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# Global Perspectives on Diagnosis and Management of Childhood Epilepsy Disorders: Focus on Dravet, Lennox-Gastaut, and Tuberous Sclerosis Complex

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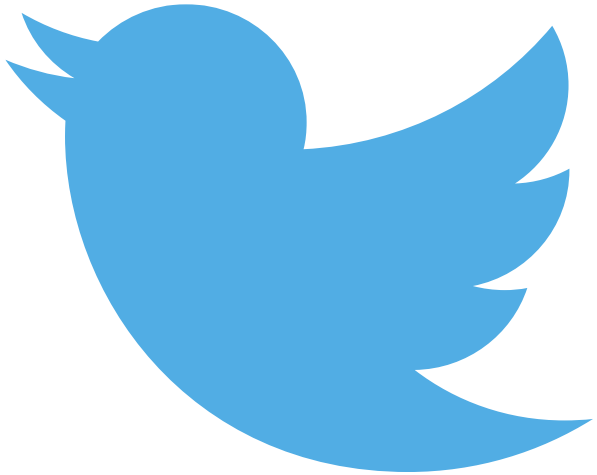

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# Elaine C. Wirrell, MD, FAAN, FRCPC

Chair and Professor of Child Neurology
Program Director of Child and Adolescent Neurology
Mayo Clinic
Rochester, MN

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# Tracy Dixon-Salazar, PhD

Executive Director,
Lennox-Gastaut Syndrome (LGS) Foundation
San Diego, CA

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# D. Samba Reddy, PhD, RPh, FAAAS, FAAPS, FAES

Regents Professor, Neuroscience and Experimental Therapeutics
Director, Institute of Pharmacology and Neurotherapeutics
Professor, Engineering Medicine, Biomedical Engineering
Texas A&M University School of Medicine
Bryan, TX

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# Adam Strzelczyk, MD, MHBA

Consultant Neurologist and Intensivist
Epilepsy Center Frankfurt Rhine-Main
Department of Neurology
Goethe-University Frankfurt and University Hospital Frankfurt
Frankfurt am Main, Germany

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# Bethany Thomas, DNP

Epilepsy Nurse Practitioner
Neurology NP Clinical Coordinator
Penn Medicine, Neurology Department
Philadelphia, PA

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# Learning Objective 1

Utilize appropriate investigations to achieve early and accurate diagnosis of early-onset seizure disorders, including LGS, DS, and TSC.

# DE, EE, or DEE?

## Developmental Encephalopathy (DE):

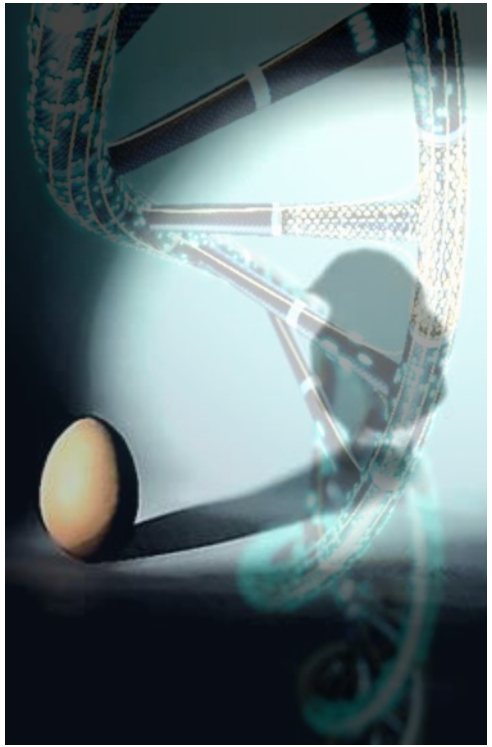
- Developmental impairments due to underlying cause of the epilepsy
- Epilepsy itself does **not** contribute to impairments

## Epileptic Encephalopathy (EE):

- Cognitive and/or behavioral impairments directly caused by frequent seizures or epileptiform discharges
- Impairments **not** present prior to epileptic onset

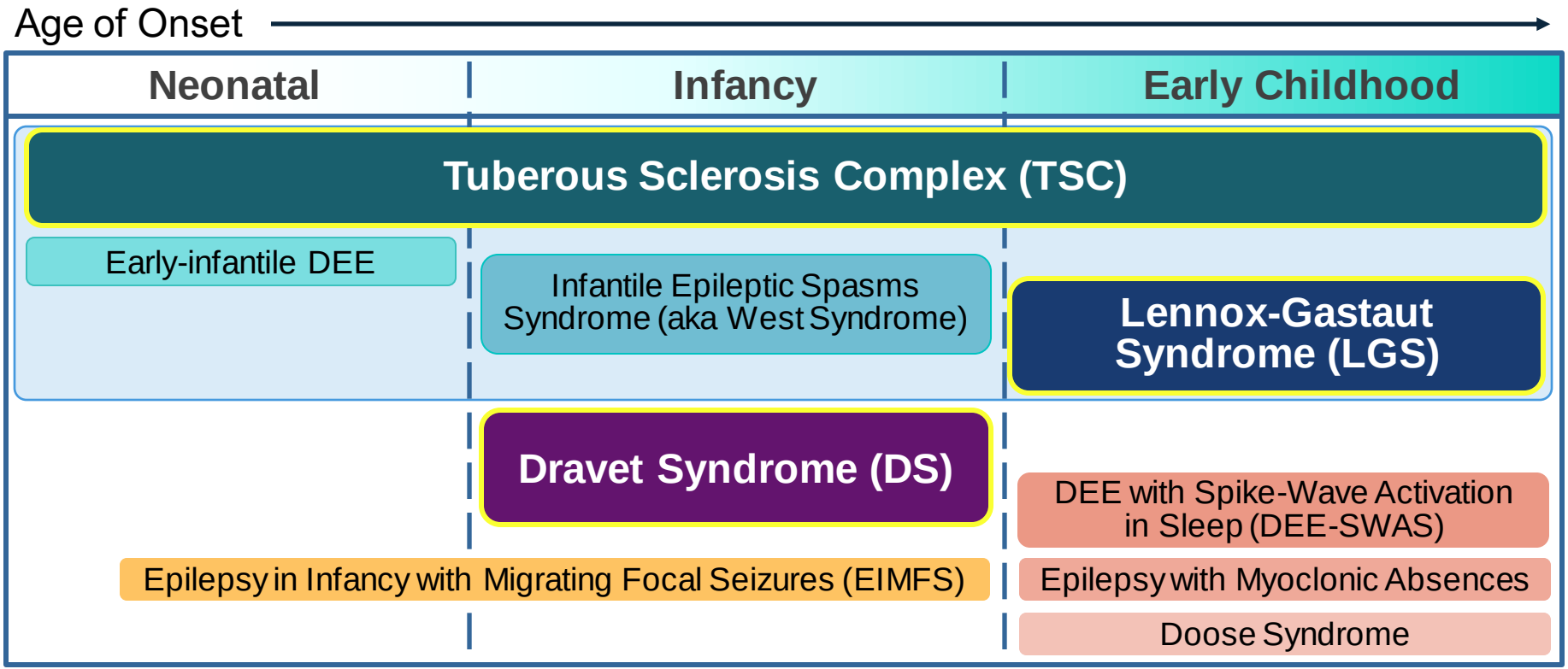
## Developmental and Epileptic Encephalopathy (DEE):

- Impairments due to BOTH underlying cause of the epilepsy AND frequent seizures or epileptiform discharges
- Epilepsy often drug-resistant, and comorbidities are common



Scheffer IE, et al. *Epilepsia*. 2017;58(4):512-521. Raga S, et al. *Epileptic Disord*. 2021;23(1):40-52. Specchio N, Curatolo P. *Brain*. 2021;144(1):32-43. Scheffer IE, Liao J. *Eur J Paediatr Neurol*. 2020;24:11-14.

# Early-Onset DEEs




Scheffer IE, Liao J. *Eur J Paediatr Neurol*. 2020;24:11-14. Zuberi SM, et al. *Epilepsia*. 2022;63(6):1349-1397. Specchio N, et al. *Epilepsia*. 2022;63(6):1398-1442. Riney K, et al. *Epilepsia*. 2022;63(6):1443-1474.

# DS, TSC, LGS Early Recognition

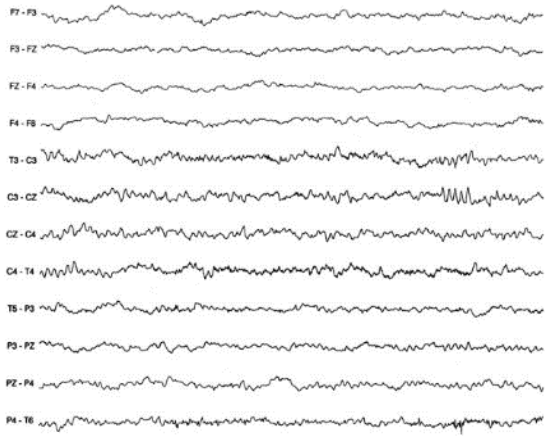
| Syndrome | Etiology | Key Onset Features | Comments |
|---|---|---|---|
| **Dravet Syndrome (DS)** | ***SCNA1* variant** voltage-gated sodium channel structure | **Intractable focal or generalized convulsive seizures**<br><br>**Seizures can be febrile or afebrile** and sensitive to vaccination | Other seizure types appear over time including, atypical absence, myoclonic, and atonic |
| **Tuberous Sclerosis Complex (TSC)** | ***TSC1* or *TSC2* mutation** mTOR signaling of cell size and proliferation | **Infantile spasms and/or focal seizures**, including focal to bilateral tonic-clonic<br><br>**Multiple benign tumors (hamartomas),** especially in brain, eyes, skin, kidneys, heart, and lungs | Often detectable prior to seizure onset<br><br>Can be underlying cause of other epilepsy syndromes |
| **Lennox-Gastaut Syndrome (LGS)** | **Variable** structural brain abnormalities, pathogenic gene variant | **Multiple intractable seizure types, including tonic and 1+ others** (GTC, atypical absence, atonic, spasms, etc.)<br><br>**Diffuse slow spike-and-wave pattern on interictal EEG** | 10-30% evolve from earlier onset epilepsy syndromes<br><br>Generalized paroxysmal fast activity in sleep common on EEG |

EEG = electroencephalograph; GTC = generalized tonic-clonic. Strzelczyk A, Schubert-Bast S. *CNS Drugs*. 2022;36(10):1079-1111. Specchio N, et al. *Epilepsia*. 2022;63(6):1398-1442. Zuberi SM, et al. *Epilepsia*. 2022;63(6):1349-1397

# Patient Case: Ella (11-month-old female)

**CC/HPI**: Frequent seizures despite treatment

- Unremarkable pregnancy and delivery at 35 weeks gestation
- 8 months: Treated for RSV; Mother reported multiple episodes of “shivering” with fluctuating alertness
- 9 months: Presented to ED with febrile left-sided to bilateral tonic-clonic seizure x 25 min
  - No epileptic activity identified on EEG
  - Labs and exams all WNL
  - Prescribed only rescue diazepam
- 10 months: Pediatrician documented right-sided hemiclonic seizure x 15 min
  - Started on levetiracetam
  - EEG, MRI, and CSF all WNL




CC = chief complaint; CSF = cerebrospinal fluid; ED = emergency department; HPI = history of present illness; MRI = magnetic resonance imaging; RSV = respiratory syncytial virus; WNL = within normal limits

# Audience Response

**Which investigation should be performed next to identify the etiology of Ella's seizures?**

A. Genetic epilepsy panel
B. Continuous EEG monitoring
C. PET/CT with tracer
D. Immunoglobulins blood test
E. I'm unsure

# Dravet Syndrome Diagnosis

| | | |
|---|---|---|
| **IF:** | 2- to 15-months-old | Developmentally normal |
| **AND** one or more occur with or without fever or recent vaccination: | | |
| Focal or generalized convulsive, prolonged seizure(s) or status epilepticus | Brief, recurrent hemiclonic or convulsive seizures | |
| **AND** all WNL: | MRI | Lab studies | +/- CSF studies |
| **THEN:** | **Perform targeted *SCN1A* testing for DS**<br>(Can be part of epilepsy panel; NGS superior to Sanger) | |

| | |
|---|---|
| **Alerts:** | Lack of fever sensitivity, positive response to sodium-channel agents |
| **Exclusionary:** | History of epileptic spasms or focal lesions |

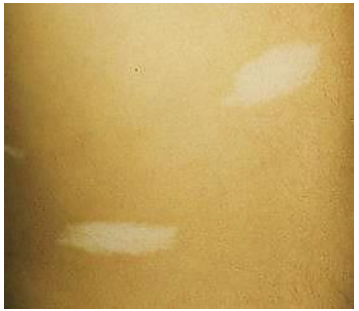
NGS = next generation sequencing. Wirrell EC, et al. *Epilepsia*. 2022;63(7):1761-1777. Zuberi SM, et al. *Epilepsia*. 2022;63(6):1349-1397. Lee J, et al. *Ann Clin Lab Sci*. 2020;50(5):625-637.

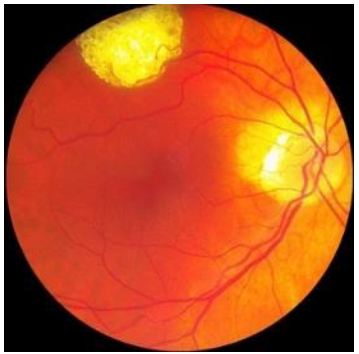
# Patient Case: Kai (20-month-old male)

**CC/HPI**: Developmental delays, possible seizures

- Normal development until ~18-months-old
  - Makes verbal noises but no expressive language
  - Crawls, scoots, and stands with support but no independent walking
- Parents report multiple episodes of staring spells
- Physical exam reveals 2 hypopigmented macules on trunk (ovoid, ~1.5 cm, no signs of scale or inflammation, no color change when pressed)
- Neurological exam reveals mild spasticity in lower limbs and bilateral retinal hemartomas

**You suspect TSC and order an EEG and MRI.**





Hemady N, Noble C. *Am Fam Physician*. 2007;75(7):1053-1054. Ryu S, et al. *Yonsei Med J*. 2023;64(2):133-138.

# Audience Response

**What finding would confirm a diagnosis of TSC in Kai?**

A. Temporal sharp-wave spikes on EEG
B. Hypsarrhythmia on EEG
C. Multiple cortical tubers on MRI
D. Hippocampal atrophy on MRI
E. I'm unsure

# TSC Diagnosis

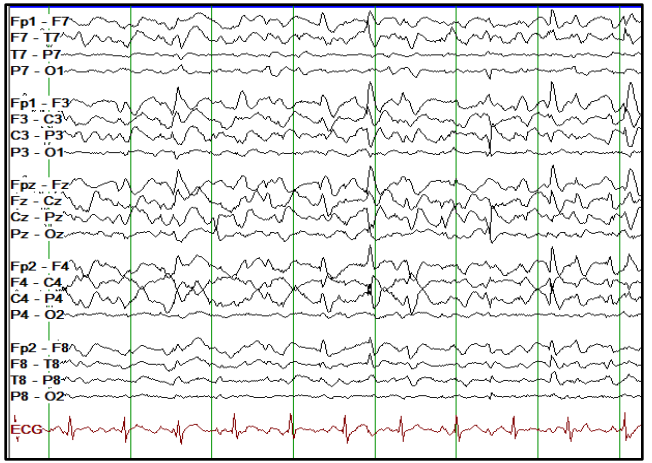
| Diagnostic Criteria | Major Features | Minor Features |
|---|---|---|
| **Definite TSC:**<br>Confirmed genetic criteria OR<br>≥ 2 major features OR<br>1 major + ≥ 2 minor features | ≥ 2 Cortical tubers +/or radial migration lines | "Confetti" skin lesions |
| | ≥ 3 Hypomelanotic macules ≥5mm across | ≥ 4 Dental enamel pits |
| | ≥ 2 Ungual fibromas | ≥ 2 Intraoral fibromas |
| | ≥ 2 Retinal hamartomas | Retinal achromatic patch |
| **Possible TSC:**<br>1 major feature OR<br>≥ 2 minor features OR<br>*Only angiomyolipomas + LAM major features | Shagreen patch | ≥ 2 Renal cysts |
| | Cardiac rhabdomyoma | Sclerotic bone lesions |
| | Subependymal giant cell astrocytoma (SEGA) | Nonrenal hamartomas |
| | ≥ 2 Subependymal nodules (SEN) | **Genetic Criteria** |
| **Notes:**<br>Infantile spasms/seizures + any clinical feature should trigger suspicion of TSC. | ≥ 3 Angiofibromas or fibrous cephalic plaques | Pathogenic variant in *TSC1* or *TSC2* gene |
| | ≥ 2 Angiomyolipomas* | Note: Negative DNA test NOT exclusionary |
| | Lymphangioleiomyomatosis (LAM)* | |

Northrup H, Krueger DA. *Pediatr Neurol*. 2013;49(4):243-254. Northrup H, et al. *Pediatr Neurol*. 2021;123:50-66.
Staley BA, et al. *Pediatrics*. 2011;127(1):e117-e125.

# Patient Case: Sam (3-year-old female)

**CC/HPI**: Frequent, intractable seizures despite treatment

- Diagnosed with West syndrome/infantile spasms at 8-months-old
  - Hypsarrhythmia noted on EEG
  - No etiology identified with neuroimaging or genetic testing at that time
  - Failed multiple antiseizure medications (ASM); ~50% frequency reduction with clobazam
- Parents report new episodes of unresponsive staring in recent months, and tonic "spasms" now last minutes instead of seconds
- Moderate developmental delays apparent on exam, including limited ability to communicate and lack of independent walking




- Background diffuse theta-delta slowing + interictal generalized slow spike-and-wave complexes (< 2.5 Hz) noted on EEG

# Audience Response

**Which of Sam's signs/symptoms is most supportive of a diagnosis of LGS?**

A. Moderate developmental delays
B. Unresponsive staring episodes
C. Diffuse theta-delta slowing
D. Generalized slow spike-and-wave complexes
E. I'm unsure

# LGS Diagnosis

## Mandatory

**Tonic seizures** (often more prominent in sleep)

**≥ 1 additional seizure type**, which may include:

- Atypical absences
- Atonic
- Myoclonic
- GTC
- Focal impaired awareness
- Epileptic spasms
- Nonconvulsive status epilepticus (remains a risk at any age)

**Generalized slow spike-and-wave** complexes < 2.5 Hz (or history of this finding on prior EEG)

**Generalized paroxysmal fast activity in sleep** (or history of this finding on prior EEG)

## Alerts

Photoparoxysmal response at low frequencies (consider CLN2 disease)

**Syndrome-in-evolution**: ~50% of infants with a severe DEE evolve to LGS over time

> 8 years old at onset

No developmental impairments

## Exclusionary

Persistent focal abnormalities without generalized spike-and-wave pattern

**Notes:** Neuroimaging and genetic testing not required for diagnosis but helpful for evaluating etiology and guiding treatment.

Specchio, et al. *Epilepsia*. 2022;63(6):1398-1442. Berg AT, et al. *Epilepsia*. 2018;59(11):2096-2105. Smith KM, et al. *Neurol Clin Pract.* 2018;8(5):397-402.

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# Learning Objective 2

Incorporate patient/caregiver QoL assessments and treatment goals into team-based management of early-onset epilepsy syndromes.

# Savannah's LGS Journey (Age 1-5 years)

## ETIOLOGY

**Unknown at birth**

## EVOLUTION

**1st seizure**

Age 2 years old

**Epilepsy**

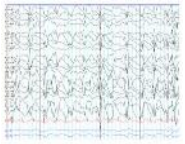
4 seizures total at age 2, 6 months w/o seizure, back with a vengeance at age 3.

**Treatment resistant epilepsy**

Age 3 years old

Other seizure types emerge

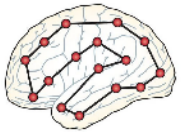
Developmental delay

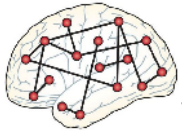


Frequent epileptiform activity

100s of seizures a day

Interplay leads to DEE



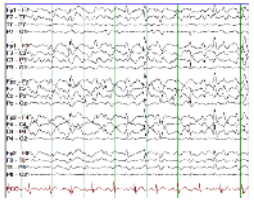


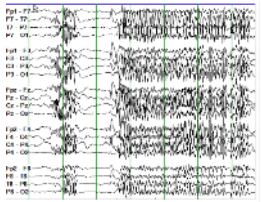
Toddler brain development

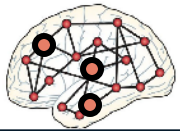
## BRAIN DAMAGE

**LGS**

Diagnosed at age 5







Warren AEL, et al. *Neurology*. 2019;93(3):e215-e226.

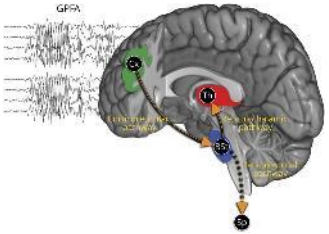
# Savannah's LGS Journey (Age 5-18 years)

## LGS

Age 5-18 years old

**# of Seizures:** > 40,000
**# Years to Get LGS Diagnosis:** 3 years
**# Years to Find Etiology:** 15
**# Neurologists**: 7
**# Treatments Tried**: 26
**# Hospitalizations**: 15
**# Surgeries**: 5
**# Rescue Med Uses/Month**: 2-5
**Monthly drug cost:** $1,640
**Emergency med use**: $183 / dose
**Last stay**: $53,475

**LGS + DEE + IDD +**
**+**
**Intractable Epilepsy**
**+**
**Unknown Etiology**



## IMPACT

**Seizures (all the time!):**
- Weekly status & clusters/SUDEP
- Frequent aspiration pneumonia
- Regular ER visits & hospitalizations
- Brain matter atrophy

**Developmental Delay/Intellectual Disability**
(Inability to safely navigate the world):
- **Behavior:**
  - Aggression
  - Temper tantrums
  - Inattention
  - OCD
- **Academic/Communications Issues:**
  - Can't read or write
  - Speech & language delay/slurred
  - Inability to communicate needs
  - Memory issues/psychological slowing
- **Mobility & Physical Care Issues**
  - Severely off balance/low tone
  - Can't walk long distances
  - Doesn't dress, toilet, feed self

**Sleep Issues:**
- Excessive Daytime Sleepiness
- Nocturnal seizures
- Excessive Nighttime Waking

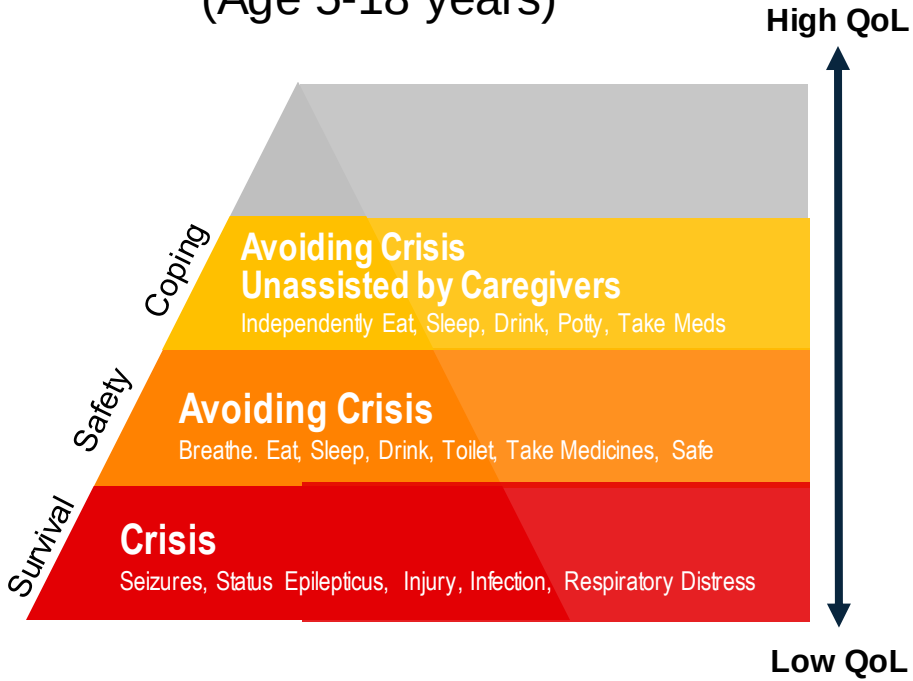
**Constipation**
**Low Bone Density**
**Social Isolation**
**Weight Loss**
**Liver Issues**

**The Whole Family:**
- Sibling issues
- Sleep issues
- Social isolation
- Financial challenges
- Access to care challenges
- Caregiver fatigue

Warren AEL, et al. *Neurology*. 2019;93(3):e215-e226.

# Savannah's LGS Evolution (Age 18-29 years)

## Our Hierarchy of Needs
(Age 5-18 years)




## LGS
Age 18-29 years old

Age 18
95% reduction in seizures on verapamil
99% reduction in clusters/status epilepticus
STARTED LEARNING AGAIN!!!
Savannah is now 29!

# Caregiver/Family QoL Impacts

Inability to make plans

Managing complex medical care (appointments, specialists, medications, etc.)

Battling system-level barriers (insurance, finances, advocacy)

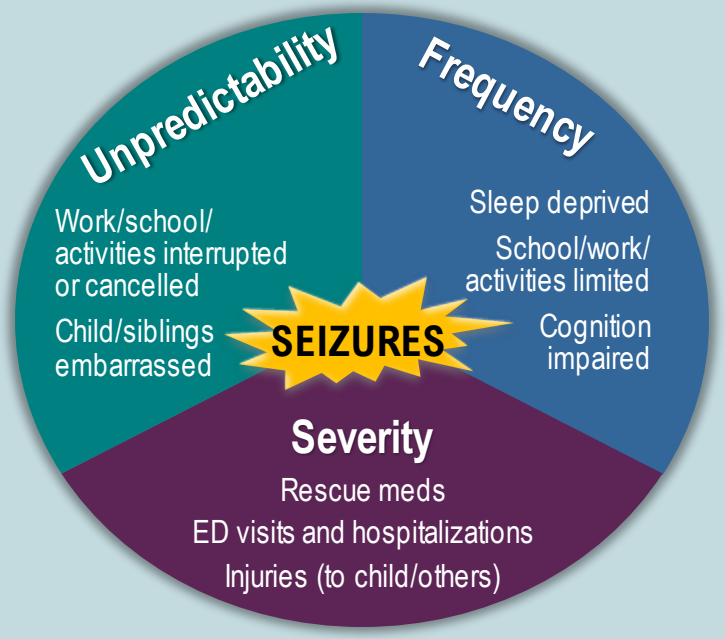
Educating self, family, outside caregivers (school, home nurse)

Balancing impacts/needs of other family members

Stranger in home (home nurse)

Monitoring seizures, behavior, cognition, sleep (SUDEP), diet

## Implications and Consequences




## Chronic Traumatic Stress

Constant stress overload

Constant fear/anxiety/worry

Self-sacrifice and guilt about not doing enough

Chronic sleep deprivation, 24/7 exhaustion

Wear on relationships (marriage, siblings, friends)

Isolation and depression

Loss of hope

Fear for the future

"*Surviving- Not thriving*"

SUDEP = sudden unexpected death in epilepsy

Berg AT, et al. *Epilepsia Open*. 2019; 4: 293– 301. Bailey LD, et al. *Epilepsy Behav*. 2020;112:107377.

# DEE QoL Correlates and Priorities

- Seizure burden, including unpredictability
- Healthcare access + utilization
- ASM burden + adverse effects
- Functional capacity + independence
- Caregiver/family impacts
- Language, learning, + cognition
- Comorbidity burden, including mental health
- Socialization + stigma

**Transition of care**

Conway L, et al. *Epilepsia*. 2016;57(8):1256-1264. Chiang S, et al. *Epilepsy Behav*. 2021;123:108282. Chiang S, et al. *Epilepsia*. 2023;64(1):170-183. Lagae L, et al. *Dev Med Child Neurol.* 2018;60(1):63-72. Zöllner JP, et al. *Neurol Res Pract.* 2021;3(1):35. Makiello P, et al. *Epilepsia*. 2023;64(4):1012-1020.

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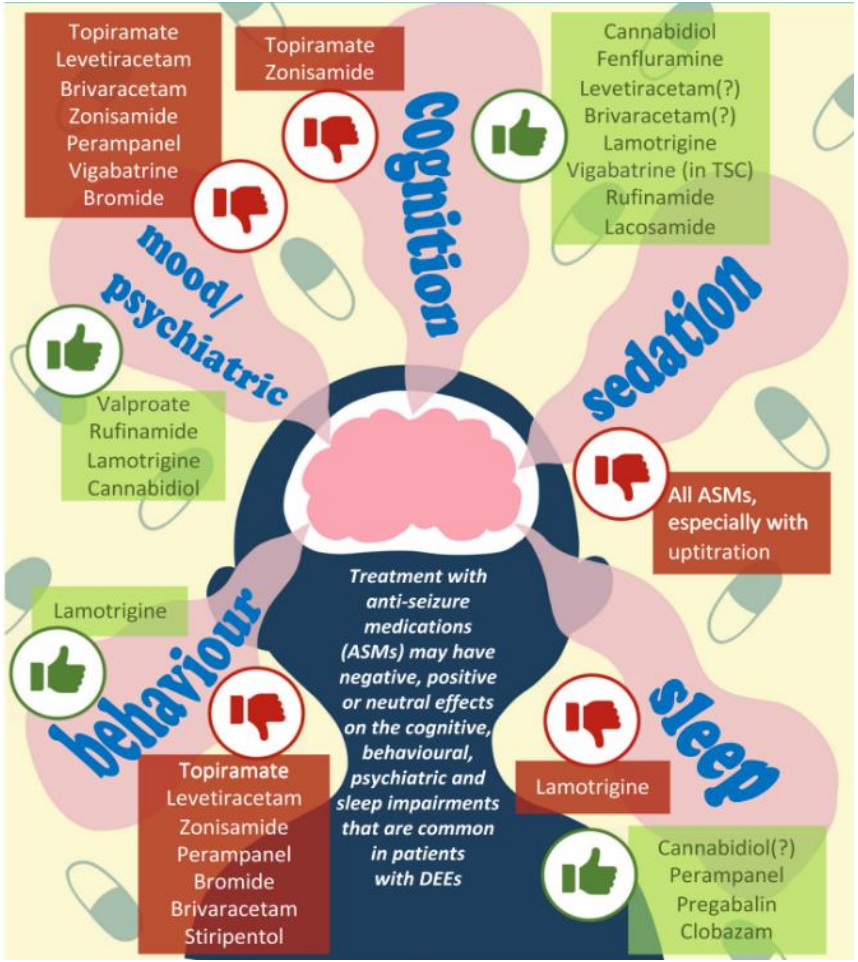
# Learning Objective 3

Examine the role of pharmaceutical CBD in antiepileptic therapy, including outcomes data, formulation/dosing considerations, augmentation strategies, and regulatory requirements.

# Psychobehavioral and Cognitive Adverse Events of ASMs in DEE

| DEE | Classification of Evidence | | Caution |
|---|---|---|---|
| | Class I-II | Class III-IV | |
| DS | Valproate<br>Topiramate<br>Stiripentol*<br>Clobazam<br>Cannabidiol*<br>Fenfluramine* | Bromide<br>Levetiracetam<br>Zonisamide<br>Ethosuximide<br>Perampanel<br>Brivaracetam | Predominant sodium channel blockers<br>Gabapentinoids<br>Tiagabine<br>Vigabatrin |
| LGS | Valproate<br>Topiramate*<br>Lamotrigine*<br>Rufinamide*<br>Clobazam*<br>Cannabidiol*<br>Fenfluramine* | Felbamate*<br>Levetiracetam<br>Zonisamide<br>Ethosuximide<br>Perampanel<br>Brivaracetam | Carbamazepine<br>Oxcarbazepine<br>Gabapentinoids<br>Phenytoin |
| TSC | Vigabatrin*<br>Everolimus”<br>Cannabidiol* | Seizure type(s) dependent | Seizure type(s) dependent |
| Notes | *Carries approved indication for specified condition | | |



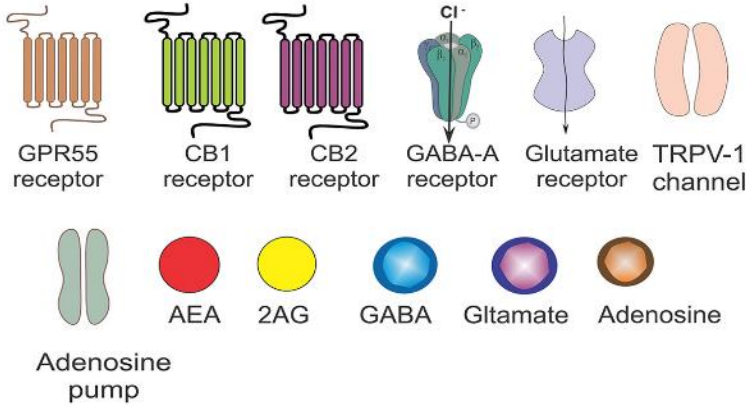

Strzelczyk A, Schubert-Bast S. *CNS Drugs*. 2022;36(10):1079-1111. Wirrell EC, et al. *Epilepsia*. 2022;63(7):1761-1777. Strzelczyk A, Schubert-Bast S. *CNS Drugs*. 2022;36:217–237. Northrup H, et al. *Pediatr Neurol*. 2021;123:50-66. Montouris G, et al. *Epilepsy Behav*. 2020;110:107146. Strzelczyk A, Schubert-Bast S. *CNS Drugs*. 2021;35(1):61-83.

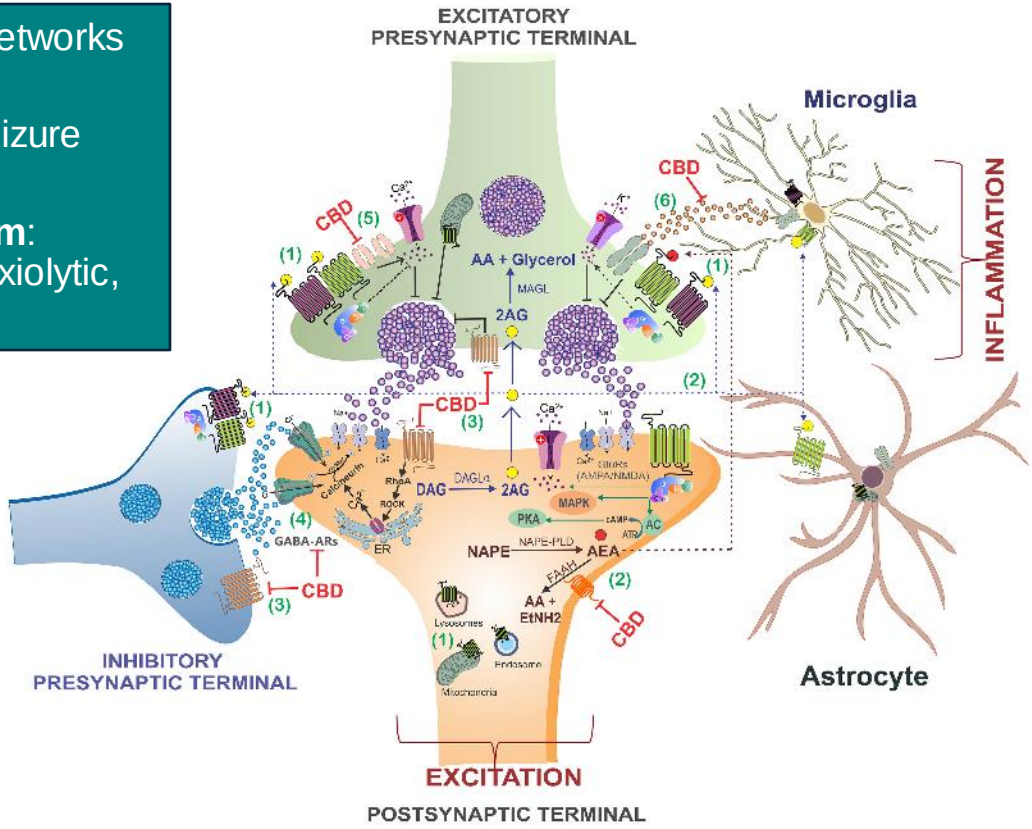
# Antiepileptic Mechanisms of CBD

**Targets**: neuronal and non-neuronal microglia networks

**Regulates**: overall network excitability and neuroinflammation, resulting in attenuation of seizure activity as well as comorbid signs

**Other actions within endocannabinoid system**: anti-inflammatory, antioxidant, neurogenesis, anxiolytic, analgesic, and neuroprotective activities




Reddy DS. *Exp Neurol*. 2023;359:114237. Talwar A, et al. *Exp Neurol*. 2023;359:114238. Rosenberg EC, et al. *Neuron*. 2023;111(8):1282-1300.e8.

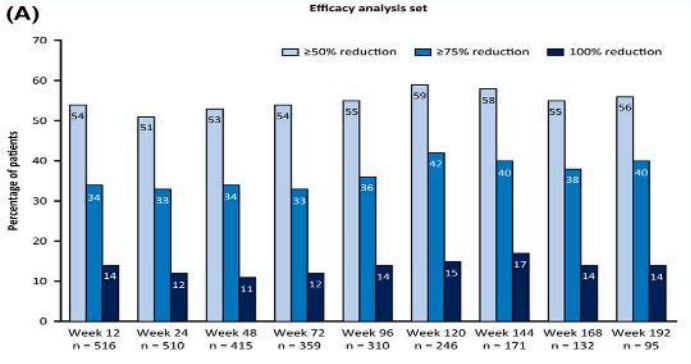
# CBD Product Comparison

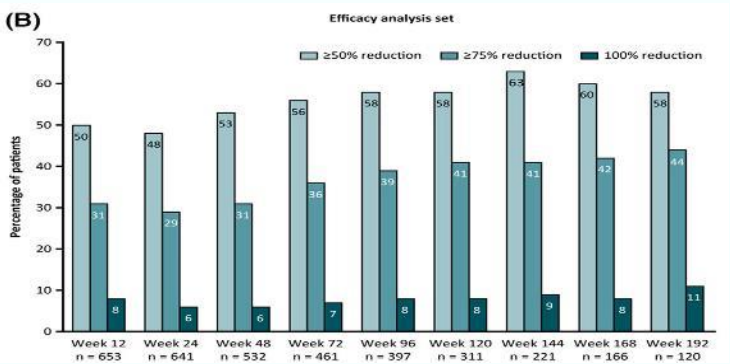
| | Pharmaceutical-grade CBD | Artisanal CBD | Medical Cannabis |
|---|---|---|---|
| **Contents** | 100mg/mL highly purified CBD | Defined as hemp product containing < 0.3% THC | Whole plant cannabis or extracts containing a mix of cannabinoids |
| **Psychoactivity** | None | Possible | Yes |
| **Regulatory approval** | Federally approved treatment for seizures associated with DS, TSC, and LGS | Classified as agricultural product (not approved to treat or prevent any disease) | Variable and complex legal status |
| **Evidence for efficacy** | Multiple randomized, controlled trials and real-world studies | Not translatable to individual products | Limited with significant safety concerns |
| **Quality control** | Highly regulated and standardized to guarantee purity, consistency, and accurate dosing | None | None |
| **Access** | Available by prescription through designated specialty pharmacies | Widely available | Legal and logistical barriers vary |

THC = tetrahydrocannabinol

# CBD: Long-term Safety and Efficacy

## Four-year results from CBD expanded access program for treatment-resistance epilepsies (DS, TSC, LGS): Treatment response rates for (A) convulsive and (B) total seizures




**AEs in ≥ 20%:** diarrhea (33%), seizure (24%), somnolence (23%; 33% w/ clobazam, 13% w/o clobazam); 7% D/C'd due to AEs

## BECOME Survey of Caregiver Reported Improvements:

**Seizure related:** frequency (84%), severity (68%), seizure-free days per week (67%), convulsive seizures (72%), drop seizures (71%), nonconvulsive/nondrop seizures (68%), night-time seizures (62%), use of rescue meds (57%), ED visits (54%), hospitalization (53%), and seizure-related injuries (48%)

**Non-seizure related**: emotional functioning (82%), cognition and executive function (81%), language and communication in non-verbal (79%) and verbal patients (74%), activities of daily living (51%), sleep (51%), and physical functioning (46%)

Szaflarski JP, et al. *Epilepsia*. 2023;64(3):619-629. Kühne F, et al. *Epilepsia Open*. 2023;10.1002/epi4.12699. Dixon Salazar T, et al. *Neurology*. 2022;98(18)884. Berg A, et al. *Neurology*. 2022;98(18)88.

# SMART Goals

## Specific, Measurable, Attainable, Relevant, Timely

- Recognize and investigate early signs and symptoms of developmental and epileptic encephalopathies to achieve timely diagnosis.
- Routinely assess patient/caregiver QoL and adapt care plans accordingly to address evolving needs and priorities.
- Educate patients/caregivers as needed on the roles of pharmaceutical-grade cannabidiol within a care plan.

# To Ask a Question

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