Epidiolex in Dravet Syndrome and Lennox-Gestaut Syndrome (LGS)

27 September 2018

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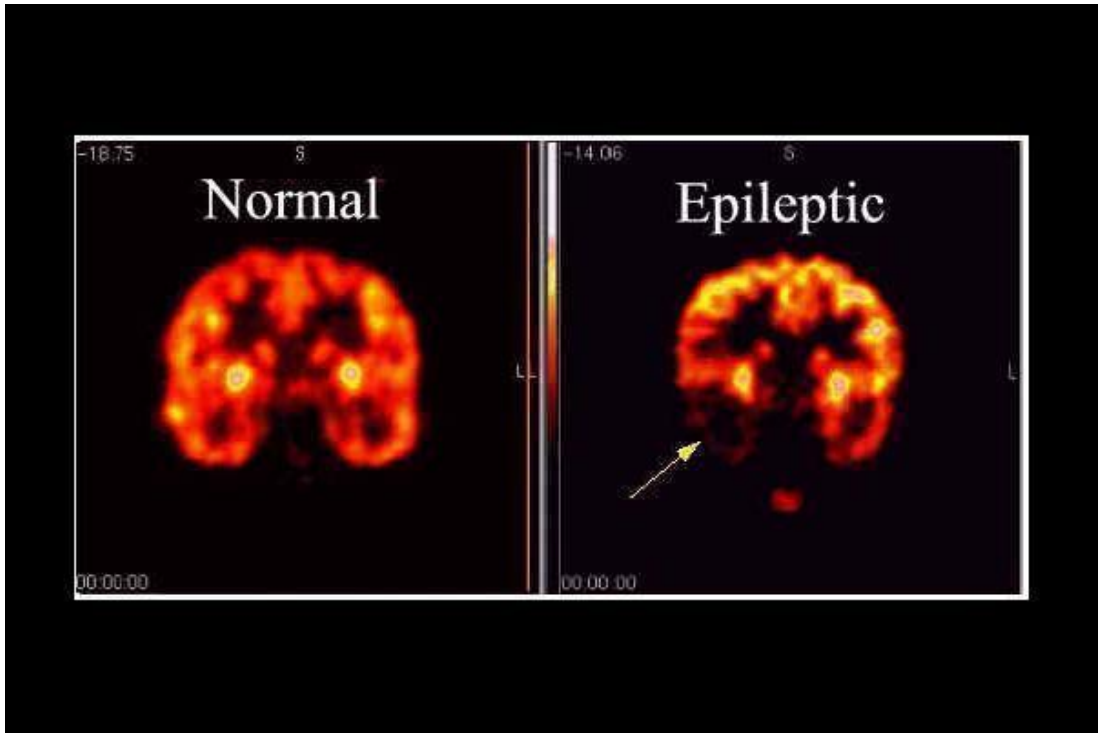
Objectives

- To understand the epidemiology and pathophysiology of LGS and Dravet Syndrome
- To understand the mechanism of action of Epidiolex and its use in LGS and Dravet Syndrome
- To determine Epidiolex's place in therapy for LGS and Dravet Syndrome

Epilepsy

- A condition in which a person has recurrent seizures due to an underlying chronic cause
- Incidence: 61 per 100,00 person-years
- Lifetime prevalence: 7.60 per 1,000 persons
- Normal neuronal activity is disrupted
- A seizure is an occurrence due to abnormal/excessive neuronal transmissions in the brain
  - One single seizure is not epilepsy
  - Two or more seizures are needed to diagnose epilepsy



Epilepsy Information Page | National Institute of Neurological Disorders and Stroke. Nnih.gov. Published 2018.
Fiest K, Sauro K, Wiebe S et al. Prevalence and incidence of epilepsy. Neurology. 2016;88(3):296-303.

Epilepsy Syndromes

Represent clinical and pathologic characteristics that are suggestive of an etiology

~~Such~~ characteristics may include:

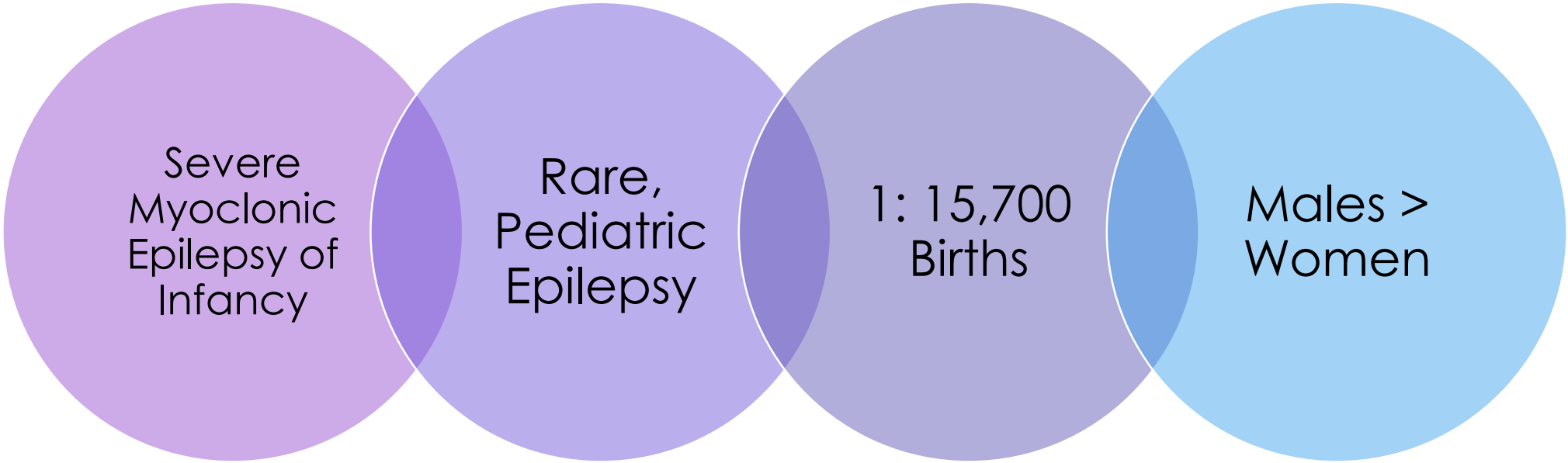
- ~~The~~ age of onset
- ~~The~~ part of the brain involved, provoking factors
- ~~The~~ severity/frequency
- EEG patterns

Various Epilepsy Syndromes include:

- Angelman syndrome
- Doose Syndrome
- Frontal Lobe Epilepsy
- Juvenile Absence Epilepsy
- Sunflower Syndrome
- **Dravet Syndrome**
- **Lennox-Gastaut Syndrome (LGS)**

Types of Epilepsy Syndromes. Epilepsy Foundation. https://www.epilepsy.com/learn/types-epilepsy-syndromes. Published 2018.

Dravet Syndrome



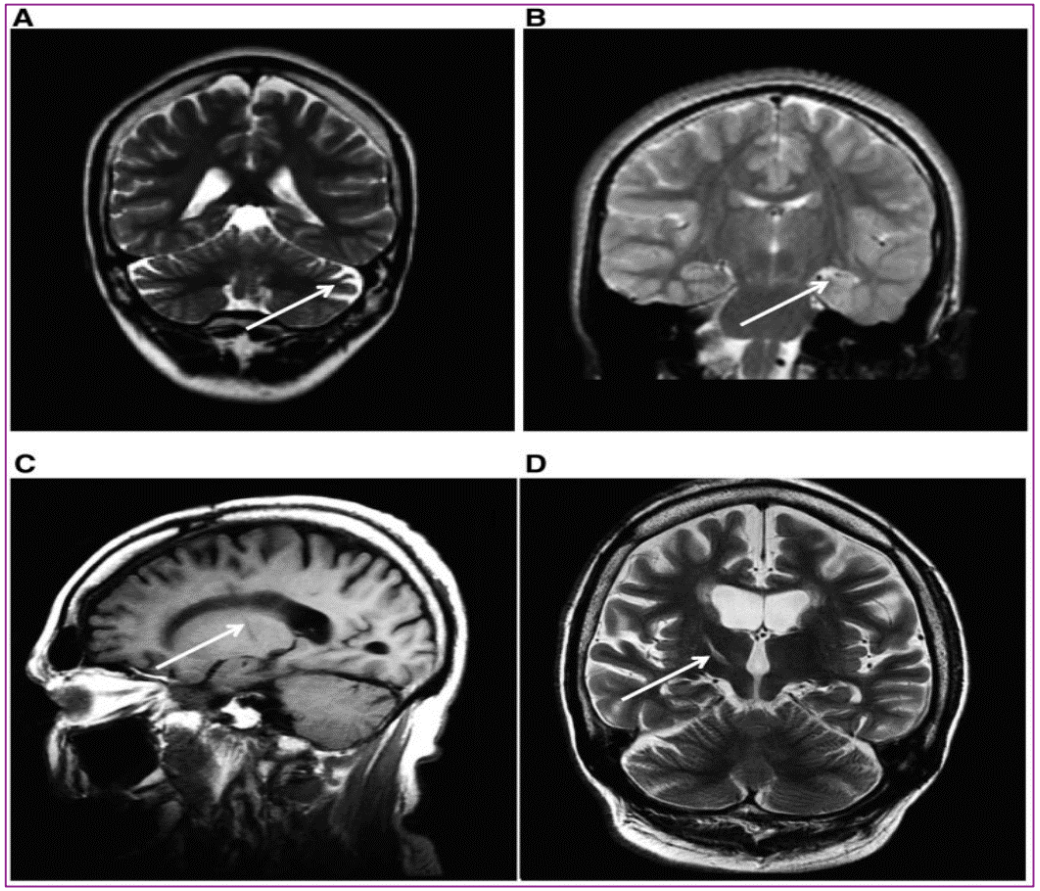
Dravet Syndrome Seizure Types

Convulsive	Myoclonic	Atypical Absences	Focal with/without secondary generalization	Tonic seizures
Present throughout	1-5 years of age	4 months to 6 years of age	4 months to 4 years of age	Uncommon
Hemiclonic Seizures	Head and trunk	+/- myoclonic attacks	Mainly autonomic	Sporadic
Status Epilepticus	Variable intensity	Variable intensity	Similar to atypical absences	Axial tonic features in LGS

Dravet C. The core Dravet syndrome phenotype. *Epilepsia*. 2011;52:3-9.

Dravet Syndrome Pathophysiology

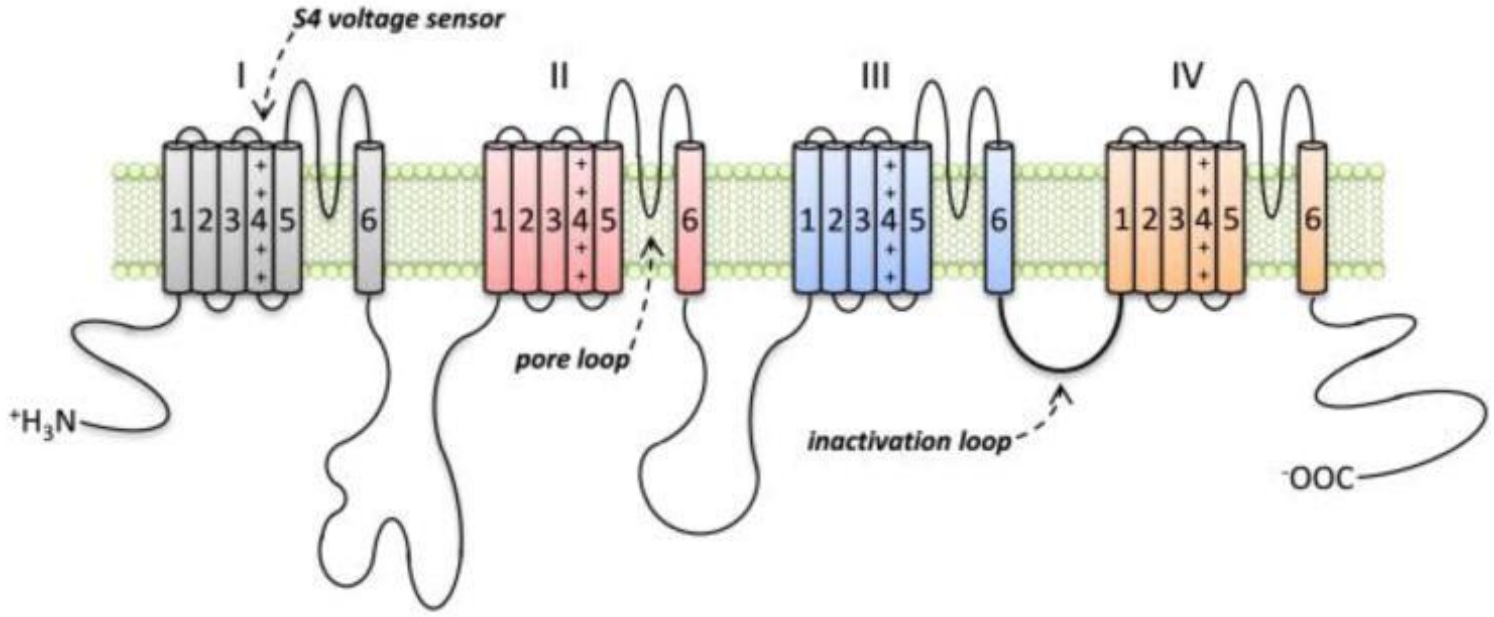
- Associated with mutations in the voltage-gated sodium ion channels
- 75% of cases are linked to the $Na_v1.1$ channel loss of function which is encoded by the *SCN1A* gene
  - Hapaloinsufficiency
- Animal models have shown ataxia, death, and seizures with *SCN1A* deletion



Dravet Syndrome and *SCN1A* mutation MRI images

Catarino C, Liu J, Liagkouras I et al. Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology. *Brain*. 2011;134(10):2982-3010.

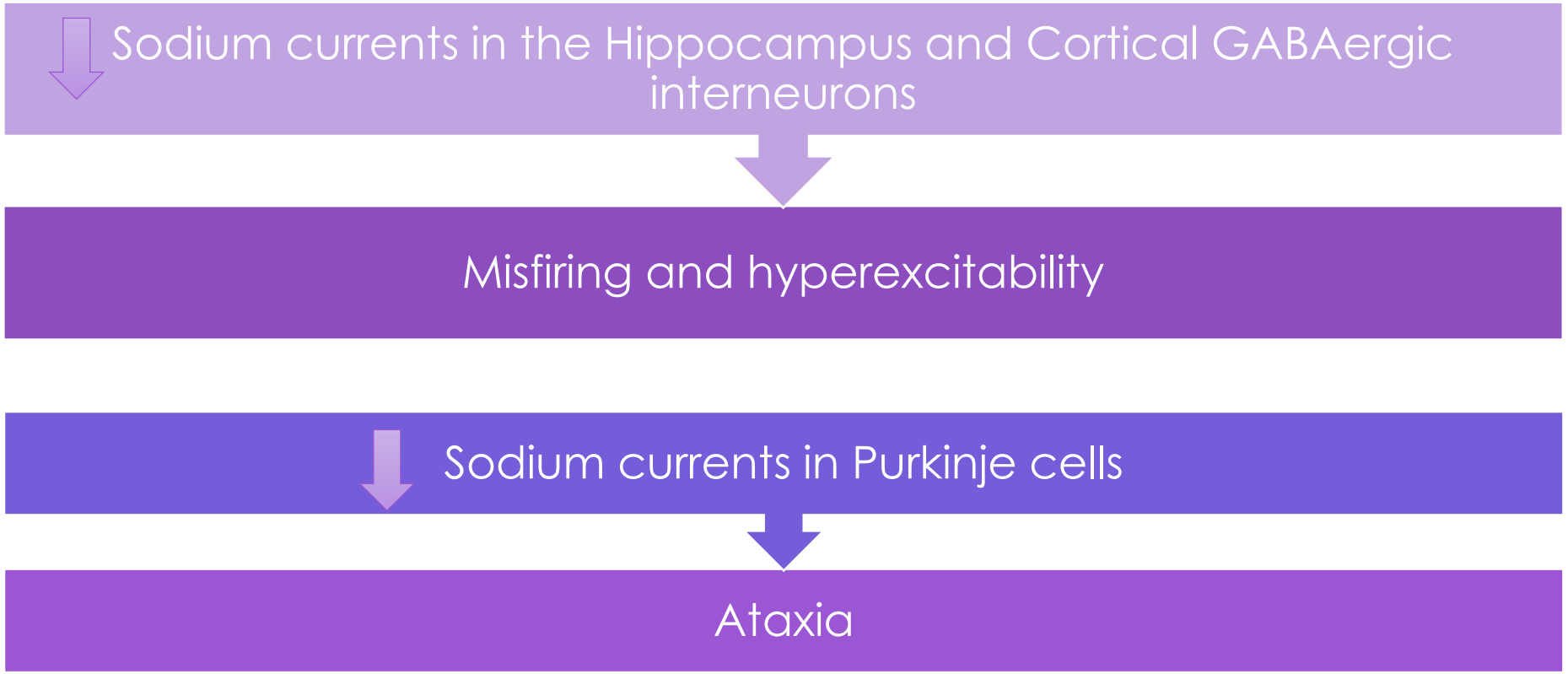
Dravet Syndrome Pathophysiology (Cont.)



$Na_v1.1$ alpha subunit

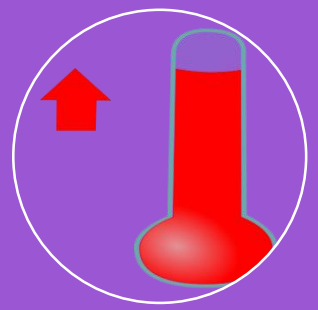
Bender A, Morse R, Scott R, Holmes G, Lenck-Santini P. SCN1A mutations in Dravet syndrome: Impact of interneuron dysfunction on neural networks and cognitive outcome. *Epilepsy & Behavior*. 2012;23(3):177-186.

Dravet Syndrome Pathophysiology (Cont.)



Catarino C, Liu J, Liagkouras I et al. Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology. *Brain*. 2011;134(10):2982-3010.

Dravet Syndrome Precipitating Factors



Elevation of temperature

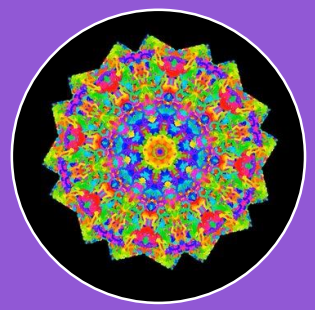


Photo and patterns

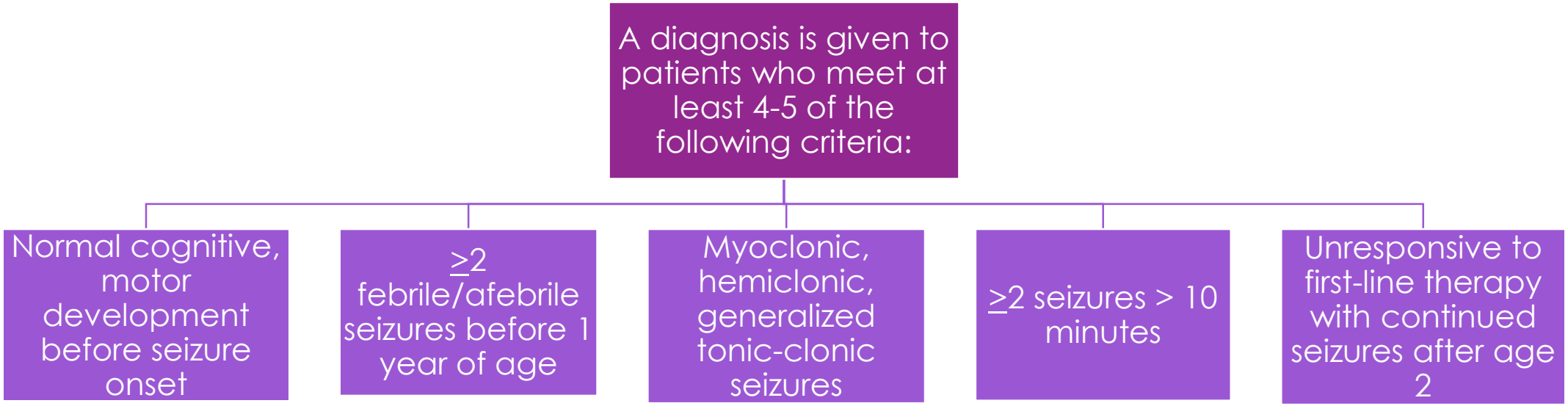
Environmental light

Physical exercise

Noisy environments

Factors that can precipitate the disease

Dravet Syndrome Diagnosis



Wu Y, Sullivan J, McDaniel S et al. Incidence of Dravet Syndrome in a US Population. *Pediatrics*. 2015;136(5):e1310-e1315.

Dravet Syndrome Signs, Symptoms

Prognosis is very poor

Developmental and cognitive defects are common after age 2

- Vary in severity
- Walking, talking, motor skills, attention

Neurologic signs

- Appear with developmental and cognitive defects
- Hypotonia, ataxia, incoordination

Chronic infections, growth problems, unsteady walking, gait

Wu Y, Sullivan J, McDaniel S et al. Incidence of Dravet Syndrome in a US Population. *Pediatrics*. 2015;136(5):e1310-e1315.

Dravet Syndrome Treatment

Treatment refractory

Valproate (valproic acid), Topamax (topiramate), Onfi (clobazam)

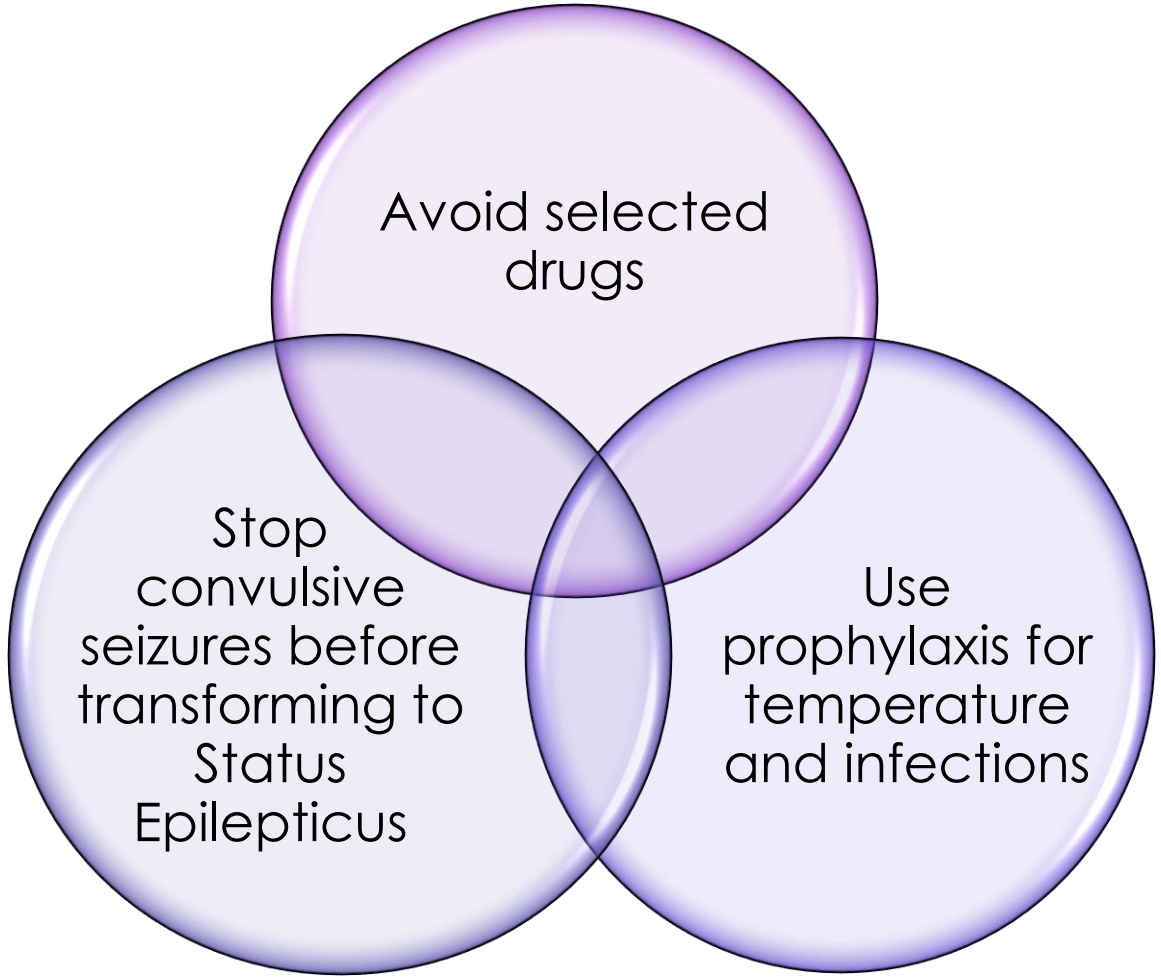
Stiripentol (Europe)

- Used with clobazam or valproate
- GABA-mediated activity
- Non-linear PK
- Drowsiness, decreased appetite, ataxia, nausea

Carbamazepine, lamotrigine

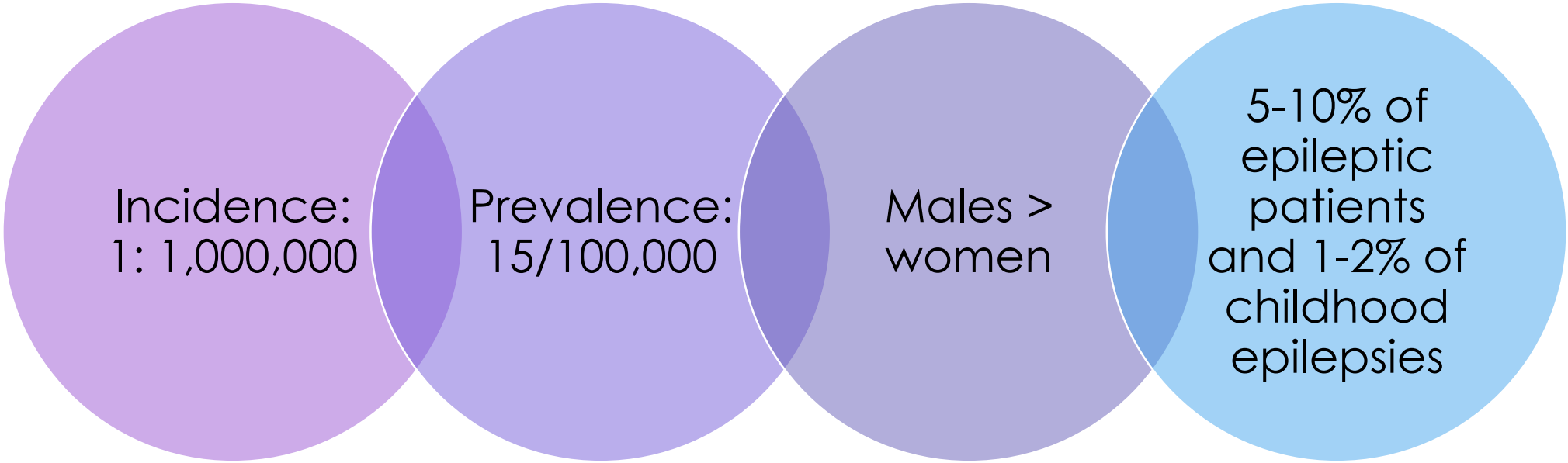
Wu Y, Sullivan J, McDaniel S et al. Incidence of Dravet Syndrome in a US Population. *Pediatrics*. 2015;136(5):e1310-e1315.
Incorpora G. Dravet syndrome. *Ital J Pediatr.* 2009;35(1):27.

Dravet Syndrome Key Points



Dravet C. The core Dravet syndrome phenotype. *Epilepsia*. 2011;52:3-9.

Lennox-Gastaut Syndrome



Asadi-Pooya A. Lennox-Gastaut syndrome: a comprehensive review. *Neurological Sciences*. 2017;39(3):403-414.

Lennox-Gastaut Syndrome Seizure Types

Atypical Absence

- Less responsive to medications
- Associated with brain abnormalities
- Lasts for several seconds

Generalized, Tonic-Clonic

- Most common
- Tonic muscle contraction followed by clonic phase
- Impairment of consciousness

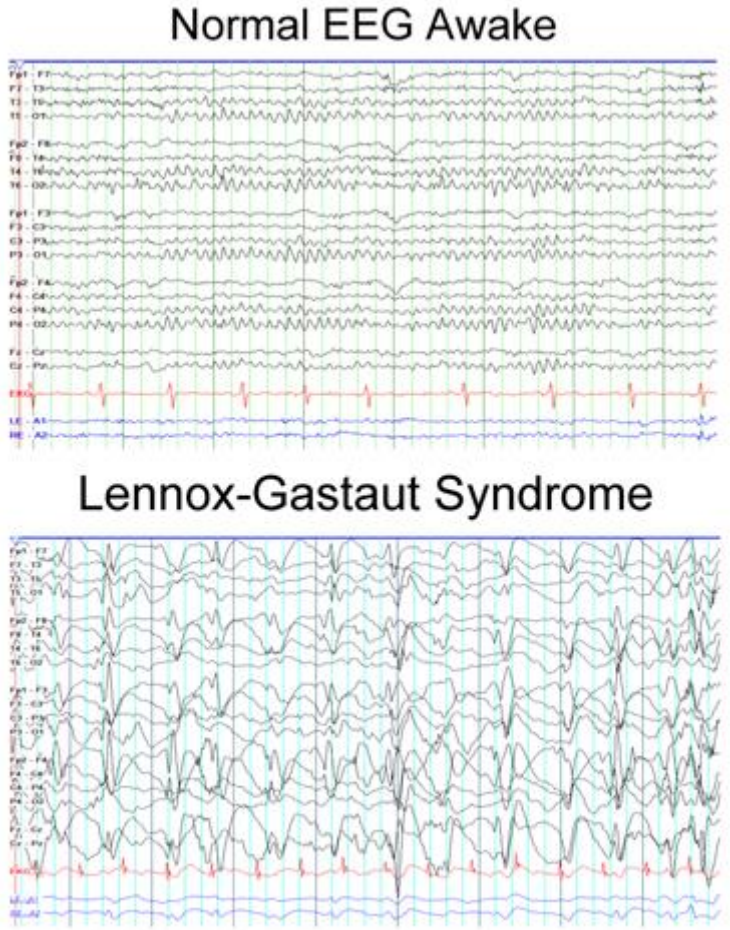
Atonic Seizures "Drop Attacks"

- Dangerous
- Loss of postural muscle tone
- No recollection

Lennox-Gastaut Syndrome - NORD (National Organization for Rare Disorders). NORD (National Organization for Rare Disorders). Published 2018.

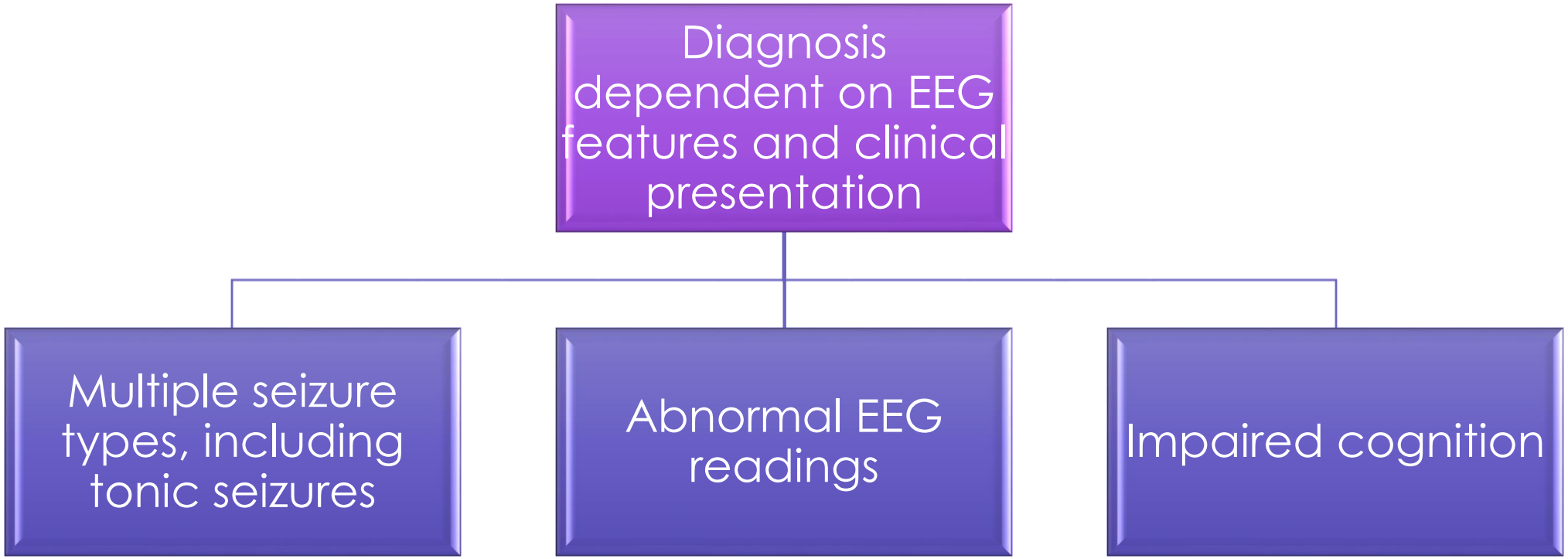
Lennox-Gastaut Syndrome Pathophysiology

- 75% of cases are symptomatic
- 25% of cases are idiopathic
- Cause is unknown
- Result from brain injury, or *de novo*
- EEG shows slow spike-and-wave bursts



Camfield P. Definition and natural history of Lennox-Gastaut syndrome. *Epilepsia*. 2011;52:3-9.

Lennox-Gastaut Syndrome Diagnosis



Bourgeois B, Douglass L, Sankar R. Lennox-Gastaut syndrome: A consensus approach to differential diagnosis. *Epilepsia*. 2014;55:4-9.

Lennox-Gastaut Syndrome Signs and Symptoms

Poor prognosis

Onset before age 8

EEG may show slow waves and fast waves

Developmental delays are often seen at the time of diagnosis

- Increase with time
- Psychotic symptoms

Symptoms are infrequent and limited to seizures

Arzimanoglou A, French J, Blume W et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *The Lancet Neurology*. 2009;8(1):82-93.

Lennox-Gastaut Syndrome Treatment

Until recently, there have been no phase I, II studies on the treatment of LGS

Diagnosis and management with an epilepsy specialist

According to the ***American Academy of Neurology***:

- Topamax (topiramate) and Lamictal (lamotrigine) for drop attacks
- Clobazam, rufinamide: Two FDA approved adjunctive treatments for LGS

Other treatments used for LGS:

- Valproate (valproic acid)
- Lamictal (lamotrigine)
- Topamax (topiramate)
- Banzel (felbamate)

Arzimanoglou A, French J, Blume W et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *The Lancet Neurology*. 2009;8(1):82-93.
Kanner A, Ashman E, Gloss D et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy. *Neurology*. 2018;91(2):82-90.

New FDA-Approved Treatment for Dravet Syndrome and LGS

Epidiolex
(Cannabidiol)

Cannabis

Two main active components of cannabis

- Delta-9-tetraydrocannabinol **(THC)**
  - Dronabinol
- Cannabidiol **(CBD)**
  - Epidiolex

Cannabidiol Pharmacology

Multi-targeted drug

Exact mechanism to prevent seizures is unknown

Cannabidiol Receptors:
GPR55, TRPV1, TRPV2, TRPV3, TRPA1, TRPM8, 5HT1A,

- Modulation of intracellular calcium

Devinsky O, Cilio M, Cross H et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*. 2014;55(6):791-802.

GPR: G-Protein Coupled Receptor, TRP= Transient Receptor Potential, 5HT= serotonin receptor

Cannabidiol Metabolism and Formulation

Metabolism:

CYP3A2

CYP3A4

CYP2C9

Devinsky O, Cilio M, Cross H et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*. 2014;55(6):791-802.

Cannabidiol
Indications and Side Effects

Possible Indications
Analgesia
Anti-oxidant
Muscle relaxant
Anxiolytic/antipsychotic
Neuroprotection

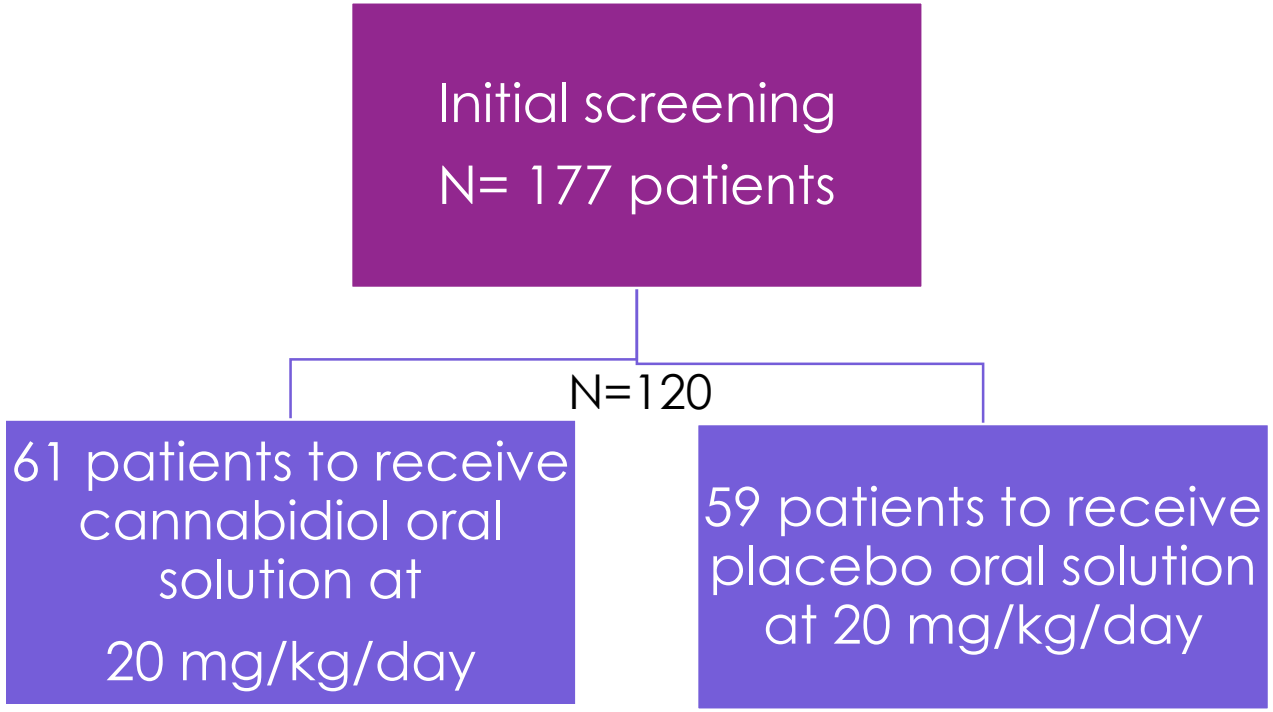
Possible Side Effects
Decreased appetite, weight loss
Diarrhea
Drowsiness, fatigue, dizziness,
Liver injury (↑ clobazam, valproate)

Hill K. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems. *JAMA*. 2015;313(24):2474.

Cannabidiol for Drug-Resistant Seizures in Dravet Syndrome

Devinsky et al., 2017

- Randomized, double-blind, placebo-controlled trial



Selected Inclusion Criteria:

- Diagnosis of Dravet Syndrome
- Taking one or more anti-epileptic drugs
- Documented history of DS which is not controlled

Selected Exclusion Criteria:

- Unstable mental conditions
- Abnormalities in EKG at screening and randomization
- The use of cannabis within the past three months

Devinsky O, Cross J, Laux L et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *New England Journal of Medicine*. 2017;376(21):2011-2020.

Devinsky et al., 2017
Primary & Selected Secondary Outcomes

Primary Outcome:

- Percentage change per 28 days from the 4-week baseline period in convulsive seizure frequency during the 14-week period

Selected Secondary Outcomes:

- Caregiver Global Impression of Change (CGCIC) on a 7-point scale
- Number of patients with reduction in convulsive-seizure frequency of 25-100%
- Reduction in total seizure frequency and reduction of seizure subtypes
- Duration of seizure subtypes as assessed by CGIC in Seizure Duration (CGICSD)

Devinsky O, Cross J, Laux L et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *New England Journal of Medicine*. 2017;376(21):2011-2020.

Devinsky et al., 2017 Results: Primary and Selected Secondary Outcomes

Outcome	Cannabidiol	Placebo	*P* Value	Confidence Interval
Percentage Change in Convulsive-Seizure Frequency	-38.9	-13.3	0.01	-22.8 (-41.1 to -5.4)
Improvement from baseline in **CGIC Score**	62%	34%	0.02	-1 (-1 to 0)
Percentage Change in **Total Seizures**	28.6%	9%	0.03	-19.20 (-39.25 to -1.17)

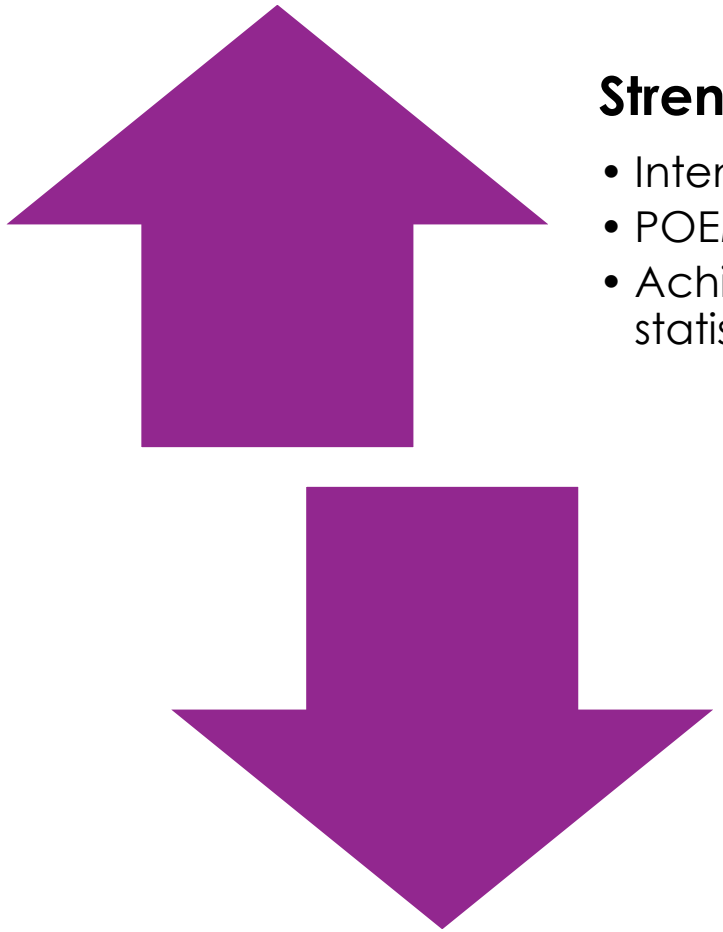
Devinsky O, Cross J, Laux L et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *New England Journal of Medicine*. 2017;376(21):2011-2020.

Devinsky et al., 2017
Results: Selected Safety Outcomes

Safety Measure	Cannabidiol	Placebo
	% of patients	
Adverse events experienced in either group	93%	75%
Diarrhea	31%	10%
Fatigue	20%	3%
Decreased appetite	28%	5%
Somnolence	16%	10%

Devinsky O, Cross J, Laux L et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *New England Journal of Medicine*. 2017;376(21):2011-2020.

Devinsky et al., 2017 Limitations and Strengths



Strengths

- Intention to treat analysis
- POEM
- Achieved 80% power to detect statistical significance

Limitations

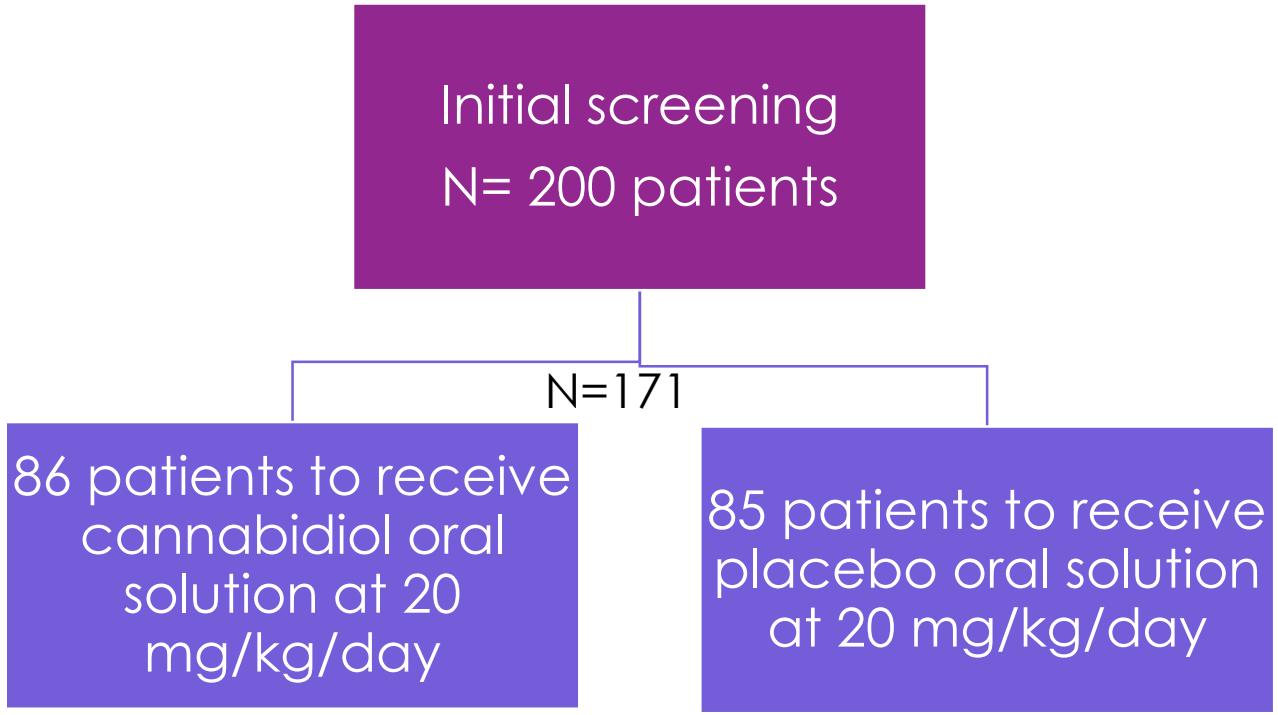
- 17 of 20 secondary outcomes were insignificant
- Gender characteristics were not even in both male and female groups, respectively
  - 57% v 46%; 43% v 54%
- Did not provide detailed information in regards to elevated LFTs
- Pertinent trial information was hard to find

POEM= Patient-oriented evidence that matters

Cannabidiol in patients with seizures associated with Lennox-Gastaut Syndrome

Thiele et al., 2018

- Randomized, double-blind, placebo-controlled trial



Selected Inclusion Criteria:

- Diagnosis of LGS
- Refractory to 1-4 other anti-epileptic medications
- Evidence of generalized seizures including drop seizures for at least 6 months

Selected Exclusion Criteria:

- Unstable mental conditions
- The use of cannabis within the past six months

Thiele et al., 2018
Primary & Secondary Outcomes

Primary Outcome:

- Percentage change in month frequency of drop seizures from baseline during a 14-week period

Selected Secondary Outcomes:

- Proportion of patients in each treatment group that achieved a reduction of 50% or more in monthly frequency of drop seizures
- Percentage change in total seizure frequency of drop seizures

Thiele et al., 2018
Results: Primary and Selected Secondary Outcomes

Outcome	Cannabidiol	Placebo	*P* Value	Confidence Interval
Percentage Change in Frequency of Drop Seizure	43.9%	21.8%	0.0135	-30.32 to -4.09
Reduction of ≥50% in monthly frequency of drop seizures	44%	24%	0.0043	1.33 to 4.97
Percentage Change in Total Drop Seizures	41.2%	13.7%	0.0005	-33.26 to 9.37

Thiele et al., 2018
Results: Selected Safety Outcomes

Safety Measure	Cannabidiol	Placebo
	% of patients	
Adverse events experienced in either group	86%	69%
Diarrhea	19%	8%
Fatigue	15%	9%
Decreased appetite	13%	2%
Pyrexia	13%	9%

Thiele et al., 2018 Limitations and Strengths

Limitations

- Per protocol analysis for primary and secondary endpoints
- Serious adverse events including elevations of LFTs, AFTs were not given an analyses
- Patient ethnicity was predominately white (at least 80% in both groups)

Strengths

- POEM
- Achieved 80% power to detect statistical significance
- Most of patient demographics were even throughout both treatment groups

Epidiolex (Cannabidiol) Place in Therapy

Cannabidiol may be a safe and possibly effective treatment for Dravet Syndrome and Lennox-Gastaut treatment

Further studies are needed to study the long-term safety and efficacy

The *American Academy of Neurology* June 2018 update for treatment-resistant epilepsy does not include cannabidiol into its treatment options

Questions?

Supplementary Slides

THC VS CBD Binding in the Brain

- THC binds with CB1 receptors in the brain producing a high
- CBD binds weakly, if at all to CB1

Devinsky et al., 2017

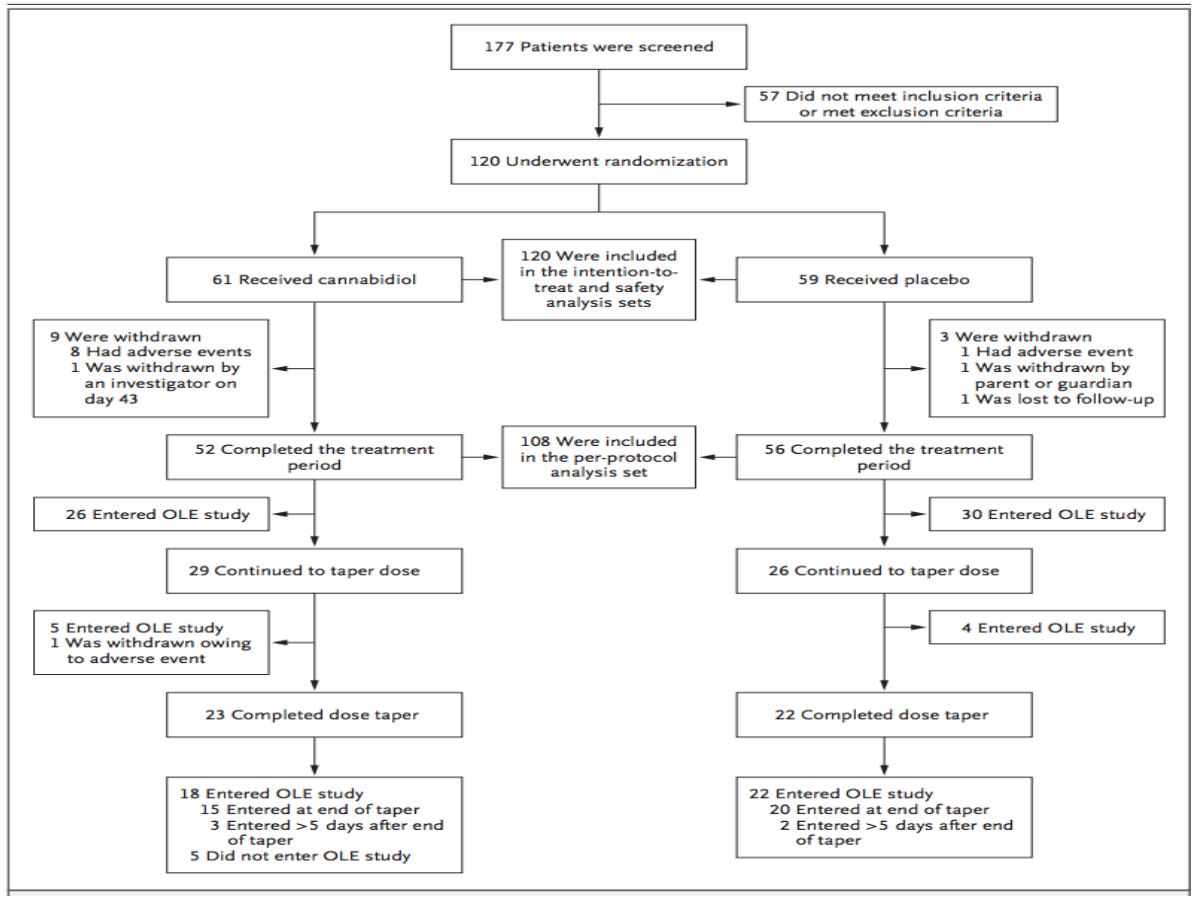


Figure 1. Screening, Randomization, Treatment Period, and Taper Period.
The primary reason that a patient in the cannabidiol group was withdrawn by an investigator on day 43 was non-adherence to trial-agent dosing. However, this patient also had seven serious adverse events that emerged during treatment by day 32, resulting in discontinuation of the trial agent. The 29 patients in the cannabidiol group who continued to taper the dose included 3 patients who were withdrawn during the treatment period and who tapered the trial agent. The 5 patients in the cannabidiol group who completed the dose taper but did not enter the open-label extension (OLE) study included 2 patients who were not eligible to enter the OLE study because they were withdrawn during the treatment period.

Devinsky et al., 2017

Table 1. Key Baseline Characteristics of the Trial Groups.*

Characteristic	Cannabidiol (N=61)	Placebo (N=59)	Total (N=120)
Age — yr			
Mean	9.7±4.7	9.8±4.8	9.8±4.8
Median (range)	9.1 (2.5–18.0)	9.2 (2.3–18.4)	9.2 (2.3–18.4)
Sex — no. (%)			
Female	26 (43)	32 (54)	58 (48)
Male	35 (57)	27 (46)	62 (52)
Geographic region — no. (%)			
United States	35 (57)	37 (63)	72 (60)
Rest of world	26 (43)	22 (37)	48 (40)
Body-mass index at baseline†	18.3±4.5	19.1±4.7	18.7±4.6
No. of previous antiepileptic drugs‡	4.6±4.3	4.6±3.3	4.6±3.8
No. of concomitant antiepileptic drugs	3.0±1.0	2.9±1.0	2.9±1.0
Antiepileptic drugs — no. (%)			
Clobazam	40 (66)	38 (64)	78 (65)
Valproate, all forms	37 (61)	34 (58)	71 (59)
Stiripentol	30 (49)	21 (36)	51 (42)
Levetiracetam	16 (26)	17 (29)	33 (28)
Topiramate	16 (26)	15 (25)	31 (26)
Other interventions — no. (%)			
Ketogenic diet	6 (10)	4 (7)	10 (8)
Vagus-nerve stimulation	6 (10)	9 (15)	15 (12)

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ These drugs were no longer being taken.

Devinsky et al., 2017

Table 3. Summary of Secondary End-Point Results during the Treatment Period (Intention-to-Treat Analysis Set).*

End Point	Cannabidiol vs. Placebo		P Value†
	Difference (95% CI)	Odds Ratio (95% CI)‡	
Change from baseline in CGIC score	−1.0 (−1.0 to 0.0)§		0.02
Reduction in convulsive seizures from baseline¶			
≥25% reduction		2.10 (1.01 to 4.35)	0.05
≥50% reduction: key secondary end point		2.00 (0.93 to 4.30)	0.08
≥75% reduction		2.21 (0.82 to 5.95)	0.11
100% reduction	4.9 (−0.5 to 10.3)‖		0.08
Percentage change from baseline in seizure frequency**			
Total seizures	−19.20 (−39.25 to −1.17)§		0.03
Total nonconvulsive seizures	0.00 (−21.36 to 31.59)§		0.88
Reduction from baseline in duration of seizure subtypes††			
Tonic–clonic seizures		2.48 (0.94 to 6.51)	0.07
Tonic seizures		3.40 (0.52 to 22.23)	0.20
Clonic seizures		1.25 (0.15 to 10.57)	0.84
Atonic seizures		7.44 (0.27 to 204.96)	0.24
Myoclonic seizures		2.89 (0.58 to 14.47)	0.20
Countable partial seizures		6.01 (0.83 to 43.21)	0.08
Other partial seizures		1.00 (<0.01 to >999.99)	1.00
Absence seizures		0.61 (0.14 to 2.62)	0.50
Change from baseline in other variables‡‡			
Sleep-disruption score	−0.4 (−1.5 to 0.7)		0.45
Epworth Sleepiness Scale score	1.5 (−0.2 to 3.2)		0.08
Quality of Life in Childhood Epilepsy score	1.5 (−3.8 to 6.8)		0.58
Vineland-II score	−2.6 (−6.8 to 1.6)		0.21
Inpatient hospitalizations due to epilepsy	0.0 (0.0 to 0.1)		0.54

Devinsky et al., 2017

Table 4. Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term.*

System Organ Class and Preferred Term	Cannabidiol (N=61)	Placebo (N=59)
	no. of patients (%)	
Gastrointestinal		
Diarrhea	19 (31)	6 (10)
Vomiting	9 (15)	3 (5)
General		
Fatigue	12 (20)	2 (3)
Pyrexia	9 (15)	5 (8)
Infections: upper respiratory tract infection	7 (11)	5 (8)
Metabolism: decreased appetite	17 (28)	3 (5)
Nervous system		
Convulsion	7 (11)	3 (5)
Lethargy	8 (13)	3 (5)
Somnolence	22 (36)	6 (10)

* Events were classified according to the *Medical Dictionary for Regulatory Activities*, version 17.0.

Thiele et al., 2018

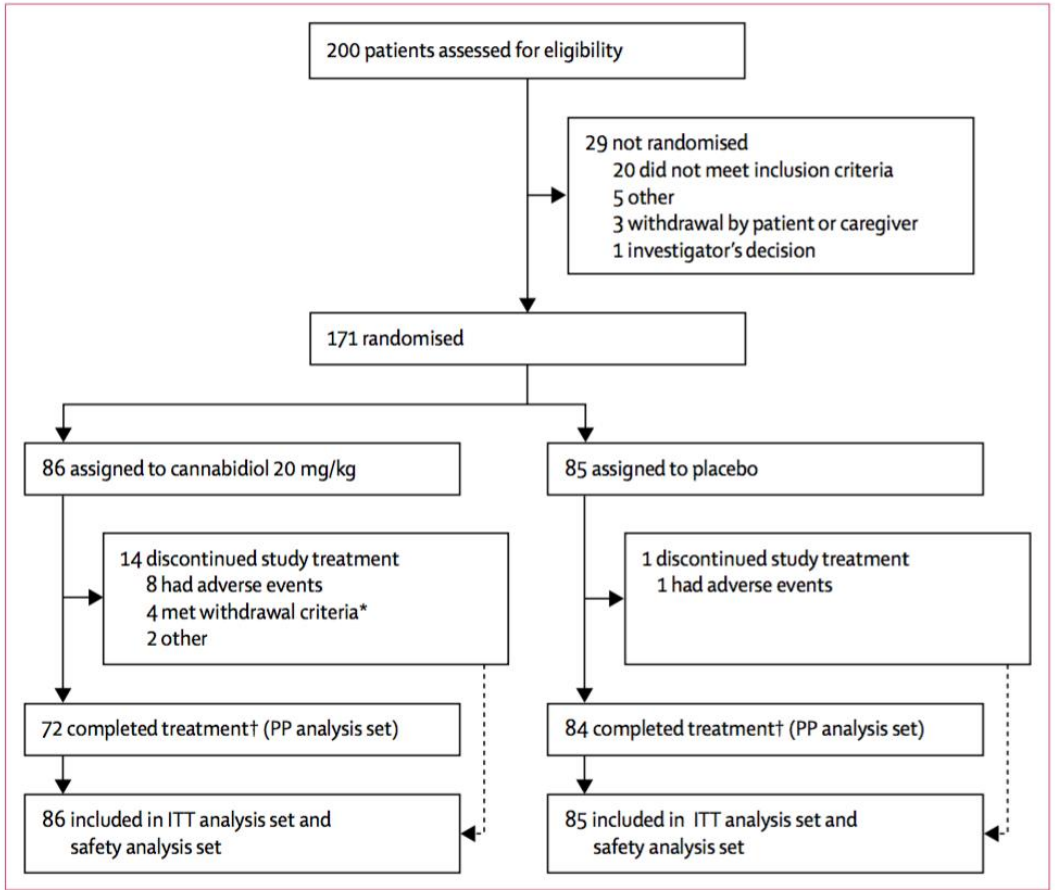


Figure 1: **Trial profile**
PP=per-protocol. ITT=intention-to-treat. *Three of the patients who met withdrawal criteria had elevations in liver transaminases that were considered adverse events. One patient who withdrew for other reasons had a viral infection that was considered an adverse event. †72 patients in the cannabidiol group and 84 in the placebo group were enrolled in the open-label extension trial.

Thiele et al., 2018

	Cannabidiol (n=86)	Placebo (n=85)
Age (years)		
Mean (SD)	15·5 (8·7)	15·3 (9·8)
Median (range)	14·2 (2·7–39·0)	13·3 (2·8–45·1)
Age group (years)		
2–5	11 (13%)	12 (14%)
6–11	26 (30%)	27 (32%)
12–17	19 (22%)	18 (21%)
18–55	30 (35%)	28 (33%)
Sex		
Female	41 (48%)	42 (49%)
Male	45 (52%)	43 (51%)
Race		
White	75 (87%)	79 (93%)
Other*	11 (13%)	6 (7%)
Region		
USA	62 (72%)	66 (78%)
Rest of world	24 (28%)	19 (22%)
AED status		
Previous AEDs per patient†	6 (1–18)	6 (0–28)
Concomitant AEDs per patient†	3 (1–5)	3 (1–4)
Current AEDs		
Clobazam	41 (48%)	43 (51%)
Valproate (all forms)	36 (42%)	33 (39%)
Lamotrigine	33 (38%)	31 (36%)
Levetiracetam	24 (28%)	34 (40%)
Rufinamide	24 (28%)	22 (26%)
Other concomitant interventions		
Ketogenic diet	4 (5%)	10 (12%)
Vagus nerve stimulation	26 (30%)	25 (29%)
Monthly frequency of seizures at baseline		
Drop seizures	71·4 (27·0–156·0)	74·7 (47·3–144·0)
Total seizures	144·6 (72·0–385·7)	176·7 (68·6–359·5)
Non-drop seizures	94·0 (19·8–311·0)‡	85·0 (20·5–220·0)§

Data are n (%), mean (SD), or median (IQR). AED=antiepileptic drug. *Includes patients who identified as black or African American, Asian, Hispanic, Latino, and Arabian. †One patient was reported as having no previous treatment with AEDs and current treatment with four AEDs, and seven patients were reported as having previous treatment with one AED and current treatment with one or more AEDs; all other patients were reported as having previous treatment with two or more AEDs. All patients met the International League Against Epilepsy definition of refractory Lennox-Gastaut syndrome (ie, inadequately managed on two or more AEDs). ‡n=77. §n=79.

Table 1: **Patient demographics and baseline characteristics**

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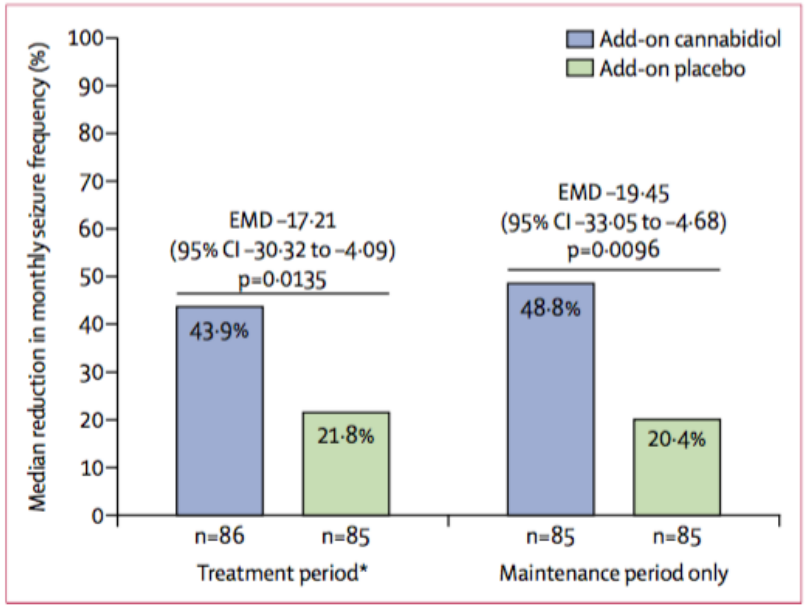

Figure 2: **Reduction in drop seizure frequency during the treatment and maintenance period**

Median percentage reduction in monthly drop seizures during the 14-week treatment period (2 weeks of dose escalation plus 12-week maintenance period alone) in cannabidiol and placebo treatment groups. EMD=estimated median difference. *Primary endpoint.

Thiele et al., 2018

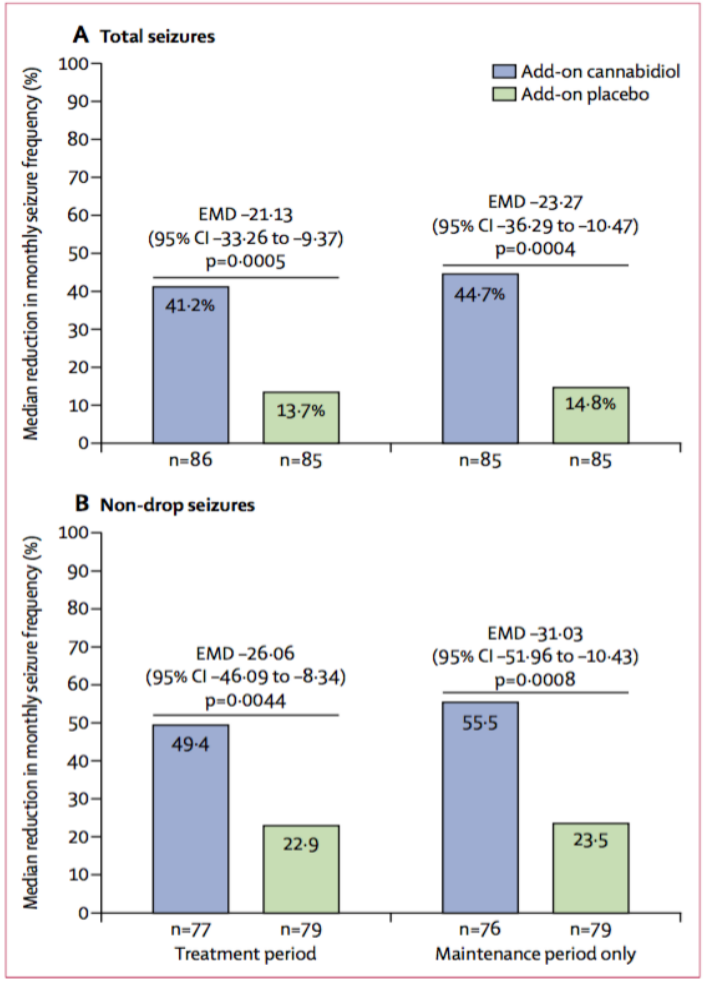

Figure 4: **Reduction in seizure frequency during the treatment and maintenance period**
Median percentage reduction in monthly (A) total seizures and (B) non-drop seizures during the 14-week treatment period (2 weeks of dose escalation plus 12-week maintenance period alone) in cannabidiol and placebo treatment groups. EMD=estimated median difference.

Thiele et al., 2018

	Cannabidiol (n=86)		Placebo (n=85)	
	All cause	Treatment related	All cause	Treatment related
Diarrhoea				
Mild	12 (14%)	9 (10%)	6 (7%)	3 (4%)
Moderate	3 (3%)	2 (2%)	1 (1%)	0
Severe	1 (1%)	0	0	0
All	16 (19%)	11 (13%)	7 (8%)	3 (4%)
Somnolence*				
Mild	5 (6%)	5 (6%)	5 (6%)	4 (5%)
Moderate	8 (9%)	7 (8%)	3 (4%)	3 (4%)
All	13 (15%)	12 (14%)	8 (9%)	7 (8%)
Pyrexia				
Mild	7 (8%)	0	5 (6%)	1 (1%)
Moderate	4 (5%)	1 (1%)	2 (2%)	0
All	11 (13%)	1 (1%)	7 (8%)	1 (1%)
Decreased appetite				
Mild	7 (8%)	5 (6%)	1 (1%)	0
Moderate	3 (3%)	2 (2%)	1 (1%)	1 (1%)
Severe	1 (1%)	1 (1%)	0	0
All	11 (13%)	8 (9%)	2 (2%)	1 (1%)
Vomiting				
Mild	3 (3%)	3 (3%)	9 (11%)	3 (4%)
Moderate	5 (6%)	2 (2%)	5 (6%)	1 (1%)
Severe	1 (1%)	1 (1%)	0	0
All	9 (10%)	6 (7%)	14 (16%)	4 (5%)

Data are n (%). The most common adverse events, defined using Medical Dictionary for Regulatory Activities preferred terms, were events that occurred in more than 10% of patients. Event names were defined according to the Medical Dictionary for Regulatory Activities. *Nine (69%) of 13 patients in the cannabidiol group and seven (88%) of eight patients in the placebo group with somnolence were taking concomitant clobazam.

Table 2: **Most common adverse events**

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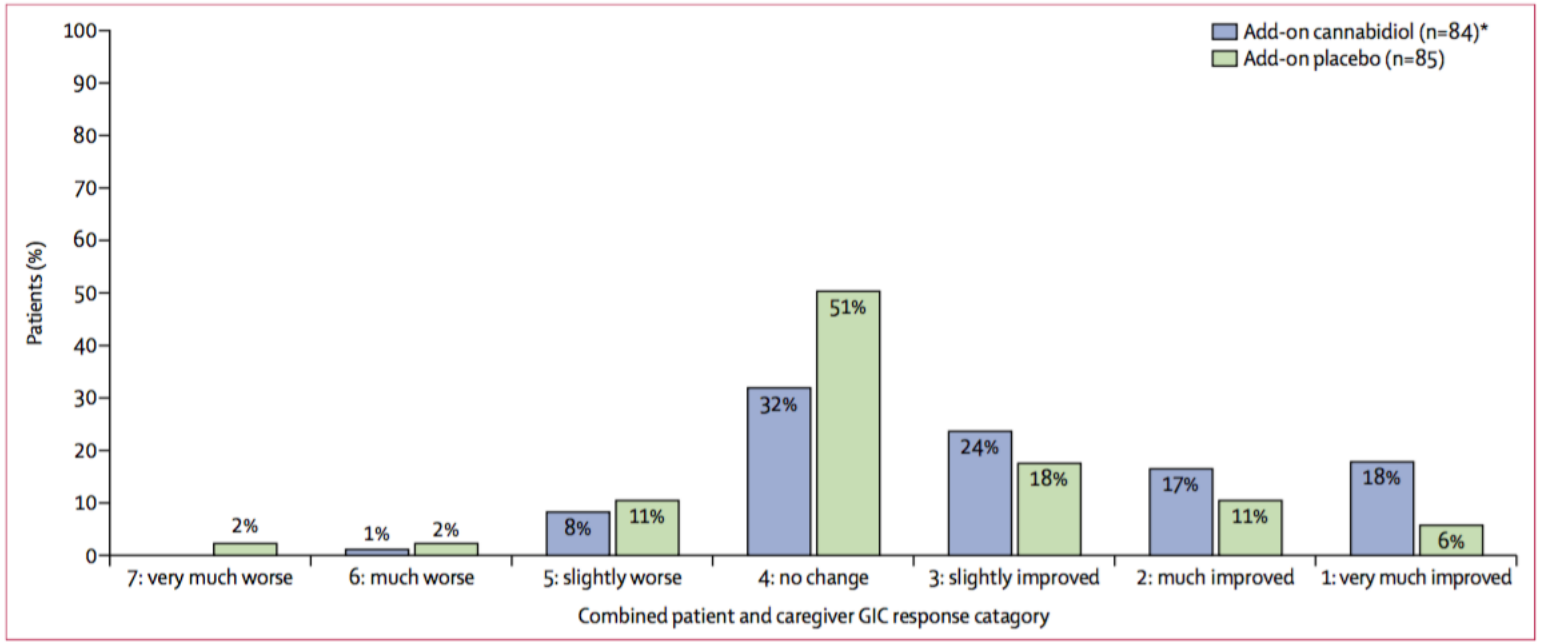

Figure 5: **Patient and caregiver GIC scores**
For the ordinal logistic regression analysis, scores ranged from 7–1 (7=very much worse, 1=very much improved). If both caregiver GIC and patient GIC questionnaires were completed, the caregiver GIC score was used. If only the caregiver GIC was completed, the caregiver GIC was used, and if only the patient GIC was completed, the patient GIC was used. GIC=global impression of change. *The questionnaire was not completed for two patients in the cannabidiol group.

Thiele et al., 2018

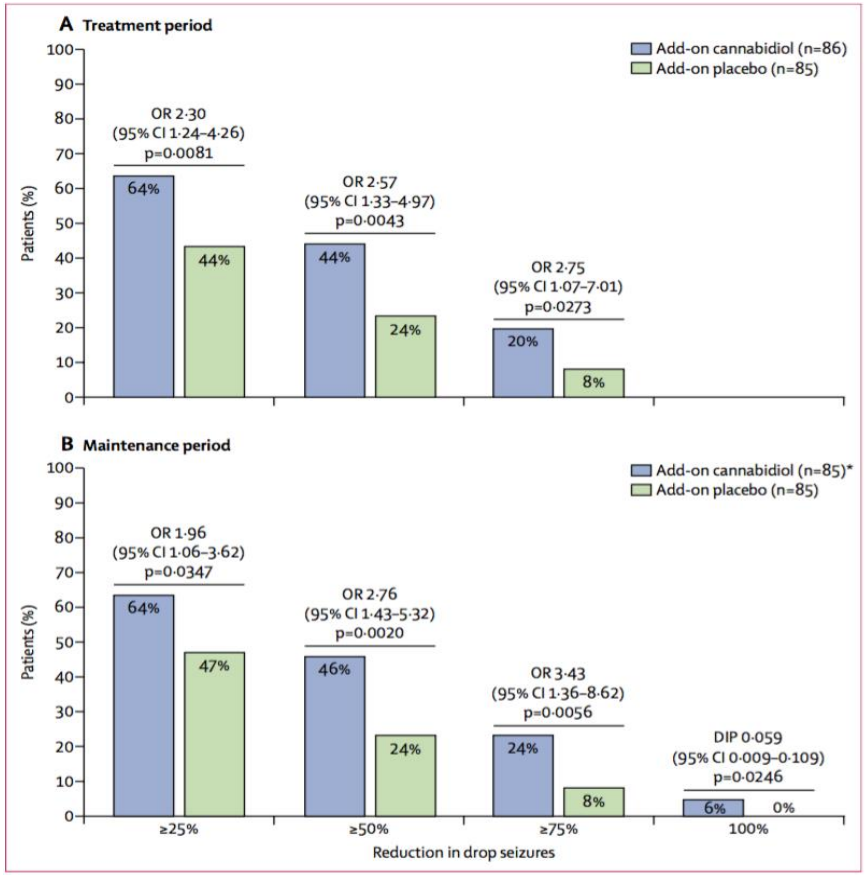

***Figure 3*: Patients who responded to treatment as measured by reduction in drop seizures**
The proportion of patients who had a reduction in drop seizure frequency of 25% or more, 50% or more, 75% or more, or 100% during the treatment period (A) and the maintenance period alone (B). Because no patients in the placebo group were free of drop seizures during the maintenance period, DIP was used to analyse the difference between groups. Of the five patients in the cannabidiol group who were free of drop seizures during the maintenance period, three patients completed the trial. OR=odds ratio. DIP=difference in proportions. *One patient in the cannabidiol group did not reach the maintenance phase.

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