New Medications in the Treatment of Pediatric Seizure Disorders

Requirements for Successful Completion:

The registered nurse in the school setting should self-report the ability to define types of pediatric seizure disorders, the pharmacology of Epidiolex® and Nayzilam® for the treatment of pediatric seizure disorders, be able to discuss considerations in regards to administration and storage of Epidiolex® and Nayzilam® and compare Epidiolex® to commercial cannabidiol (CBD) products.

To receive contact hours for this continuing education activity, the participant must attend the entire activity and complete and submit the evaluation form.

Once successful completion has been verified, a “Certificate of Successful Completion” will be awarded for 1.0 contact hours.

Conflicts of Interest:

The activity’s Nurse Planner has determined that no one who has the ability to control the content of this CNE activity – planning committee members and presenters/authors/content reviewers – has a conflict of interest.

Approval Statement:

The University of Texas at Austin School of Nursing is an approved provider of continuing nursing education by the Texas Nurses Association - Approver, an accredited approver with distinction by the American Nurses Credentialing Center’s Commission on Accreditation.

New Medications in the Treatment of Pediatric Seizure Disorders

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Objectives

- Define types of pediatric seizure disorders
- Review pharmacology of Epidiolex® and Nayzilam® for the treatment of pediatric seizure disorders
- Discuss considerations in regards to administration and storage of Epidiolex® and Nayzilam®
- Compare Epidiolex® to commercial cannabidiol (CBD) products

Disclosures

- No financial conflicts of interest
- There will be discussion of non-FDA approved drugs and non-FDA approved indications

Background

Terminology

- Seizure
  - Sudden, uncontrolled electrical disturbance in the brain
  - Many etiologies
- Epilepsy
  - Occurrence of at least two unprovoked seizures separated by 24 hours
  - A single seizure does not equal a diagnosis of epilepsy
- Epilepsy Syndrome
  - Group of features that usually occur together
  - May include seizure pattern, typical age of onset, brain anatomy, course of illness, genetic components
  - Helps guide treatment choices and expectations
- Seizure Clusters
  - Seizures of any type that occur in groups over hours or days
  - Can be treated outside a hospital if recognized early
- Status Epilepticus
  - A state of prolonged seizure
  - Generally lasting >10 minutes

Rogers S, Cavazos J. Chapter 40. Epilepsy. In: DiPiro J, et al. Pharmacotherapy: A Pathophysiologic Approach, 9e; 2014.

Epidemiology

- 8% lifetime prevalence of a single seizure
- 23-80% chance of a recurrent, unprovoked seizure within first 5 years
- 30% of new epilepsy diagnoses occur in those <18 years of age
- Bimodal distribution of first seizure occurrence
  - Newborn and young children
  - Older adults >65 years of age

Rogers S, Cavazos J. Chapter 40. Epilepsy. In: DiPiro J, et al. Pharmacotherapy: A Pathophysiologic Approach, 9e; 2014.

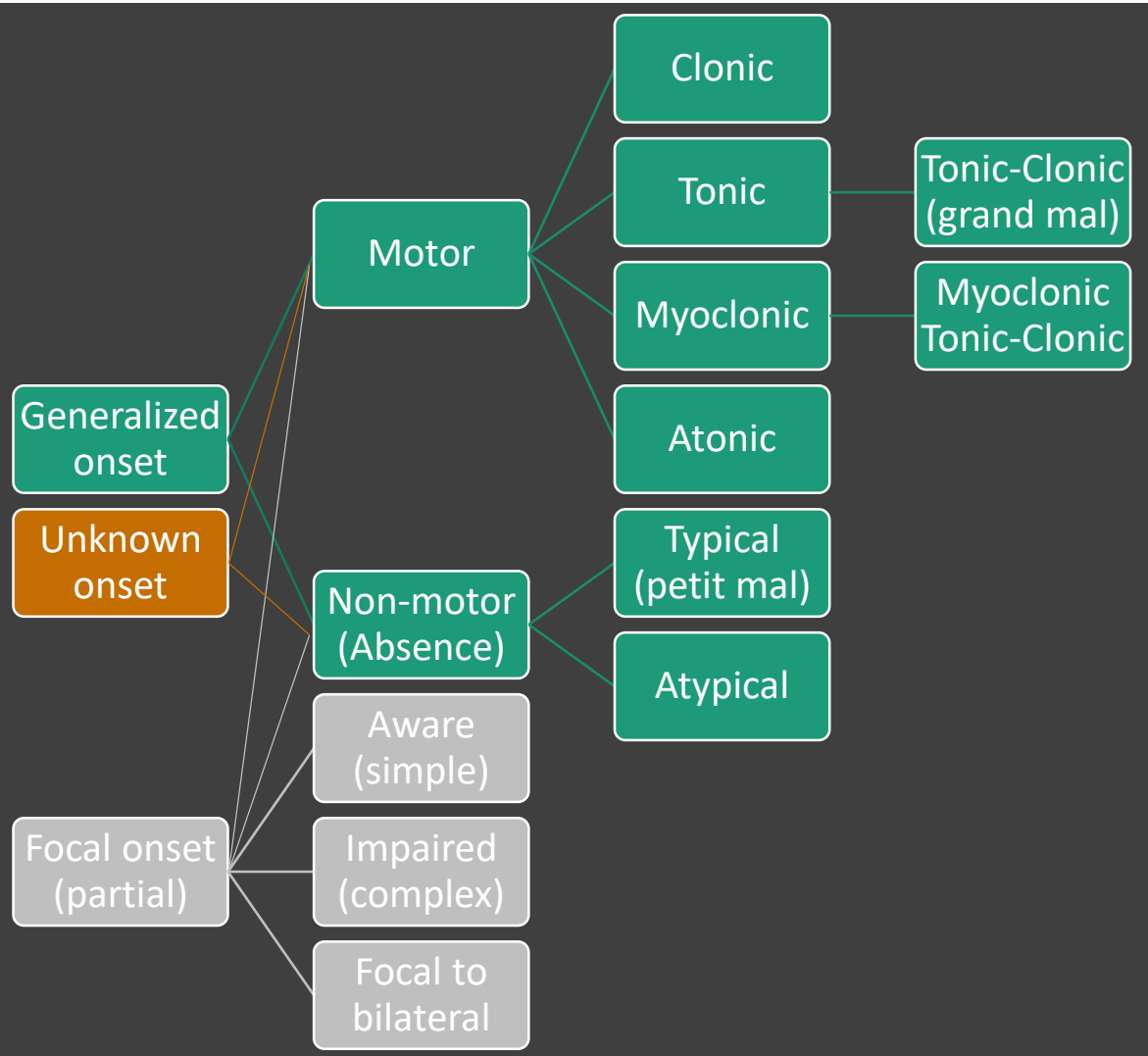
Pathophysiology

- Cortical neurons discharge abnormally
  - Changes in ion channels in neuronal membranes
  - Modifications of receptors
  - Impaired second messenger systems
  - Changes in extracellular ion concentrations
  - Imbalance of excitatory and inhibitory pathways
  - Alterations in neurotransmitter landscape
    - Glutamate (excitatory)
    - GABA (inhibitory)
    - Acetylcholine, norepinephrine, and serotonin
- Triggers hyperexcitability and/or disordered inhibition
- Excess excitability spreads locally (focal) or widely (generalized) resulting in a seizure

Rogers S, Cavazos J. Chapter 40. Epilepsy. In: DiPiro J, et al. Pharmacotherapy: A Pathophysiologic Approach, 9e; 2014.
Photo: https://epilepsyu.com/toward-quieting-the-brain-promising-anti-seizure-strategies/

Seizure Classification

- Seizure classification modified in 2017
- Seizures will fist be classified according to where they *start* in the brain
  - Unilateral (focal)
  - Bilateral (generalized)
- +/- Motor symptoms
  - Physical movement
  - Autonomic/behavioral
- +/- Change in awareness
  - Foal seizures only
  - *All* generalized seizures affect awareness



Fisher R. Curr Neurol Neurosci Rep. 2017;17(6):48.
Kiriakooulos, E. Types of seizures. Epilepsy Foundation website. March 20, 2017.

Epilepsy Syndromes

- Angelman Syndrome
- Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)
- Benign Rolandic Epilepsy
- CDKL5
- Childhood Absence Epilepsy
- Doose Syndrome
- **Dravet Syndrome (DS)**
- Early Myoclonic Encephalopathy (EME)
- Jeavons Syndrome
- Frontal Lobe Epilepsy
- Juvenile Myoclonic Epilepsy
- Landau-Kleffner Syndrome
- **Lennox-Gastaut Syndrome (LGS)**
- Rasmussen's Syndrome
- Ring Chromosome 20 Syndrome
- Sunflower Syndrome
- Temporal Lobe Epilepsy

Dravet Syndrome

- Onset before 12 months of age
- Frequent and prolonged seizures
- Normal development before onset
- Neurodevelopmental impairments occur later
- EEG and imaging typically normal
- SCN1A mutation present in 85% of cases

Lennox-Gastaust Syndrome

- Onset between 3 and 7 years of age
- Often continues through adulthood
- Multiple seizure types present
- Developmental delay common
- Characteristic EEG pattern
- No clear biological marker

Cross, J, et al. Front Neurol. 2017; 8: 505. Yvonne, W, et al. Pediatrics. 2015; 136(5): e1310–e1315.
Devinsky, et al. Epilepsia. 2014; 55(6): 791-802. Holmes, G. Types of epilepsy syndromes. Epilepsy Foundation website. September 3, 2013.

Medication Treatment

Treatment Approach

- Goal is complete elimination of seizures
- Treatment with an antiepileptic drug (AED) is not always warranted
  - For early-onset and severe epilepsy syndromes, early treatment is crucial
- Seizure type should drive initial medication choice
- When choosing an AED:
  - Monotherapy preferred
  - Combination therapy should use drugs from different classes
  - Side effect profile and quality of life must be considered
- Well-controlled does not always equal seizure-free
- Duration of therapy can be short-term or life-long

Rogers S, Cavazos J. Chapter 40. Epilepsy. In: DiPiro J, et al. Pharmacotherapy: A Pathophysiologic Approach, 9e; 2014.

AED Medication Classes*

- Barbiturates
  - Phenobarbital
  - Primidone
- Benzodiazepines
  - Clobazam
  - Diazepam
  - Lorazepam
  - Midazolam
- Calcium Channel Modulator
  - Gabapentin
  - Pregabalin
  - Levetiracetam
  - Zonisamide
- Cannabinoids
  - Cannabidiol (CBD)
- GABA Modulators
  - Tiagabine
  - Vigabatrin
- Glutamate Antagonist
  - Perampanel
- Sodium Channel Modulator
  - Carbamazepine
  - Divalproex/Valproic Acid
  - Lamotrigine
  - Lacosamide
  - Oxcarbazepine
  - Topiramate
- Succinimide
  - Ethosuximide
- Misc
  - Brivaracetam
  - Felbamate
  - Phenytoin

**Many AEDs have multiple mechanisms of actions or mechanism of action is not fully elucidated, making classification challenging*

Rogers S, Cavazos J. Chapter 40. Epilepsy. In: DiPiro J, et al. Pharmacotherapy: A Pathophysiologic Approach, 9e; 2014.

New Treatment Options

Epidiolex® (cannabidiol, CBD)

- FDA approved June 2018
- Schedule V drug
- Labeled indication:
  - Seizures associated with LGS or DS syndrome
  - Patients ≥2 years of age
- Off-label uses:
  - Refractory epilepsy (ongoing studies)

- Mechanism of action:
  - Weak antagonism at CB1 and CB2 receptors
  - Modulates intracellular calcium
    - Activates transient receptor potentials (TRPA1, TRPV1)
    - Enhances glycine receptors
  - Anti-inflammatory properties
    - Modulates TNFa and adenosine reuptake
  - → ***reduces neuronal excitability and neuronal transmission***
  - → ***anti-inflammatory effects may reduce likelihood of seizure development***

EPIDIOLEX® [pakacge insert]. Carlsbad, CA: Greenwich Biosciences; 2018. Sekar, K. Version 1. F1000Res. 2019; 8: F1000 Faculty Rev-234.
Devinsky O, et al. Epilepsia. 2014;55(66): 791-802. Photo: https://www.epidiolex.com/

Epidiolex® cont.

Usual dose:	• Initial: 2.5 mg/kg twice daily (5 mg/kg/day) • After one week: 5 mg/kg twice daily (10 mg/kg/day)
Max dose:	• 10 mg/kg twice daily (20 mg/kg/day)
Dose adjustments:	• Reduced dose recommended for hepatic impairment • If discontinuation is required, taper dose slowly
Adverse events:	• Common: somnolence, decreased appetite, diarrhea, transaminase elevation, fatigue, rash • Serious: suicidal ideation/behavior
How supplied:	• 100 mg/mL oral solution (100 mL bottle) • Clear, colorless to yellow • Strawberry flavor • Contains dehydrated alcohol, sesame seed oil, and sucralose
Storage:	• Room temperature • Discard unused solution after 12 weeks
Administration:	• Oral administration only • Supplied with bottle adapter and calibrated syringe

EPIDIOLEX® [pakacge insert]. Carlsbad, CA: Greenwich Biosciences; 2018. White, C. J Clin Pharmacol. 2019 Jul;59(7):923-934.
Photo: https://www.epidiolex.com/

Epidiolex® cont.

- Pharmacokinetic Considerations
  - Oral absorption is erratic
    - Varies intra- and inter-individually
    - Time to peak ranges 1-5 hours
  - Metabolized by the liver
    - CYP2C19, CYP3A4, and UGT
    - Concentration reduced by carbamazepine and phenytoin
  - Inhibits CYP2C19
    - Increases concentration of clobazam
  - Half life of 56-61 hours
  - Max concentration increased by high fat/high calorie meals
  - May take several weeks for full effect

EPIDIOLEX® [pakacge insert]. Carlsbad, CA: Greenwich Biosciences; 2018. White, C. J Clin Pharmacol. 2019 Jul;59(7):923-934.
Rong C, et al. Expert Opin Drug Saf. 2018;17(1):51-54. Photo: https://www.epidiolex.com/

Nayzilam® (midazolam)

- FDA approved
- Schedule IV drug
- Labeled indication:
  - Seizure clusters/acute repetitive seizures
  - Patients ≥12 years of age
- Off-label uses:
  - Status epilepticus

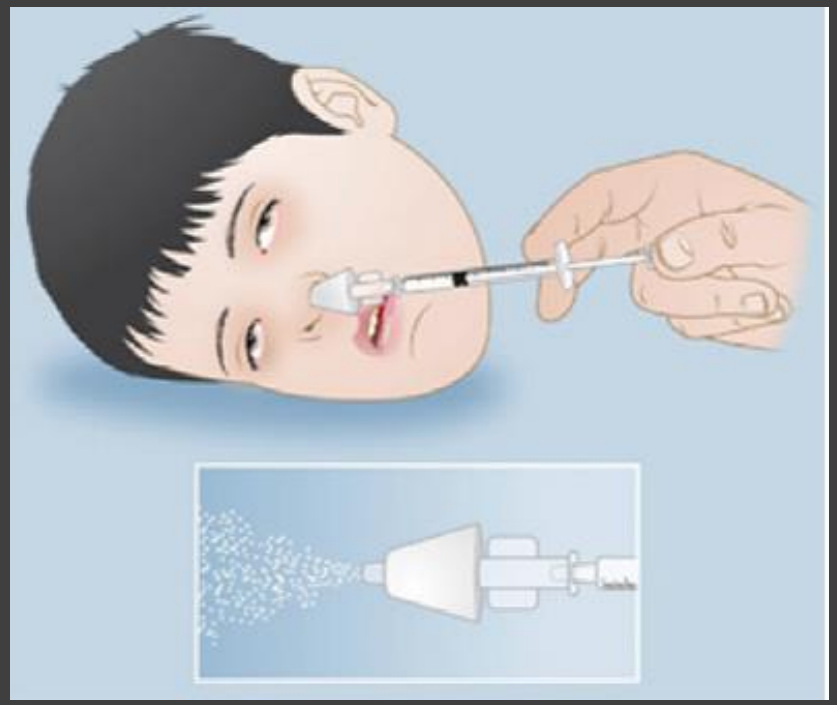
- Mechanism of action:
  - Binds to benzodiazepine site at $GABA_A$ receptor
  - Potentiates GABAergic transmission
  - ***→ reduces neuronal excitability and neuronal transmission***

NAYZILAM® [pakacge insert]. Smyrna, GA: UCB Biopharma; 2019. Smith, R. Aust Prescr. 2017 Feb; 40(1): 23–25.
Photo: https://www.ucb-usa.com/

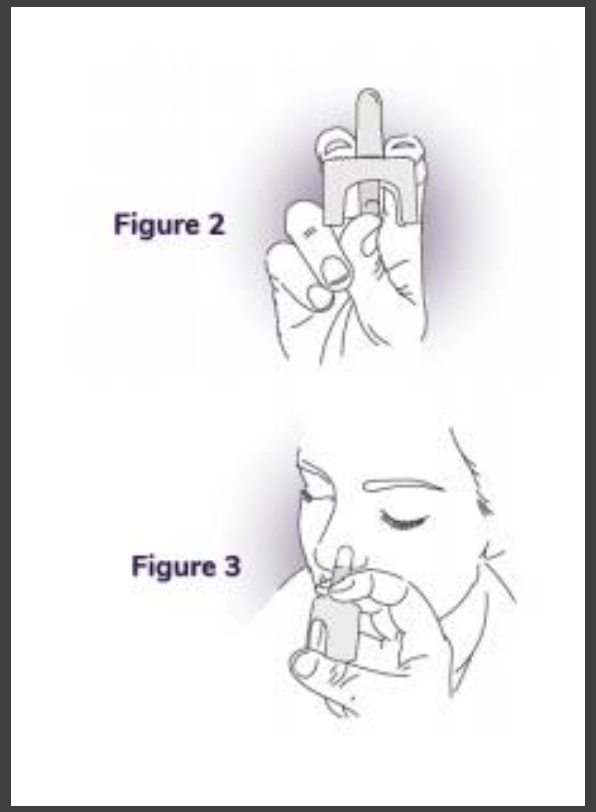
Nayzilam® (midazolam)

Nayzilam® IV (midazolam) nasal spray

Intranasal midazolam



Nayzilam®



NAYZILAM® [pakacge insert]. Smyrna, GA: UCB Biopharma; 2019.
Photo: https://www.ucb-usa.com/

Nayzilam® cont.

Nayzilam® IV (midazolam) nasal spray

Usual dose:	• Initial: 5 mg into one nostril • Second dose: May repeat one additional spray into **opposite nostril** after 10 minutes
Max dose:	• Do not use more than 10 mg to treat a seizure cluster • Not recommended to use more than every 3 days, or more than 5 episodes/month
Dose adjustments:	• Renal impairment may prolong exposure (no adjustment recommended)
Adverse events:	• Common: somnolence, headache, dysarthria, nasal discomfort, throat irritation, rhinorrhea • Serious: respiratory depression, suicidal ideation/behavior, increased intraocular pressure
How supplied:	• 5 mg/0.1 mL solution • Single-dose nasal spray unit • Clear, colorless to yellow
Storage:	• Room temperature • Do not open blister package until ready to use
Administration:	• Does NOT need to be primed • Patient does not need to be breathing deeply for dose to be effective • Do NOT administer second dose if concerned for respiratory depression/excessive sedation • Try to document time of initial and repeated dose

NAYZILAM® [pakacge insert]. Smyrna, GA: UCB Biopharma; 2019. Smith, R. Aust Prescr. 2017 Feb; 40(1): 23–25.
Photo: https://www.ucb-usa.com/

Nayzilam® cont.

Nayzilam® IV (midazolam) nasal spray

- Pharmacokinetic Considerations
  - Rapidly absorbed
  - Seizure arrest typically within 10 minutes
  - Metabolized by the liver
    - CYP3A4
    - Concentration increased by CYP3A4 inhibitors
      - Antivirals (protease inhibitors)
      - Antiarrhythmics (CCBs and amiodarone)
      - Antibiotics (macrolides)
  - Half life of 2-6 hours
    - May be greater in obese patients and those with renal impairment

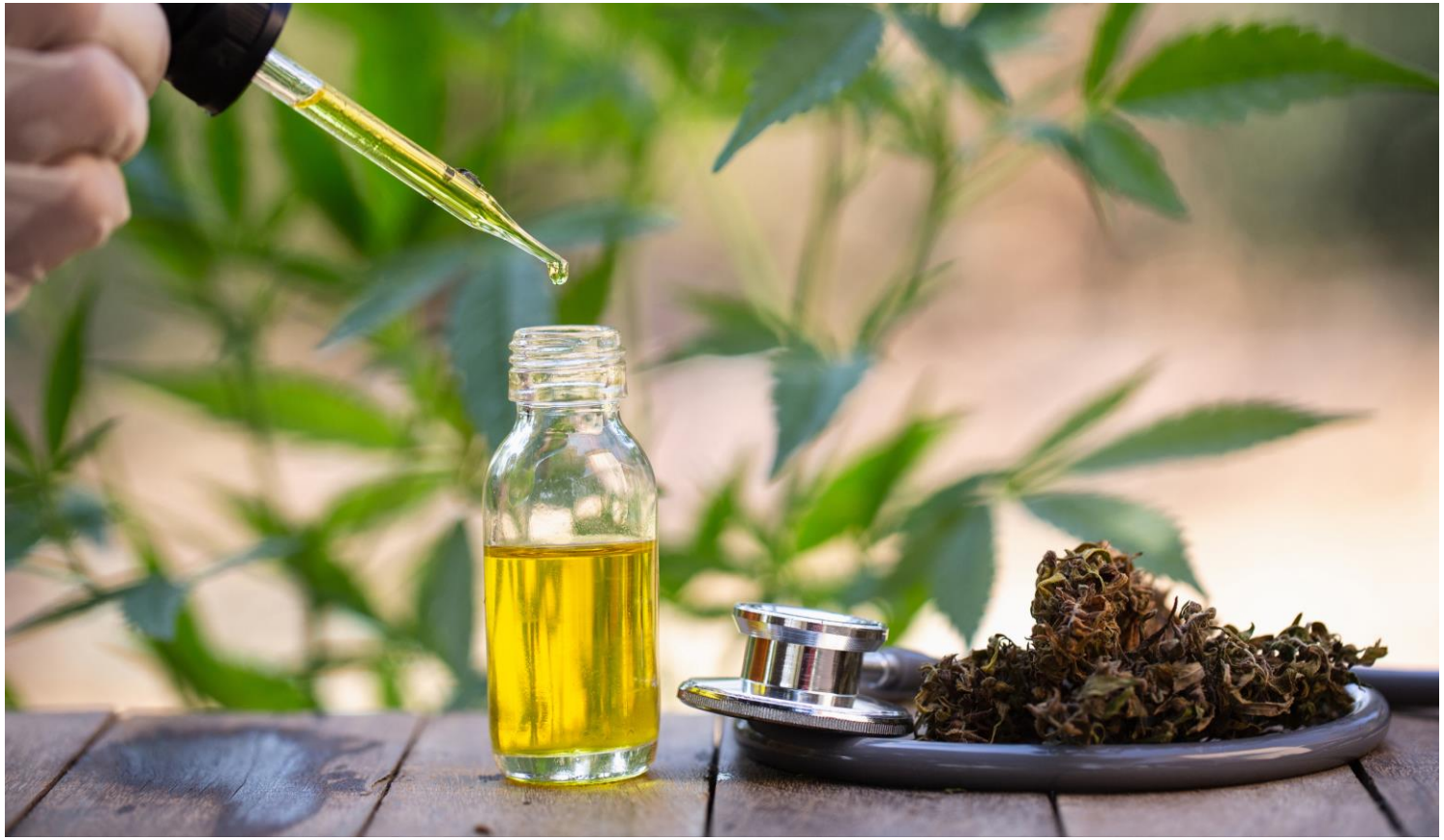
NAYZILAM® [pakacge insert]. Smyrna, GA: UCB Biopharma; 2019.
Photo: https://www.ucb-usa.com/

Case Study

MJ is a 7 y/o male with LGS who has poor seizure control on Depakote ER® (valproic acid) and Onfi® (clobazam). His parents have implemented a ketogenic diet, but this has not changed his seizure frequency. Today his parents bring a new prescription for Epidiolex® with a prescribed dose of 50 mg by mouth every 12 hours (8am and 8pm). They tell you his neurologist just added this medication to his current regimen to help improve seizure control. MJ weighs 20 kg and has NKDA.

- Is this an appropriate initial dose? How many mL should MJ receive?
- What concerns or questions might you have?
- What side effects should you monitor him for?

Photo: https://www.cnbc.com/2018/09/27/dea-schedules-epidiolex-allowing-gw-pharma-to-start-selling-the-drug.html



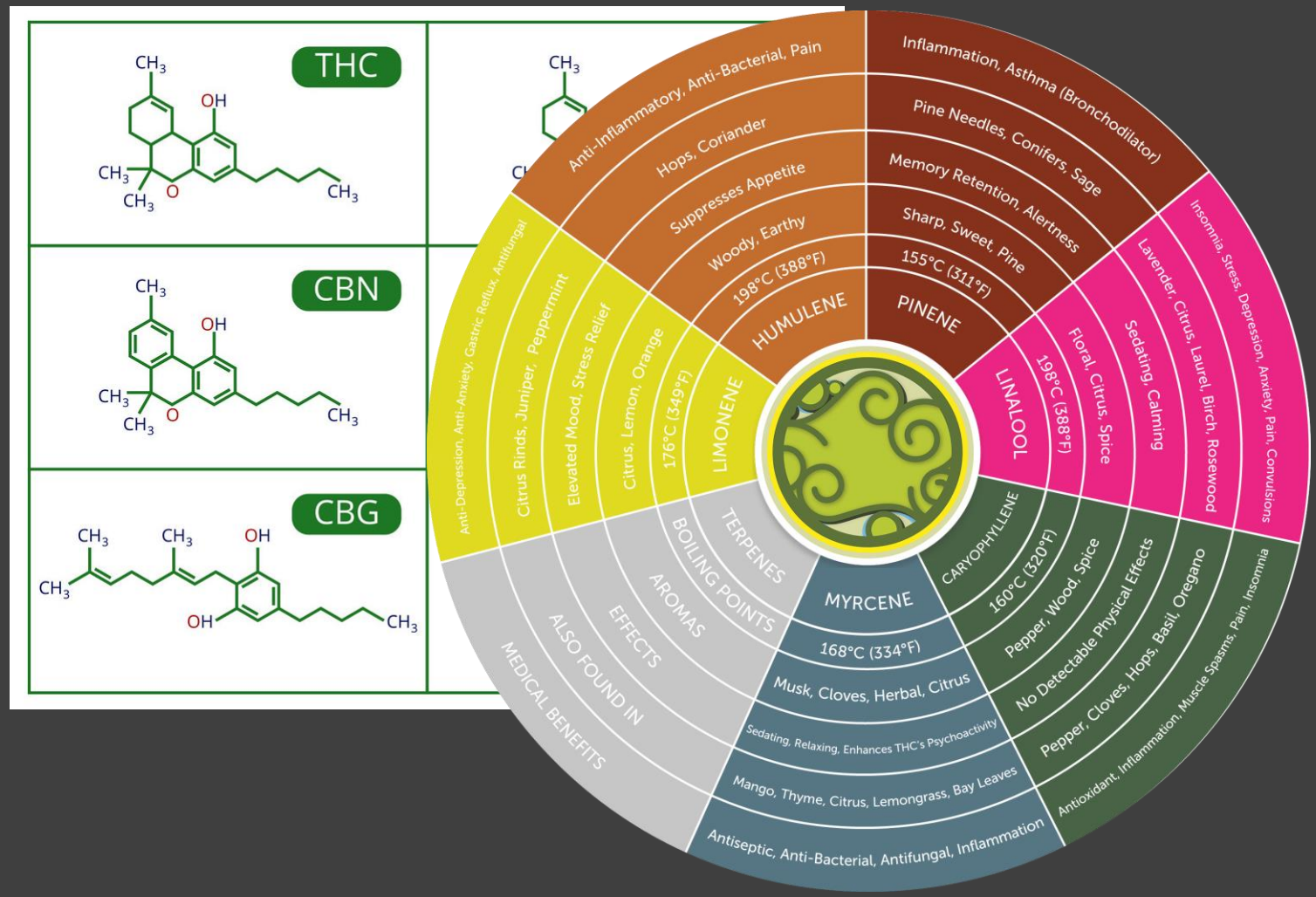
The Burning Question

- Where do commercial CBD products fit in therapy?
- What legal regulations exist for commercial CBD products?
- What pharmacological considerations exist?

Photo: https://time.com/5516745/cbd-oil-legal-healthy/

Brief Background

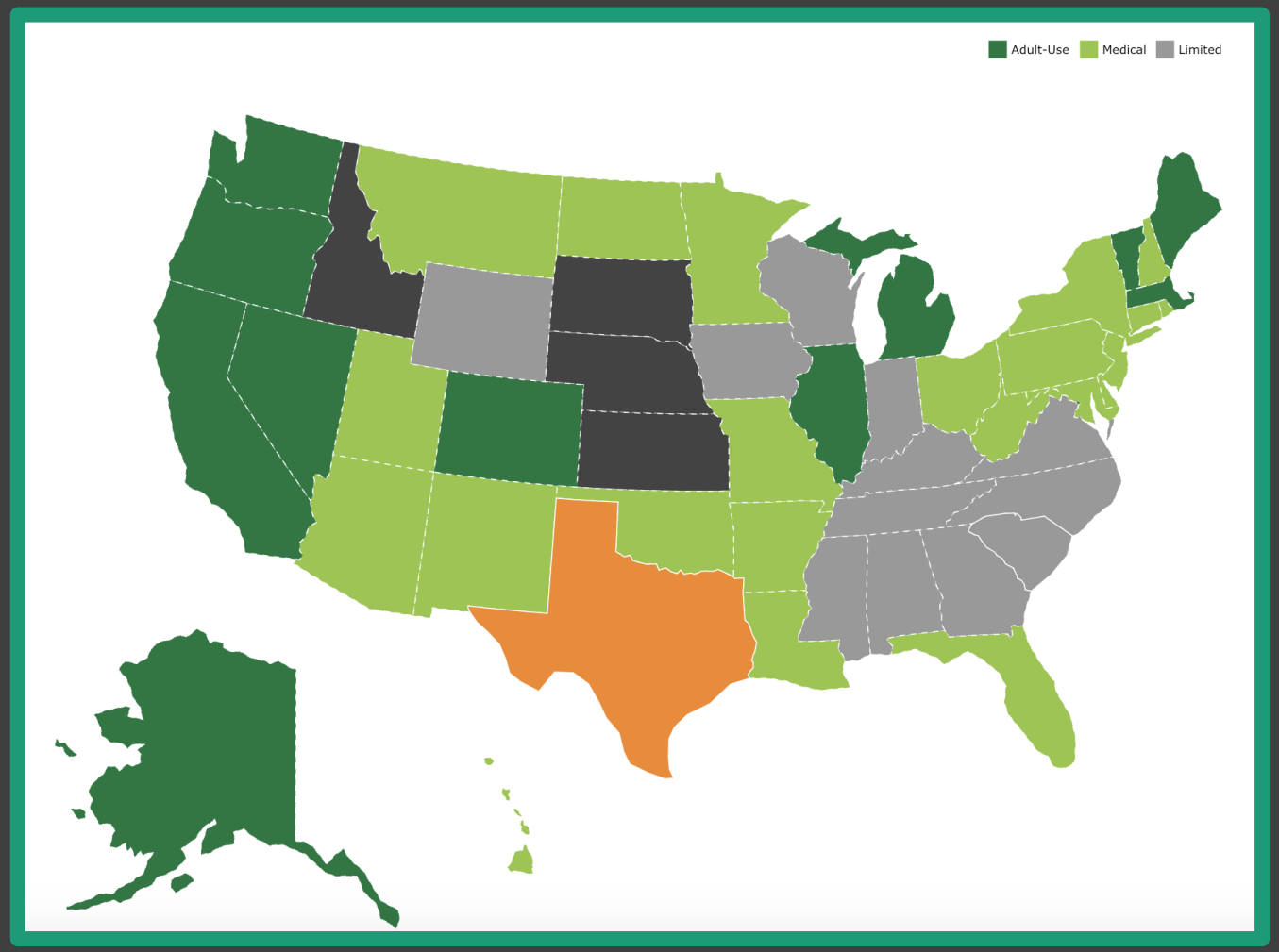
- *Cannabis sativa* L.
  - >400 chemical constituents
  - >80 cannabinoid compounds
    - Δ^9-tetrahydrocannabinol (THC)
    - **Cannabidiol (CBD)**
  - Terpenes
  - Flavonoids
- Medicinal Cannabis
- CBD oil
  - Full spectrum
  - “Pure”



White, C. J Clin Pharmacol. 2019 Jul;59(7):923-934.
NCSBN National Nursing Guidelines for Medical Marijuana (www.ncsbn.org)

Legal Status of Cannabis/CBD

- Federally illegal
  - Schedule I drug
  - Theoretically could be prosecuted
- State laws vary dramatically
  - 11 states + D.C. fully legal
  - 22 states allow medical use
  - 13 states allow limited medical use (CBD oil)
  - 4 states fully prohibited
- 2018 Farm Bill
- **TEXAS**
  - 2019: House Bill 1325



Texas Legislature Online (https://capitol.texas.gov/)
Regulations.gov (www.regulations.gov/)
Photo: https://thecannabisindustry.org/ncia-news-resources/state-by-state-policies/

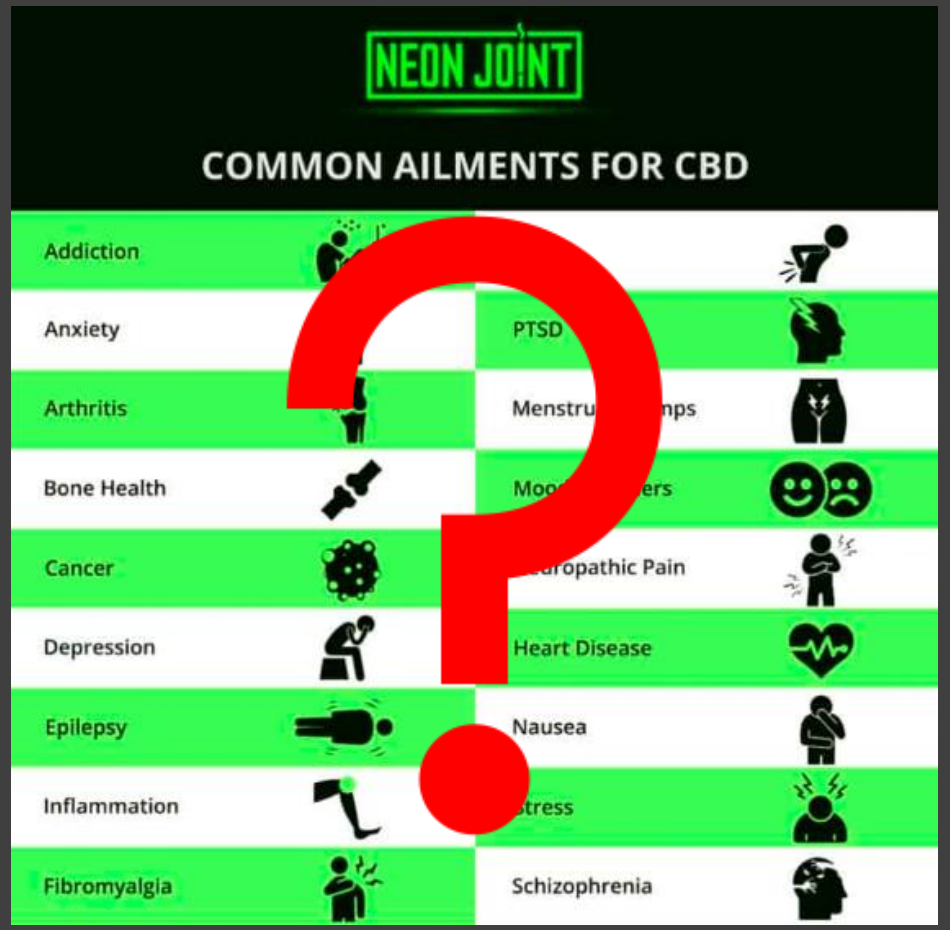
Quality Control of CBD products

- Non-FDA approved products vary in concentration and labeled ingredients
  - 2016 audit of 84 CBD products from 31 companies
    - **31% were correctly labeled**
    - 43% under-labeled
    - 26% over-labeled
    - 21% of samples contained unlabeled THC
    - Oil-based products were more likely to be labeled correctly versus tinctures or vapors
- Contamination poses a risk
  - 2016
    - Analysis of 29 CBD oil products
    - 69% found to have excessive levels of polycyclic aromatic hydrocarbons
  - 2017
    - CBD products contaminated with synthetic cannabinoid
    - 52 people harmed

Hazekamp A. Med Cannabis Cannabinoids. 2018;1:65-72.
White, C. J Clin Pharmacol. 2019 Jul;59(7):923-934.

Evidence for Commercial CBD products

- Research is lacking
  - Limited human studies
  - Quality of existing studies varies
  - Details of CBD products not always specified
- Potential uses:
  - Acute/performance based anxiety*
  - Pain/spasticity
  - Seizure disorders*
  - Schizophrenia and psychosis*



White, C. J Clin Pharmacol. 2019 Jul;59(7):923-934.
NCSBN National Nursing Guidelines for Medical Marijuana (www.ncsbn.org)
Photo: https://neonjoint.com/cbd/cbd-oil/

**Stronger evidence for use versus other indications*

Considerations for Patients and Caregivers

- Be aware of possible discrepancies in labeled dosage and ingredients
- Use the same manufacturer and product when possible
- Given lack of evidence, administration and storage of commercial CBD products should follow Epidiolex® labeling
- Patients should discuss CBD products with their healthcare provider
  - Risk for drug interactions and adverse effects
  - Potential impact on disease states

NCSBN National Nursing Guidelines for Medical Marijuana (www.ncsbn.org)
Hazekamp A. Med Cannabis Cannabinoids. 2018;1:65-72.

Photo: https://nuleafnaturals.com/product/1450mg-full-spectrum-cbd-oil-high-grade-hemp-extract/

Case Study cont.

Over a period of two months, MJ's dose of Epidiolex® is titrated to 200 mg every 12 hours. He is tolerating the medication well, with the exception of some mild somnolence a couple hours after his morning dose (although this has improved since his Onfi® dose was reduced last month). Today, MJ's parents drop off medication refills for the month. You notice that his CBD oil is not in the usual Epidiolex® bottle.

- What concerns or questions would you have?
- What are possible risks of using commercial CBD products?

Clinical Pearls

- Nayzilam® is a rescue medication for seizure clusters and should not be used as routine treatment for seizures
- Epidiolex® is a maintenance medication for rare epilepsy syndromes and may take time for full therapeutic effect
- Commercial CBD products are not interchangeable with Epidiolex®
- All CBD products should be administered with consistency in regards to route, food intake, and timing