seizures decreases

widely accepted practice-

Anti-seizure medication should be initiated after 2nd unprovoked seizure

(Evidence-Based Guideline: Management of an Unprovoked First Seizure in Adults, Krumholz, Epilepsy Currents, Vol. 15, No. 3 (May/June) 2015 pp. 144–152)

When to start anti-seizure medications? Risk in children with second unprovoked seizure

- cumulative risk of recurrence after a 2nd seizure

  -1yr-57%

  -2 yr-63%

  -5 yr- 71%

(Shinnar S, Berg AT, Moshe SL, et al. The risk of seizure recurrence following a first unprovoked afebrile seizure in childhood: an extended follow-up. Pediatrics 1996;98:216–225)

When to start anti-seizure medications? children

- common practice to start treatment with anti-seizure medications after 2nd seizure

- Are there situations where treatment may be deferred after 2nd seizure?

When to start anti-seizure medications?

Dutch childhood epilepsy study

- 14% not treated with Anti-seizure medications
- >90% were in long-term remission after 12 to 18 years of follow-up
- Epilepsy may be self-limited disorder in some children

(Geerts A, Arts WF, Stroink H, et al. Course and outcome of childhood epilepsy: a 15-year follow-up of the Dutch Study of Epilepsy in Childhood. Epilepsia 2010;51:1189–97)

When to start anti-seizure medications? Nova Scotia and Dutch cohort studies

Prospective study- children with newly diagnosed epilepsy-

151 children with 3 yr FU

inclusion criteria:

<5 lifetime seizures

1 month - 12 years

idiopathic generalized or focal epilepsies

focal epilepsy cause unknown and no significant neurological and/or intellectual deficit

not to start treatment until the end of FU except for status epilepticus or a 10th lifetime unprovoked seizure

FU- adverse events, QOL measures and seizure status

(Arts, W. F., Geerts, A. T., Brouwer, O. F., van Donselaar, C. A., Stroink, H., Peters, B. A. C., ... Camfield, C. (2019). Childhood epilepsy with a small number of seizures may be left untreated: an international prospective study. Epileptic disorders, 21(2), 141-153)

When to start anti-seizure medications?

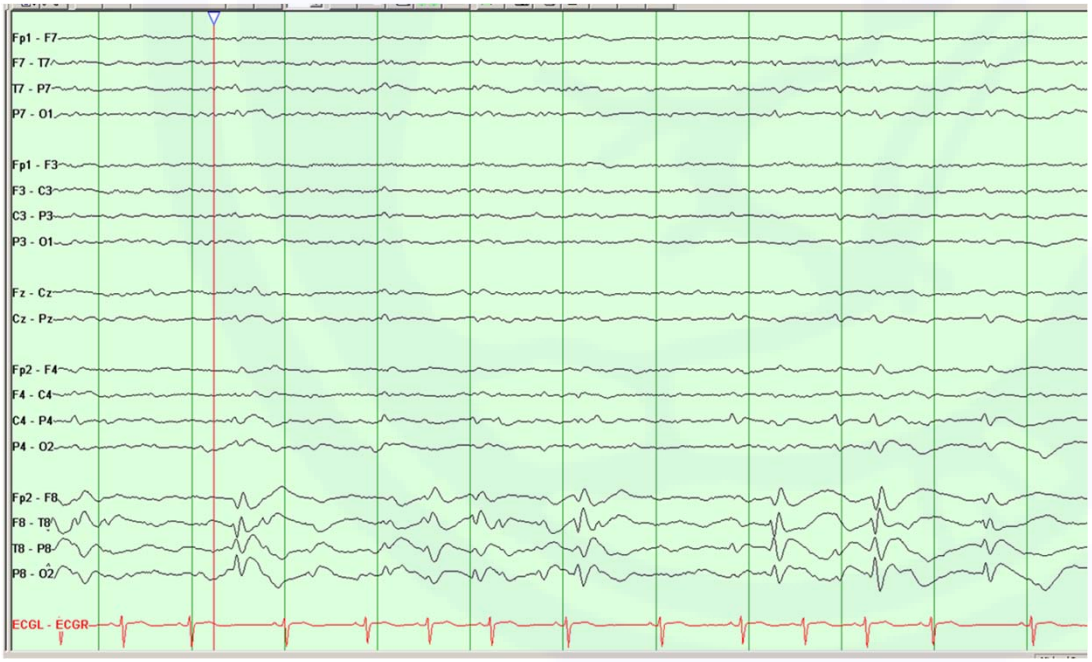
- 113 (75%) met criteria for refraining from treatment but some caregivers chose treatment
- withholding anti-seizure treatment did not alter the chance of remission as 66% of children were not treated
- Terminal remission of at least 1 year- 99 of 151 (65%) with 83/99 (84%) untreated
- Treatment did not increase the length of terminal remission
- Adverse events- no difference between treated versus untreated groups
- Quality of Life measures- better outcome in untreated group
- No deaths occurred

(Arts, W. F., Geerts, A. T., Brouwer, O. F., van Donselaar, C. A., Stroink, H., Peters, B. A. C., ... Camfield, C. (2019). Childhood epilepsy with a small number of seizures may be left untreated: an international prospective study. Epileptic disorders, 21(2), 141-153)

- Case studies

When to start anti-seizure medications? children with recurring unprovoked seizures

- 8 yr old neurologically normal male with a 2nd nocturnal episode
- left sided facial tingling followed by twitching, drooling, dysarthria. No LOC. Duration 2min, recovery of speech



When to start anti-seizure medications? children with recurring unprovoked seizures

- NB neurologically normal female- 1st seizure 7 years of age. “unresponsive in the bed covered with a blanket over her head and with vomitus”
- EEG- independent central temporal sharp wave during drowsiness and sleep state in both hemispheres potentiated in sleep
- The next episode happened 2 months later, shortly after going to bed, her mouth open, face pulled to 1 side, drooling, hands clenched, slight twitching with copious amounts of saliva.
- NB had several generalized seizures- 3 seizures in 2011, 3 seizures in 2012, 1 seizure in 2013

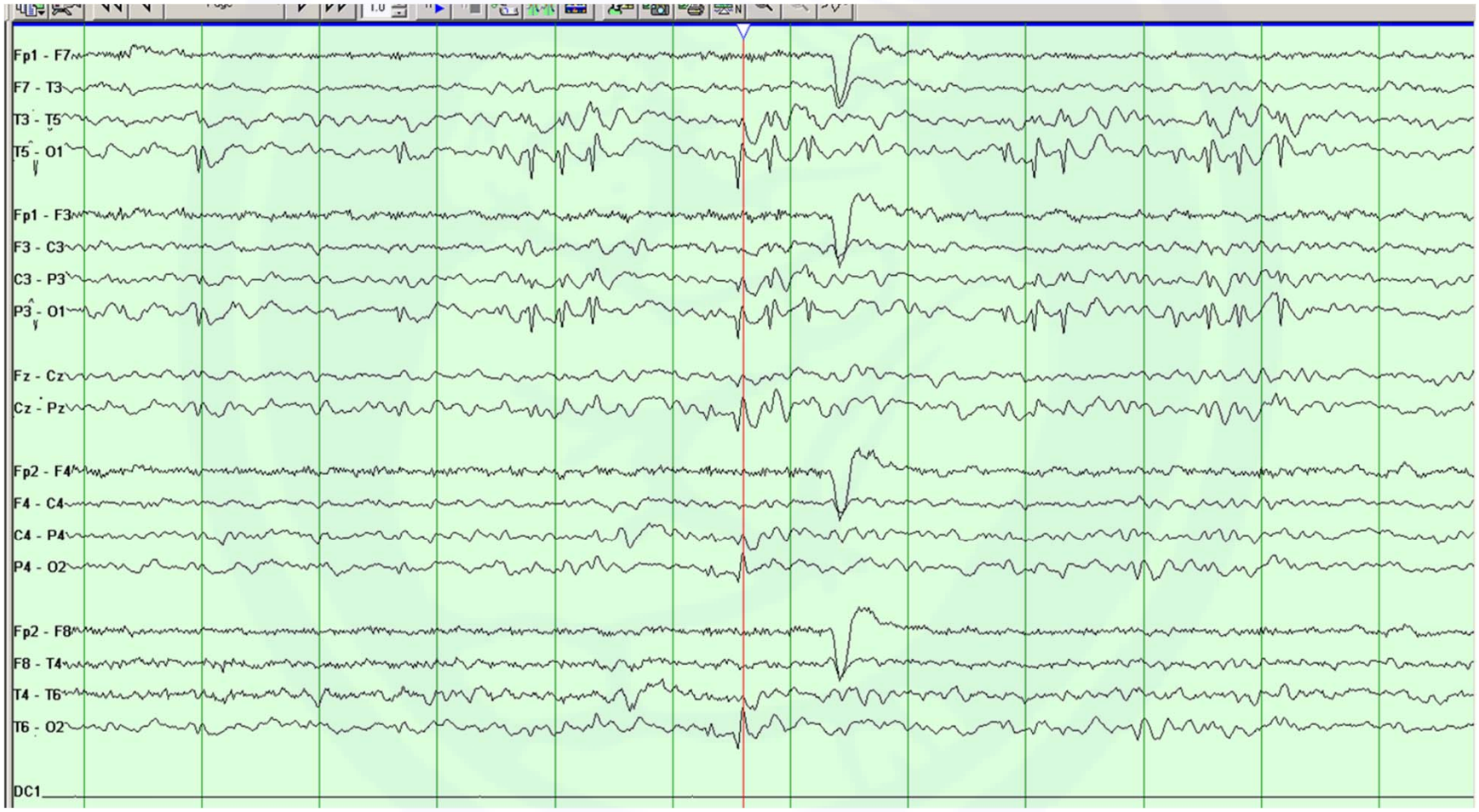
When to start anti-seizure medications? children with recurring unprovoked seizures

When to start anti-seizure medications? children with recurring unprovoked seizures

- Started OXC in June 2013. seizure free and weaned off the OXC since December 2016

When to start anti-seizure medications? children with status epilepticus

- 5 yr old previously healthy female with a nocturnal episode of vomiting followed by alteration in awareness, pallor followed by head and eye deviation to the right with right sided shaking
- Duration 25 minutes



When to start anti-seizure medications? self-limited childhood focal epilepsies

- These children have self-limited childhood focal epilepsies (with centrotemporal or occipital spikes)
- Anti-seizure treatment may not be needed in most situations

Indications for treatment

Daytime seizures

Recurrent longer seizures

Generalized tonic-clonic seizures

Caregiver preferences

When to start anti-seizure medications?

- A decision to treat should be made by a neurologist together with the family and child where relevant

When to start anti-seizure medications?

- Should a 14-year-old boy be started on drug treatment after a first unprovoked generalized tonic–clonic seizure?
- Would it make a difference if he were 17 years old and driving?
- Should treatment be recommended to a woman with early morning limb jerks? Would the advice be different if she were eager to start a family?
- Should a 3-year-old girl with intellectual disability with staring spells each week for the last several months be started on treatment? What if she were having drop attacks instead?

When to start anti-seizure medications?

- Should a 14-year-old boy be started on drug treatment after a first unprovoked generalized tonic–clonic seizure?

careful history for multiple myoclonic jerks upon awakening or history of staring spells

explore the role of alcohol and drugs

-To the 14-year-old who will not drive for another 2 years, withholding treatment may be more acceptable than to the 17-year-old whose license is still new

When to start anti-seizure medications?

- Should treatment be recommended to a woman early morning limb jerks? Would the advice be different if she were eager to start a family?

Most likely has juvenile myoclonic epilepsy

lamotrigine and levetiracetam are considered the treatments of choice

When to start anti-seizure medications?

- Should a 3-year-old girl with intellectual disability with staring spells each week for the last several months be started on treatment? What if she were having drop attacks instead?
- EEG-to evaluate for more seizures, evidence to support epileptic encephalopathy

-Treatment is always indicated in epileptic encephalopathies

When to start anti-seizure medications, and which ones?

- Pharmacokinetic and pharmacodynamic differences in the pediatric patient and the adult
- available formulations

When to start anti-seizure medications, and which ones? initial monotherapy in children with Focal onset seizures

ILAE 2013

Level A-OXC

Possibly effective (level C)

- Carbamazepine, phenobarbital, phenytoin, topiramate, valproate, vigabatrin

potentially (level D) Clobazam, lamotrigine, and zonisamide, CZP

Cochrane meta-analysis 2017

Grade: strong

carbamazepine, lamotrigine, levetiracetam

(Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes, Glauser, Epilepsia, 54(3):551–563, 2013)

When to start anti-seizure medications, and which ones? Children with generalized-onset tonic–clonic seizures

ILAE 2013

- possibly (level C) -CBZ, PB, PHT, TPM, VPA
- potentially (level D) -OXC
- CBZ and PHT may precipitate or aggravate generalized-onset tonic–clonic seizures (class IV evidence)

(Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes, Glauser, Epilepsia, 54(3):551–563, 2013)

Cochrane meta-analysis 2017

- Grade Moderate to strong

VPA, LTG, LEV

When to start anti-seizure medications, and which ones? Children with absence seizures

Level A

- ESM and VPA

possibly (level C)

- LTG
- No conclusion can be made about LEV's efficacy/effectiveness

(Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes, Glauser, Epilepsia, 54(3):551–563, 2013)

When to start anti-seizure medications, and which ones? Self-limited childhood epilepsy with centrotemporal spikes

Possibly (level C)

CBZ and VPA

potentially (level D)

GBP, LEV, OXC, and STM

(Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes, Glauser, Epilepsia, 54(3):551–563, 2013)

When to start anti-seizure medications, and which ones? Juvenile myoclonic epilepsy

Potentially (level D)

TPM and VPA

- CBZ, GBP, OXC, PHT, TGB, and VGB may precipitate or aggravate absence seizures, myoclonic seizures, and in some cases generalized tonic–clonic seizures (class IV)

(Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes, Glauser, Epilepsia, 54(3):551–563, 2013)