Choosing Antiseizure Medications in Pediatric Patients

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Epilepsy Foundation of CT

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Credits

The content of this lecture based on an article that I am co-authoring with Tal Gilboa, MD, Director of the Pediatric Epilepsy Service at Hadassah Hospital and the Neuropediatrics Unit of Hebrew University, Jerusalem, Israel.

Objectives

- To understand the physiologic changes over time that affect medication choices across the age span
- To understand adherence and formulation issues in dosing medication for children
- To learn neurocognitive side effects of medication as they relate to children

Approach

- Epilepsy is the most frequent chronic neurologic condition in the pediatric population.
- It's incidence is highest in the first year of life, then remains stable during childhood.
- FDA approval
- Differences between adults and children
  - From birth to adulthood, children develop physically, physiologically, emotionally and cognitively,
  - The brain itself matures and seizures may change over time.
  - Normal weight gain influence medication concentration requiring lab studies
- Administration issues
  - Young children are dependent on their parents for the administration of their medications, and during
  - school hours they have more limited access to their medications.
  - Adolescence
  - How are you taking the medication
- Epileptic syndromes only in children
  - few randomized controlled studies for these syndromes,
  - Some of the pediatric epilepsy syndromes are self-limiting and may not require treatment

Scientific evidence - FDA approval

- Good clinical practice (GCP) is an international ethical and scientific quality standard for trials involving humans.
  - Protects the rights and well-being of the participants and their confidentiality
  - Additional goal that clinical trial data and results are credible.
  - Since children, are incapable of informed consent, they are a vulnerable study group
  - Adolescents need to provide assent
- Trials in children are seen as more challenging and more expensive to conduct.
- So many ASDs are tested in adults and then health providers prescribe them “off-label” for children
- This means that data regarding efficacy and safety in children is not gathered systematically.

Physiology changes over the lifespan

- These take place at the cellular level, at the organ level and at the system level.
- From neonate to adult there are changes in brain receptors
- Weight gain is a typical feature of growth, especially in the first 2 years of life, and again during the pre-pubertal growth spurt.
- Hormonal changes during adolescence influences the brain structure development.

- γ-amino-butyric acid (GABA)
  - In the adult, GABA is inhibitory
    - Causes hyperpolarization via chloride moving into the cell.
  - In immature neurons, GABA is excitatory
    - When GABA binds it opens the Cl^- channel, however inside cells of immature neuron have a high Cl level so opening that channel leads to Cl moving out of the cell

Pharmacokinetics

Many physiological changes occur during development

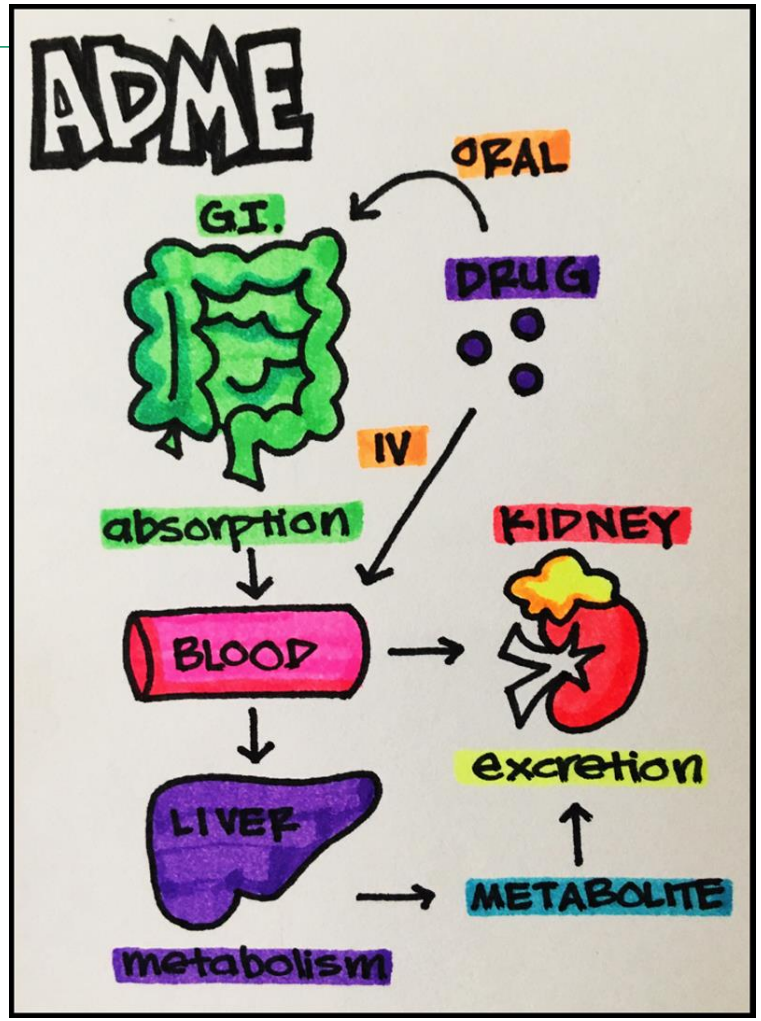
- intestinal absorption rate
- body water composition
- extracellular fluid volume
- body fat composition
- binding of drugs to plasma proteins
- renal activity improves

➢Lead to changes in pharmacokinetic profile of ASM

- absorption, distribution, metabolism/half-life, excretion/clearance

➢leading to an altered treatment response

- Weight based or body surface area (m^2) based dosing
  - used to try to address differences across the age span
  - knowledge about optimal dosing for each age group is often incomplete



Why do we need such a high dose?

- Children show 40-50% faster clearance of ASM
  - zonisamide, topiramate, *lamotrigine*, felbamate, carbmazepine, oxcarbazepine, valproate, and *levetiracetam*
- Liver metabolism
  - at birth is about 50–70% of adult levels
  - By 2–3 years of age, exceeds the adult values,
    - young children have an increased ability to metabolize drugs compared with adults.
  - The CYP enzymatic activity decreases to adult levels around puberty.
- Kidney clearance is faster in children
  - levetiracetam (Keppra) could be dosed three times daily and dosed by weight

"Gee, mom, none of the other kids are wearing their childproof caps."

Adherence

- Adherence rate ranged between 58 - 73% in a meta analysis of 18 studies on children with epilepsy
- Infants and young children
  - unable to understand their condition, so cannot use reasoning
  - Top Factors affecting adherence In children under the age of 12 years,
    - The taste of the medicine
    - Refusal or inability to swallow it
    - Caregiver's capabilities, disease understanding and beliefs – Forgetting to administer the medicine

Adherence in Adolescence

Non-adherence is a major obstacle in the treatment of adolescents.

- Shift of responsibility from parents
- Not yet able to fully comprehend the consequences of non-adherence
- Tend to take risks and are more impulsive compared to adults
- Social and peer pressures
- Comorbid psychiatric issues such as attention deficit and depression

- What helps?
  - Phone alarms
  - Pill containers – so parents can check if they took it, without it being perceived as nagging
  - Placement of the medication (near their toothbrush!)

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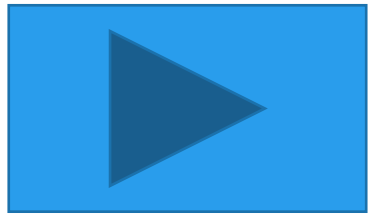
Formulation

- Liquid vs pill preparations
  - Most children do not know how to swallow pills and can only take liquid formulations.
    - With increased dose/age, a large volume in the liquid formulation - children are reluctant to take it
  - Patients with g-tubes typically need alternate forms of medications.
  - No tablet forms = no once daily preparations.
    - For adolescents once daily preparations increase the chance of adherence
  - Bioavailability of liquid formulations is higher and the drug half-life is shorter than the tablet form for some medications
  - Liquid formulation has a more noticeable flavor and taste compared to a tablet swallowed as a whole
    - Can identify the medication even when mixed with juice



Formulation 2 - no liquid form?

- When no easy-to-take formulation is available, parents and caregivers tend to manipulate the drug, even when they are instructed not to
  - Dividing tablets and using them for smaller doses may not be a reliable solution
- Other formulations are available
  - Chewable (carbamazepine, lamotrigine, phenytoin).
  - Sprinkles (valproate and topiramate) can be administered on soft foods which increases their acceptance by children.
    - cannot be used via g-tube.
  - Orally dissolving tablets (lamotrigine and clonazepam)
  - Powder – zonisamide in capsule, vigabatrin in sachet
  - Newer preparations
    - 3-D printed dissolving levetiracetam (Spritam ™)
    - Clobazam in oral film preparation (Sympazam ™)


YOU MEAN TO TELL ME
YOU DON'T GO ANYWHERE
WHEN WE PLAY PEEKABOO?

Side effects

Screening for side effects:

- direct questioning of the patient and caregivers
- physical exam
- blood tests
  - Blood draws from children are harder than from adults and involve significant emotional stress for the child and his parents.
  - Thus, preferring an AED that does not require frequent blood tests is warranted if possible.
- other specific tests for some medications (vision testing, echocardiogram)

Side effects: Weight and growth

- Several AEDs are known to either increase or decrease body weight, neither are desirable in a developing child.
- Valproate, carbamazepine and gabapentin have been associated with weight gain,
- Topiramate, zonisamide, cannabidiol, stiripentol, and fenfluramine are associated with poor appetite and weight loss.
- Valproate may be associated with insulin resistance.
  - high fasting and postprandial insulin levels with normal serum glucose levels

Neurocognitive Effects

The main difference between adults and children is the process of brain development.

- Assessment of neurocognitive effects of a medication on children is challenging
  - Some milestones are not yet reached.
  - Can’t measure the neurocognitive effect of an AED on a specific domain, if the normal developing child is not expected to be capable of performing a specific test.
- The younger the patient is the more vulnerable the brain is
- Prenatal - Pregnancy registries
  - some AEDs are teratogenic and significantly increase the risk for major defects when given to women during pregnancy
  - Anatomical malformations occur mainly due to first trimester exposure,
  - Neurocognitive and behavioral damage occur with third trimester exposure.

Neurocognitive Effects: Clinical trials

- Most studies focus on safety and efficacy of new medications.
- Most studies are several months in length – cannot measure long term cognitive effect.
- Long term neurocognitive effects are hard to study
  - this type of study is costly,
  - It is difficult to track patients over time,
  - continuing seizures may contribute to the poor neurocognitive functions
  - underlying brain disorder or condition causative of the epilepsy may have a role
  - refractory patients often change medications over time

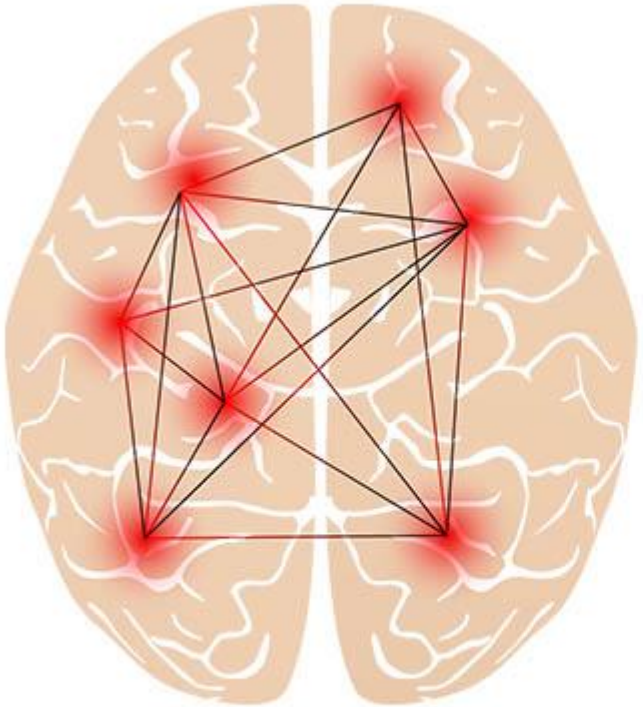
Behavioral effects

- Most common:
  - Hyperactivity
  - Aggression
  - Irritability
  - Slowed down/tired
- Possibly more common in patients who are developmentally disabled

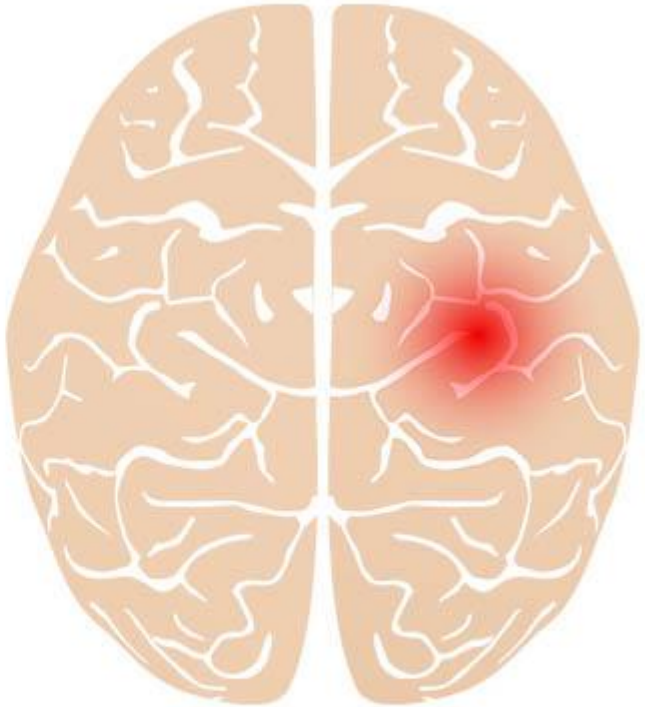
- Psychiatric: Depression/suicidal ideation warning on all ASMs

Is it possible? Yes! But . . .

The vast majority of patients have no behavior effects! The effects are reversible when you stop the medication.



Generalized Seizure



Focal Seizure

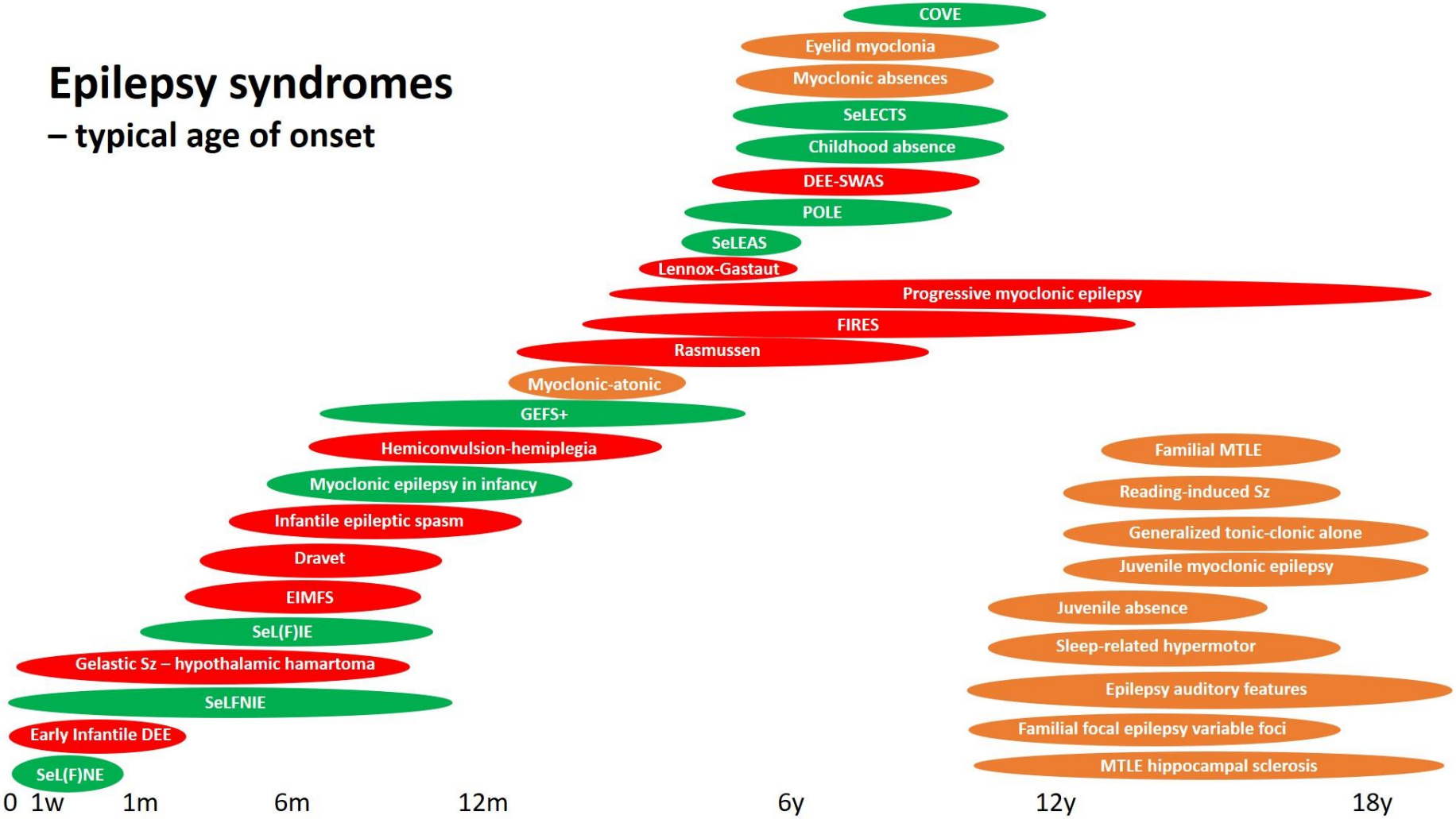
https://magazine.medlineplus.gov/article/understanding-different-kinds-of-seizures

Pediatric epileptic syndromes

- Several epileptic syndromes are unique to the pediatric population; not only do they begin during childhood but mostly spontaneously resolve before adulthood with the exception of a few “juvenile” onset syndromes.

- Tailored treatment or personalized medicine
  - Hope is if we know the genetics → we tailor treatment to the disorder or even the individual
  - However true mutation tailored treatment is not available.
  - There have been attempts at rational treatment based on mechanism,
  - however for most we use emerging clinical guidelines, clinical diagnosis and experience

Epilepsy syndromes
– typical age of onset



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Pediatric epileptic syndromes - neonatal

- Benign Familial Neonatal Epilepsy (BFNE) and Benign Neonatal Epilepsy,
  - No specific data to support one treatment regimen over another in this condition.
- Early Myoclonic Encephalopathy, Early Infantile Epileptic Encephalopathy/Ohtahara syndrome.
  - For Ohtahara Syndrome weak evidence of efficacy (AAN GRADE C) of ACTH, topiramate, other AEDs was cited in the 2015 ILAE Summary of Recommendations for the Management of Infantile Seizures.
- Pyridoxine dependency

Pediatric epileptic syndromes - infants

- Infantile spasms or West syndrome
  - ACTH, other hormonal therapies (synthetic ACTH, prednisolone) and vigabatrin
- Dravet's syndrome = Severe myoclonic epilepsy of infancy (SMEI)
  - Myoclonic seizures and other seizure types over the first year of life and beyond
  - Plus developmental plateau to cognitive decline and ataxia, stooped gait
  - The most beneficial drugs:
    - stiripentol in combination with valproic acid and clobazam
    - cannabidiol
    - Fenfluramine
  - Most patients have a loss-of-function mutation in the SCN1a gene
    - So sodium channel blocker AEDs, such as CBZ, OXC and PHT may aggravate their seizures

Pediatric epileptic syndromes - children

- Childhood Epilepsy with Centro-temporal spikes (CECTS)
- Childhood Absence Epilepsy (CAE)
  - Childhood Absence epilepsy Study - Optimal treatment is ethosuximide → valproate → lamotrigine
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) and Landau-kleffner
  - Treatment regimens
    - typical antiepileptic medications, including valproate, benzodiazepines, ethosuximide and levetiracetam,
    - treatment with high dose benzodiazepines, IVIG and steroids (daily and pulse dose regimens of oral steroids and ACTH),
    - carbamazepine may worsen
    - epilepsy surgery and the ketogenic diet have all been used with some published reports of efficacy.
  - Despite treatments that are showing efficacy overall cognitive outcome is poor even if there is resolution of the ESES and seizure control.

Pediatric epileptic syndromes - Adolescents

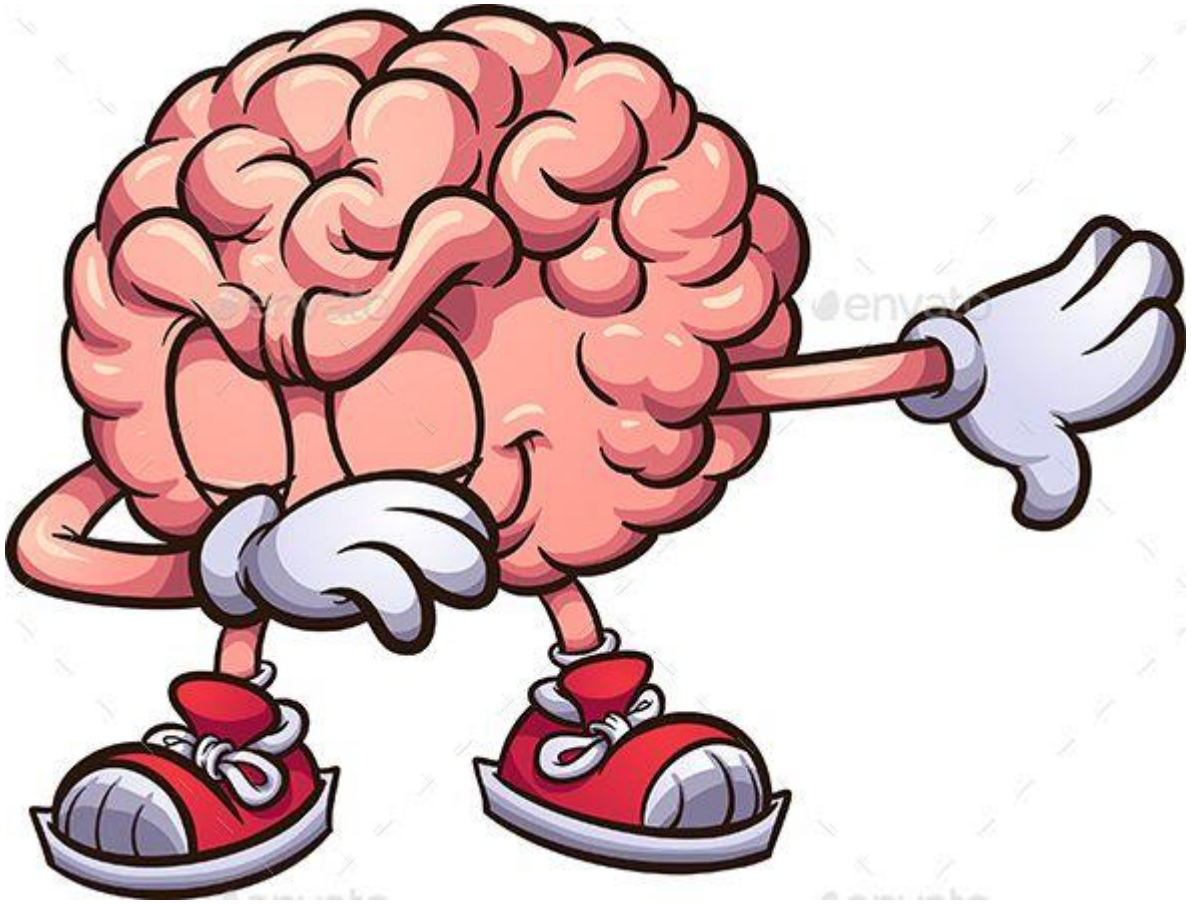
- Generalized epilepsies
  - Juvenile Absence Epilepsy – primary absences
  - Juvenile Myoclonic Epilepsy – myoclonic jerks, absences and convulsions
  - Broad spectrum medications are used for these disorders.
  - Valproic acid is the most effective treatment
  - Levetiracetam is known to treat myoclonic seizures
  - Treatment chosen with the knowledge that these diagnoses will likely be lifelong.
  - Medications for teenage girls should consider that in 10+ years teens be in their childbearing age
    - Meds with a favorable profile in pregnancy should be used first line.
    - However valproic acid should still be considered bearing in mind that low dosages are often very effective

- Overall it is important to classify the patients epilepsy and if features of an age specific epilepsy syndrome are present consider if treatment needs to be tailored to the syndrome.

Summary

- When considering the appropriate anti-epileptic medication for a child with epilepsy take into account:
  - developmental stage,
  - epileptic syndrome,
  - side-effects profile,
  - patient's ability to adhere to the therapeutic regimen,
  - drug formulation,
  - scientific evidence of efficacy and safety
  - And parents' and patient's views and beliefs.
- Despite the challenges of research in this age group, further research is required to better characterize the efficacy, safety and long-term effects of anti-epileptic drugs in children.

Thank you!



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Chloride and GABA in the newborn brain

- Brain pathophysiology changes - Voltage and transmitter-gated ionic currents follow a developmental sequence and the response to endogenous and exogenous molecules changes.
  - The high intracellular Cl^- concentration in immature neurons
    - high level of expression of sodium chloride and sodium potassium chloride cotransporters (NCCs and NKCCs)
    - low level of potassium chloride cotransporters (KCCs)
  - This could mean low efficacy of antiepileptic drugs in neonatal seizures .

- γ-amino-butyric acid (GABA)
  - In the adult, GABA is inhibitory
    - Causes hyperpolarization via chloride influx.
  - In immature neurons, GABA is excitatory
    - When GABA binds it opens the Cl^- channel,
      - Cl^- flux is outward, leading to depolarization
    - Phenobarbital - binds to $GABA_A$ receptors, opens the Cl- channel,
  - GABA receptors, such as benzodiazepines and barbiturates have low efficacy rates in neonates

- Bumetanide - loop-diuretic, NKCC1 inhibitor
  - Phenobarbital in combination with bumetanide suppressed ictal activity in hippocampal preparation model better than phenobarbital alone.
  - the current clinical data does not support this theory

Examples/applications of pharmacokinetics 1 Absorption and Distribution

- Decreased absorption leads to decreased the bioavailability
  - Incomplete maturation of gastric acid secretion in the first 2 weeks of life
  - Reduces elemental absorption of phenobarbital in this age group
  - May need an increase in total dose when switching from intravenous to oral administration
- Volume of distribution in neonates and infants
  - Increased total body water–to–body fat ratio and decreased plasma-binding proteins
  - Leading to larger loading doses in young infants compared to older children (phenobarbital and phenytoin).
- Decreased plasma-binding proteins in neonates
  - measuring total concentrations of the drug in the serum is not a reliable method for therapeutic drug monitoring since
  - Will underestimate the unbound or active concentration of the AEDs
  - Affects the highly protein-bound AEDs, like phenytoin and valproic acid

Examples/applications of pharmacokinetics 3 Multifactorial

- Physiology of Phenytoin
  - levels in newborn infants are often difficult to maintain
    - May never achieve a level despite repeated loading and maintenance doses
  - Clearance (per kilogram body weight) and bioavailability are low
  - half-life is longer in premature newborns compared to those born at term
- Topiramate side effects of hypohidrosis and hyperthermia
  - Much higher in children
  - Symptoms - facial flushing, lethargy, itching sensation, irritability, hyperthermia or heat intolerance
  - occur in up to third of the patients
  - Mechanism is unclear – smaller blood volume relative to body surface area, greater surface to mass ratio and reduced sweating rate in children

Neurocognitive Effects: examples

- Phenobarbital
  - Early exposure to phenobarbital may temporarily lower the global IQ scores of children during treatment
  - When tested years after drug discontinuation, those who were treated with PB, despite similar IQ, scored lower on reading achievement as well as on memory and comprehension tests compared to those who received placebo.
  - Other studies, found no change in global IQ after 12 months of PB treatment,
  - Phenobarbital may also affect verbal skills
- Phenytoin
  - some evidence of slowing of information processing, was found when comp, but not phenytoin or valproate, negatively affected memory (Forsythe).
- Ethosuximide
  - very little information about cognitive or behavioral effects
  - Childhood Absence epilepsy study - When compared to VPA and LTG, it had neutral effect on attention
- Valproate
  - Conflicting data.
  - Childhood Absence Epilepsy study showed decreased attention
  - Better cognitive function and behavior when compared to PB

Neurocognitive Effects: examples 2

- Hope with new AEDs?
  - some with less drug-drug interaction and larger safety profile compared to the first and second generation AEDs,
  - Review of the literature by Moavero et al found that drug-related cognitive and behavioral adverse events were common even in the second and third generation AEDs, including attention problems, cognitive function, aggressiveness and mood changes
- Levetiracetam
  - Children with new focal epilepsy treated with LVT or CBZ
  - all underwent neuropsychological evaluations before and after treatment.
  - No significant change was noted in their neuropsychological tests
- Lamotrigine
  - newly diagnosed epilepsy were prescribed either lamotrigine or carbamazepine and their cognitive function was re-evaluated after 24 weeks of treatment.
  - There were no statistically significant differences in the intelligence of the two groups during treatment, but better attention was noted in the CBZ group .
- Topiramate
  - childhood epilepsy with centrotemporal spikes – compared TPM vs CBZ.
    - large neuropsychological battery – 2 with differences - arithmetic test - decreased in the TPM group, maze test - more improvement for CBZ group
  - Childhood epilepsy with centrotemporal spikes, compared TMP, OXC, and LMT
    - deterioration of some language skills was apparent only in those who were treated with TPM
  - Evidence of TMP interference in frontal and parietal lobes functions, and especially language tasks in functional MRI in adults - further investigation is needed in children.
- Eliscarbazepine
  - No different effect on attention and working memory when compared to placebo
- Perampanel
  - No effect on CBCL scores and executive functions in adolescents with focal resistant epilepsy