Beyond Seizures:

Addressing Neurodevelopment, Quality of Life and Emerging Therapies in Dravet Syndrome Patients

ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

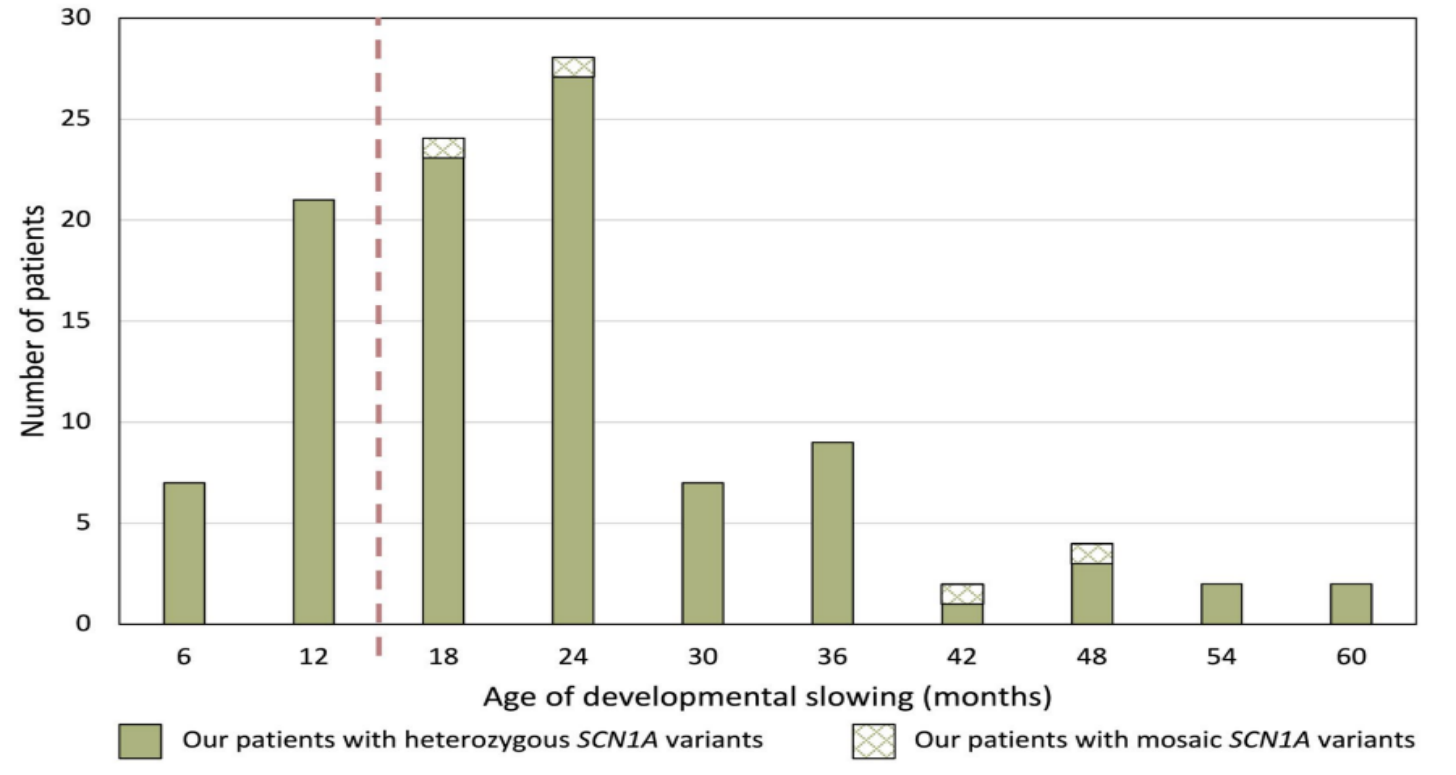
This activity is supported by an educational grant from UCB.

DS is a Developmental and Epileptic Encephalopathy (DEE)

- Onset in normal infants
  - Between ages 1-20 mos
    - Mean 5-6 mos
  - Initial presentation with seizures, often prolonged
    - Triggered by low grade fever, vaccines, excitement, hot baths
    - Presenting as either hemi clonic or bilateral tonic-clonic
  - Initial brain MRI normal
    - Cortical atrophy, hippocampal sclerosis noted in some patients over time
- Characterized by
  - Seizures
  - Intellectual disability
  - Plateaued neurodevelopment
  - Behavior abnormalities
  - Autistic features

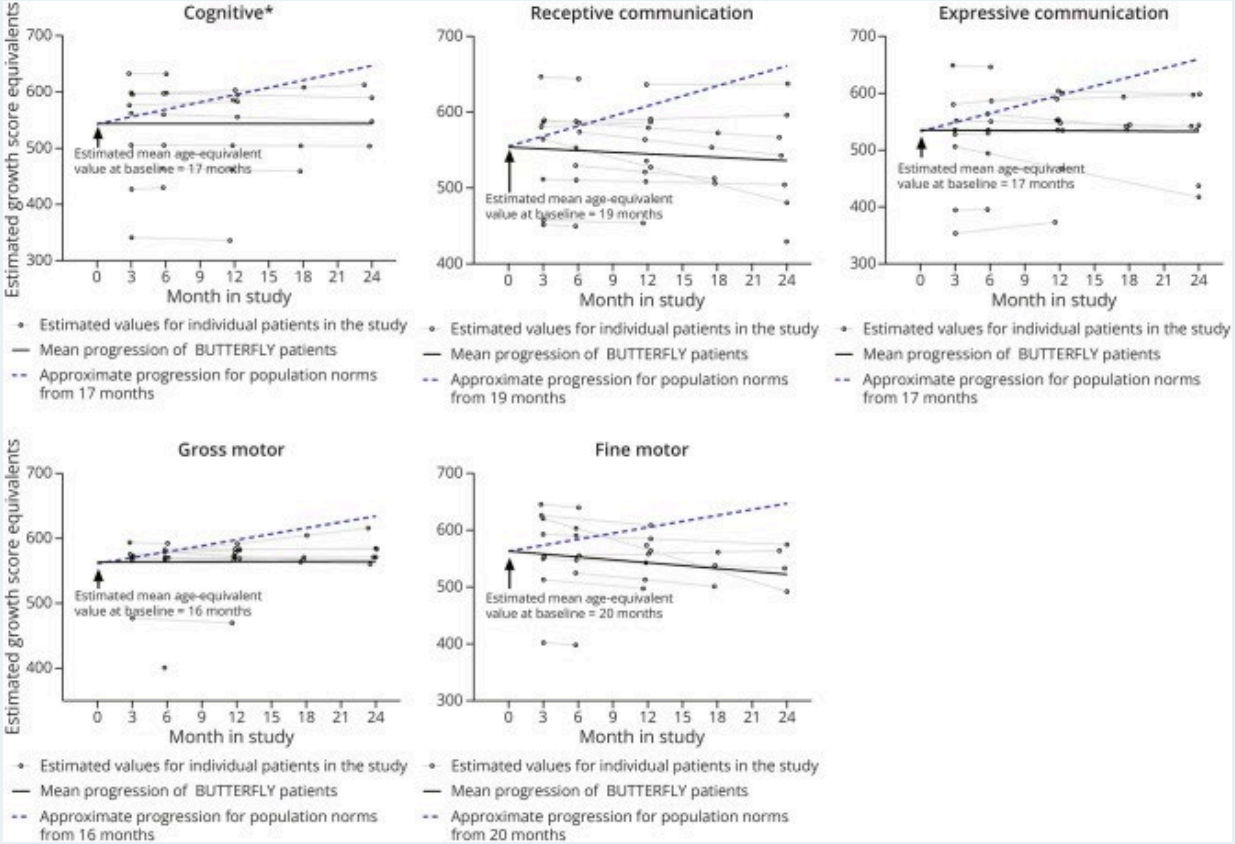
1. Li W, et al. *Epilepsia*. 2021;62:2025-2217.
2. Wirrell E, et al. *Epilepsia*. 2022;63:1761-1777.

Developmental Course



Natural History of Children & Adolescents with Dravet Syndrome (BUTTERFLY Study)

- Prospective study of children with DS aged 2-18 y
- Showed a widening gap between persons with DS and their neurotypical peers



Other Comorbidities

- Gait abnormalities
  - Mildly delayed walking
  - Presence of ataxia
  - Crouch gait in half of school children and most teens & adults

- Growth & feeding difficulties
  - Problems with appetite, eating difficulties, and weight loss frequency reported
  - Reduced height & weight growth trend with age

1. Rodda JM, et al. *JAMA Neurol*. 2012;69(7):873-878.
2. Clayton LM, et al. *Neurol Clin Pract.* 2024;14:e200288.

Other Comorbidities

- Parental reported behavior problems:
  - Inattention & hyperactivity - 69%
  - Perseveration in - 49%
  - Oppositional behavior - 35%

- High rates of parental reported sleep problems
  - Initiating and maintaining sleep - 39%
  - Sleep wake transition disorder - 35%
  - Sleep breathing disorder - 33%

1. Knupp KG, et al. *Pediatr Neurol*. 2017;76:60-65.
2. Licheni SH, et al. *Dev Med Child Neurol*. 2018;60(2):192-198.

Pathophysiology

- Mutations in the *SCN1A* gene
  - Encodes the α subunit of voltage-gated sodium channel NaV1.1
  - >90% due to de novo pathogenic variants of SCN1A
    - ~10% inherited in an autosomal-dominant pattern

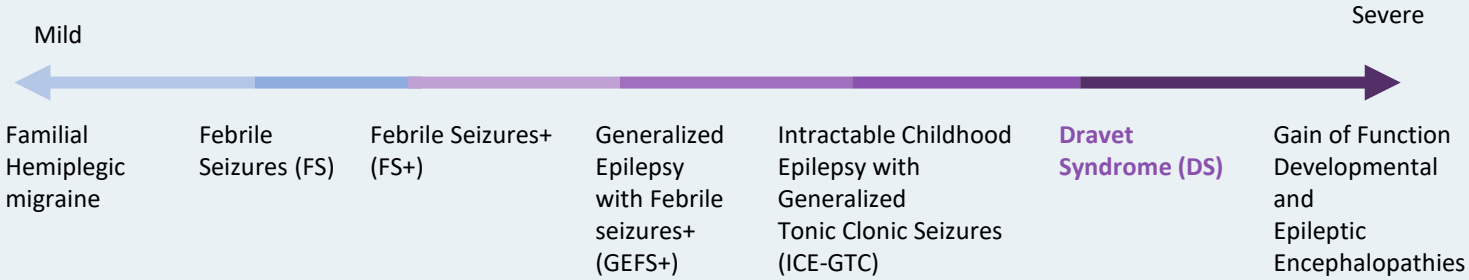
- The SCN1A haploinsufficiency results in
  - Reduced firing of parvalbumin positive (PV+) inhibitory GABAergic interneurons
    - Disinhibition of excitatory pyramidal tract neurons → Seizures
    - Activation of parasympathetic neurons → Suppression of HR and SUDEP

SUDEP: Sudden Unexpected Death in Epilepsy

1. Li W, et al. *Epilepsia*. 2021;62:2025-2217.
2. Xu X, et al. *Hum Mutat*. 2015;36:861-872.
3. Shao W, et al. *Transl Psychiatry*. 2025;15(1):84.

Pathophysiology

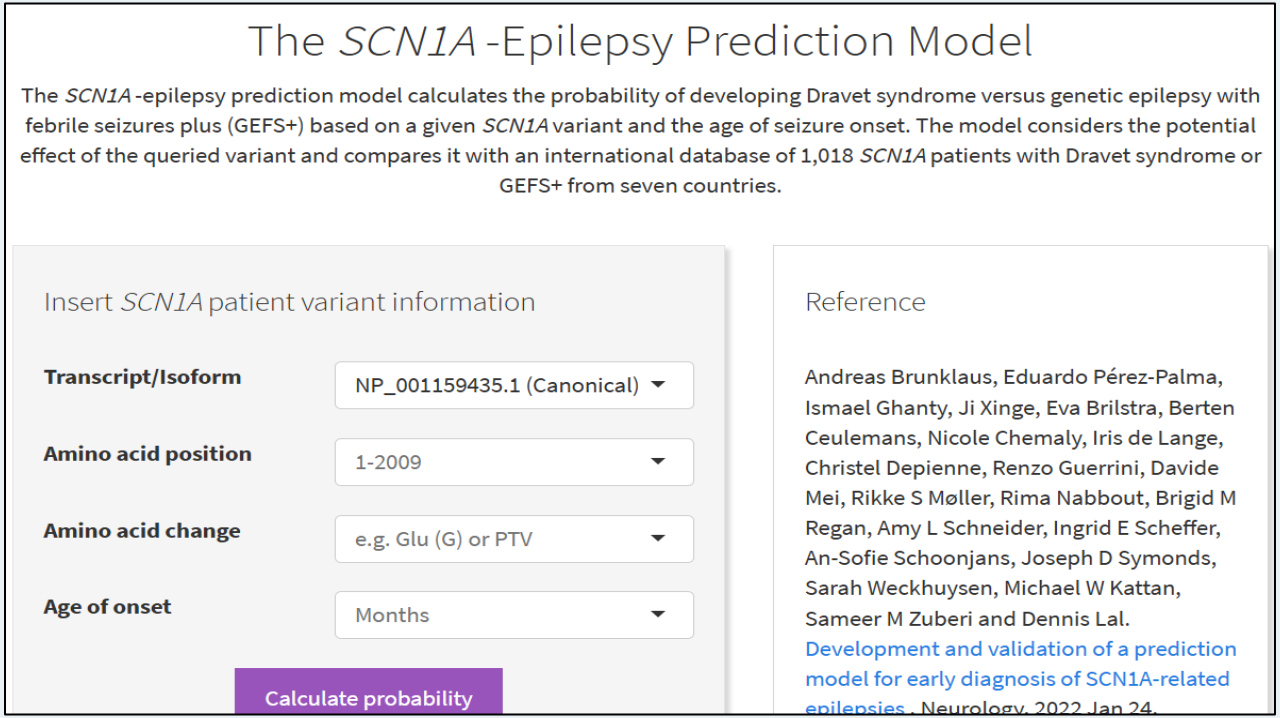
- Not all SCN1A gene mutations result in Dravet syndrome



- Rarely, mutations in other genes such as GABRG2, GABRA1, SCN1B can result in Dravet syndrome
- The diseases listed are phenotypically different

1. Ding J, et al. *Front Neurol*. 2021;12:743726.
2. Dravet Syndrome Foundation. Genetics of Dravet Syndrome. 2025. Accessed March 18, 2026. https://dravetfoundation.org/what-is-dravet-syndrome/genetics-of-dravet-syndrome.

SCN1A Prediction Model



The *SCN1A* -Epilepsy Prediction Model

The *SCN1A* -epilepsy prediction model calculates the probability of developing Dravet syndrome versus genetic epilepsy with febrile seizures plus (GEFS+) based on a given *SCN1A* variant and the age of seizure onset. The model considers the potential effect of the queried variant and compares it with an international database of 1,018 *SCN1A* patients with Dravet syndrome or GEFS+ from seven countries.

Insert *SCN1A* patient variant information

Transcript/Isoform NP_001159435.1 (Canonical)

Amino acid position 1-2009

Amino acid change e.g. Glu (G) or PTV

Age of onset Months

Calculate probability

Reference

Andreas Brunklaus, Eduardo Pérez-Palma, Ismael Ghanty, Ji Xinge, Eva Brilstra, Berten Ceulemans, Nicole Chemaly, Iris de Lange, Christel Depienne, Renzo Guerrini, Davide Mei, Rikke S Møller, Rima Nabbout, Brigid M Regan, Amy L Schneider, Ingrid E Scheffer, An-Sofie Schoonjans, Joseph D Symonds, Sarah Weckhuysen, Michael W Kattan, Sameer M Zuberi and Dennis Lal. Development and validation of a prediction model for early diagnosis of SCN1A-related epilepsies . Neurology. 2022 Jan 24.

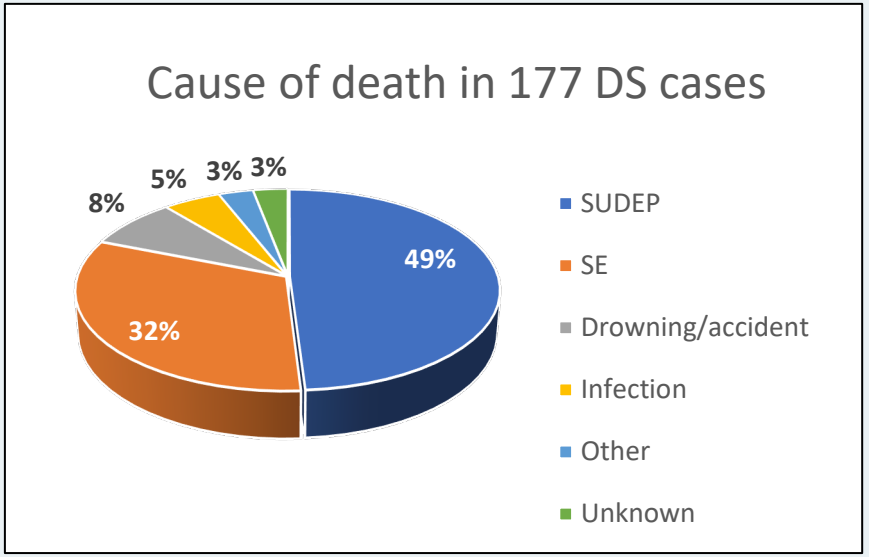
The SCN1A-Epilepsy Prediction Model. 2022. Accessed March 18, 2026. https://scn1a-prediction-model.lalresearchgroup.org/ -

Disease Burden

- Significant burden
  - Patients → epilepsy, comorbidities, treatment-related adverse effects→ impaired HRQoL
  - Caregivers → social, professional, personal life impacted → impaired HRQoL
  - Healthcare system → Requires multidisciplinary care

- SUDEP
  - Reported leading cause of death in DS

- Unmet needs
  - Better management of
    - Seizures
    - Behavior abnormalities and other comorbidities
    - Decreasing caregiver burden
    - Preventing neurodevelopmental disability



SE, status epilepticus

1. Sullivan J, et al. *Epilepsy Behav*. 2022;130:108661.
2. Shmuely S, et al. *Epilepsy Behav*. 2016;64:69-74.
3. Campbell JD, et al. *Epilepsy Behav*. 2018:80:152-156.

Diagnosis

- Febrile seizures but key features include:
  - Atypical febrile seizures that often last longer than 10-15 minutes
  - Can occur in clusters
  - Presenting as either hemi clonic or bilateral tonic-clonic
    - Often switch sides from one seizure to the next
    - Evolving to other types: focal impaired, myoclonic, absence, atonic, status epilepticus lasting > 30 minutes
- Triggers
  - Fever – but often lower grade
  - Hyperthermia/hot baths
  - Vaccination
  - Excitement

1. Li W, et al. *Epilepsia*. 2021;62:2205-2217.
2. Sullivan J, et al. *Neurology*. 2025;105:e214388.

Diagnosis (continued)

- EEG
  - Initially normal or may show background slowing
    - With continued seizures, EEG can show focal, generalized or polyspike discharges
- MRI brain
  - Normal

Li W, et al. *Epilepsia*. 2021;62:2205-2217.

Diagnosis (continued)

- A life-long disorder
  - Symptoms beginning in infancy and continue into adulthood
- Seizures persist, but
  - Seizure frequency often decreases with age
  - Less fever sensitive
  - Less prolonged seizures or status epilepticus episodes
  - Mainly nocturnal seizures
  - Continue to require polytherapy

1. Li W, et al. *Epilepsia*. 2021;62:2205-2217.
2. Wirrell E, et al. *Epilepsia*. 2022;63:1761-1777.

Diagnosis (continued)

- Other epilepsy syndromes can mimic DS
  - PCDH19-related epilepsy
  - Epilepsy with myoclonic-atonic seizures
  - Other developmental and epileptic encephalopathies
- Importance of early genetic testing including adult patients
  - Timely initiation of effective treatment
    - Consideration for novel therapies

1. Ding J, et al. *Front Neurol*. 2021;12:743726
2. Andrade DM, et al. *Epilepsy Res*. 2021;177:106743.

Seizure Management

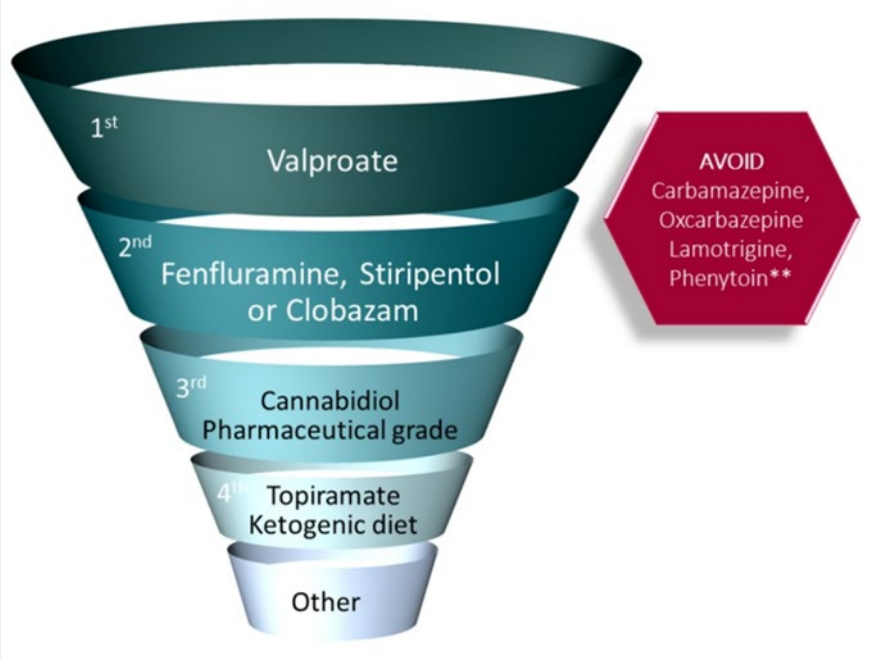
- If history suspicious for DS, should treat as DS rather than waiting for genetic confirmation
- Avoid sodium channel antiseizure medications, such as:*
  - Carbamazepine
  - Oxcarbazepine
  - Eslicarbazepine
  - Lamotrigine
    - Limited role in adults, only after the 1st-3rd line antiseizure medications have been tried
  - Phenytoin
  - Phenobarbital
  - Rufinamide

*These medications are not approved by FDA for treatment of DS

1. Wirrell E. *Can J Neurol Sci*. 2016;43:S13-S18.
2. Wirrell E, et al. *Epilepsia*. 2022;63:1761-1777.

Seizure Management

International Consensus: Antiseizure Therapies



**Phenytoin may be helpful for status epilepticus

Figure produced without modification from: Wirrell EC, et al. International consensus on diagnosis and management of Dravet syndrome. *Epilepsia*. 2022;63:1761-1777 under the terms of Creative Commons CC-BY-NC 4.0 license. ©2022. The Authors. Published by Wiley Periodicals LLC on behalf of International League Against Epilepsy.

Seizure Management

- Responder rates (> 50% reduction in seizure frequency)
  - Based on small, observational studies
    - Valproic acid → 22-48%
    - Clobazam → 28%
    - Topiramate → 35-78%
    - Levetiracetam → 11%
- There are 3 anti-seizure medications (ASMs) approved for treatment of DS
  - Cannabidiol
  - Fenfluramine
  - Stiripentol

Wirrell E. *Can J Neurol Sci*. 2016;43:S13-S18.

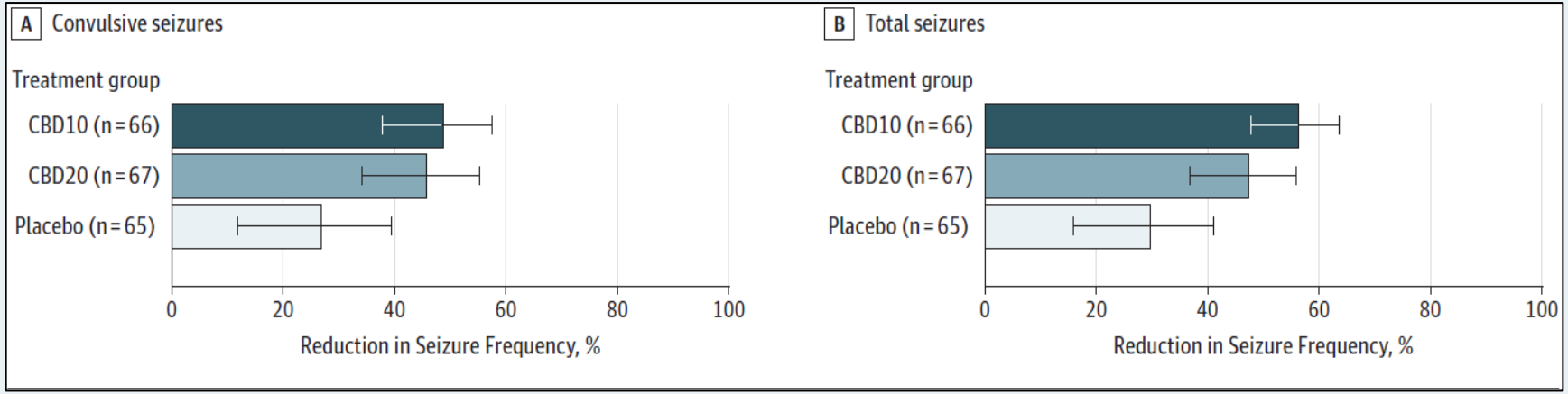
Cannabidiol (Epidiolex)

- Indication
  - Treatment of seizures in patients with DS ≥ 1 year old
- Proposed mechanism of action multifactorial, likely:
  - Agonism & desensitization of transient receptor potential vanilloid
  - 5HT1A receptors
  - Antagonism of GPR55 (G-protein coupled receptor 55)
  - Low affinity for CB1 & CB2 receptors
- Dosing
  - 10-20 mg/kg/d – divided twice daily, available as oral solution
  - Significant drug-drug interactions exist with cytochrome P450 (CYP) 3A4 enzyme inducers and drugs substrates of CYP 2C19
  - Notably, use with clobazam will results in a 2-fold increase in clobazam level and a 3-fold increase in norclobazam
    - Dose adjustment often needed

1. Epidiolex. Prescribing information. Jazz Pharmaceuticals, Inc. June 2025. Accessed February 15, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210365s023lbl.pdf -
2. Britch SC, et al. *Psychopharmacology (Berl)*. 2021;238(1):9-28.

Cannabidiol Efficacy

Similar efficacy in seizure reduction but better safety and tolerability with the 10mg/kg dose vs 20mg/kg dose



The % seizure reduction in convulsive seizures from placebo 29.8% (95%CI, 8.4%-46.2%; *P* = 0.01) for the CBD10 group and 25.7% (95%CI, 2.9%-43.2%; *P* = 0.03) for the CBD20 group; for total seizures, 38.0% for the CBD10 group (95%CI, 20.1%-51.9%; *P* < 0.001) and 25.1% for the CBD20 group (95%CI, 3.5%-41.9%; *P* = 0.03).

Cannabidiol Safety

Adverse Effects	CBD 10mg/kg/d (n=64)	CBD 20mg/kg/d (n=69)	Placebo (n=65)	CBD ≤20mg/kg/d (n=178)	CBD >20mg/kg/d (n=57)
Decreased appetite	17%	29%	17%	30%	35%
Diarrhea	17%	26%	8%	36%	61%
Somnolence	25%	23%	9%	28%	30%
Pyrexia	23%	22%	17%	34%	44%
Vomiting	6%	6%	16%	15%	30%
ALT increased	5%	13%	0%	12%	14%
AST increased	5%	12%	0-2%	3%	4%

Liver enzyme elevation occurred mostly in patients taking concomitant valproic acid
No evidence of severe drug-induced liver injury in core studies

1. Devinsky O, et al. *N Engl J Med*. 2017;376(21):2011-2020.
2. Scheffer IE, et al. *Epilepsia*. 2021;62:2505–2517.

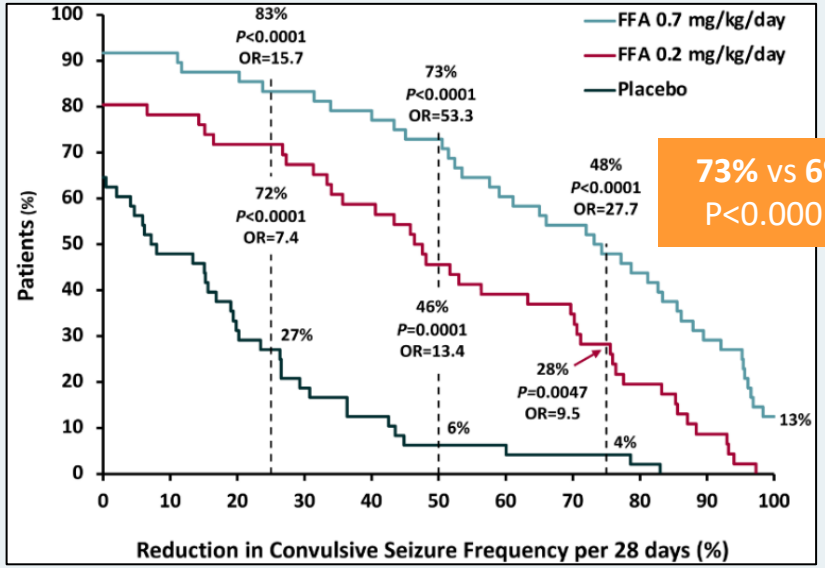
Fenfluramine (Fintepla)

- Indication
  - Treatment of seizures in patients with DS ≥ 2 y old
- Mechanism of action
  - Agonistic activity at several serotonin receptors
  - Positive modulator of Sigma1 receptor
    - Dual action restoring balance between GABAergic & glutamatergic activity
    - Improving seizure frequency
  - Potential risk of serotonin syndrome
- Dosing
  - Available in liquid form
  - Up to 0.7 mg/kg/d (max 26 mg) divided twice daily without stiripentol
  - Up to 0.4 mg/kg/d (max 17 mg) with stiripentol & clobazam

1. Fenfluramine. Prescribing information. UCB, Inc. Published 2025. Accessed February 15, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/212102s017lbl.pdf -
2. Sourbron J, et al. *Front. Pharmacol*. 2023;14:1192022.

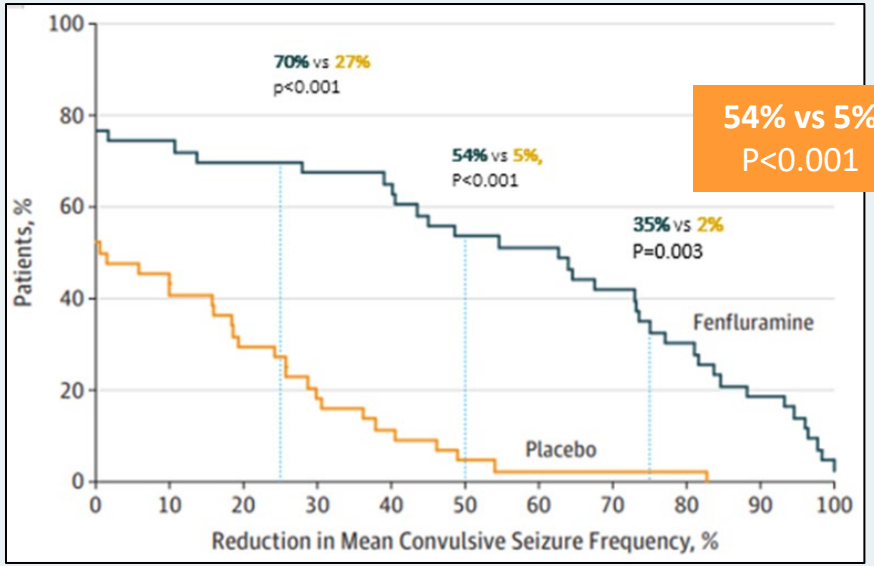
Fenfluramine Efficacy

Fenfluramine without STP[1]



73% vs **6%**
P<0.0001

Fenfluramine with STP[2]



54% vs 5%
P<0.001

STP, stiripentol

1. Figure reproduced without modification from: Sullivan J, et al. *Epilepsia*.2023;64(10):2653-2666 under the terms of Creative Commons CC-BY-NC 4.0 license. ©2023. The Author(s). Published by Wiley-Blackwell.
2. Figure reproduced without modification from: Nabbout R, et al. *JAMA Neurol*. 2020;77(3):300-308 the terms of Creative Commons CC-BY-NC-ND 4.0 license. ©2019. Nabbout R et al. *JAMA Neurol*.

Fenfluramine Safety

Adverse Effects ≥10%	Fenfluramine 0.4mg/kg/d (n=43)	Placebo (n=44)
Decreased appetite	19 (44%)	5 (11%)
Pyrexia	11 (26%)	4 (9%)
Fatigue	11 (26%)	2 (5%)
Diarrhea	10 (23%)	3 (7%)
Blood glucose decreased	6 (14%)	2 (5%)
Lethargy	6 (14%)	2 (5%)
Bronchitis	5 (12%)	2 (5%)

Adverse Effects ≥10%	Fenfluramine 0.7mg/kg/d (n=40)	Fenfluramine 0.2mg/kg/d (n=49)	Placebo (n=40)
Decreased appetite	15 (38%)	8 (20%)	2 (5%)
Diarrhea	7 (18%)	12 (31%)	3 (8%)
Fatigue	4 (10%)	4 (10%)	1 (2%)
Lethargy	7 (18%)	4 (10%)	2 (5%)
Nasopharyngitis	7 (18%)	4 (10%)	5 (12%)
Somnolence	4 (10%)	7 (15%)	3 (8%)
URT infection	0%	8 (21%)	5 (12%)
Vomiting	3 (8%)	4 (10%)	4 (10%)
Weight decrease	2 (5%)	5 (13%)	0%

Most common AE related to appetite/energy with no evidence of valvular heart disease or pulmonary hypertension

1. Nabbout R, et al. *JAMA Neurol*. 2020;77(3):300-308.
2. Lagae L, et al. *Lancet*. 2019;394(10216):2243-2254.

Stiripentol (Diacomit)

- Indication
  - Treatment of seizures in patients with DS ≥6 mos of age
  - No clinical data to support monotherapy
  - Used in combination with clobazam
    - Often also combined with valproate
- Mechanism of action
  - Potentiates GABAergic activity
  - Inhibits LDH (lactate dehydrogenase), decreasing neuronal excitability

1. Diacomit. Prescribing information. Biocodex. 2022. Accessed February 15, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/206709s003,207223s003lbl.pdf -
2. Bacq A, et al. *Adv Ther.* 2024;41:1351–1371.

Stiripentol (Diacomit)

- Dosing
  - Up to 50mg/kg/d (lower in older and bigger patients), given 2 to 3 times daily, available in capsules, powder for suspension -
  - Stiripentol inhibits metabolism of clobazam
    - Will increase levels of both clobazam and norclobazam
    - Consider clobazam dose reduction
  - Has the potential to inhibit metabolism of valproic acid as well
    - May need to reduce dose of valproic acid

1. Diacomit. Prescribing information. Biocodex. 2022. Accessed February 15, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/206709s003,207223s003lbl.pdf -
2. Bacq A, et al. *Adv Ther.* 2024;41:1351–1371.

Stiripentol Efficacy

- France and Italy STICLO studies
- STP VS Placebo
- Individuals with DS 3-18 y old
  - With 4 GTCs despite treated with VPA & CLB
- 1 month baseline
  - Followed by 2 mos STP or Placebo
  - Followed by 1-mo open label extension
    - Everyone received STP

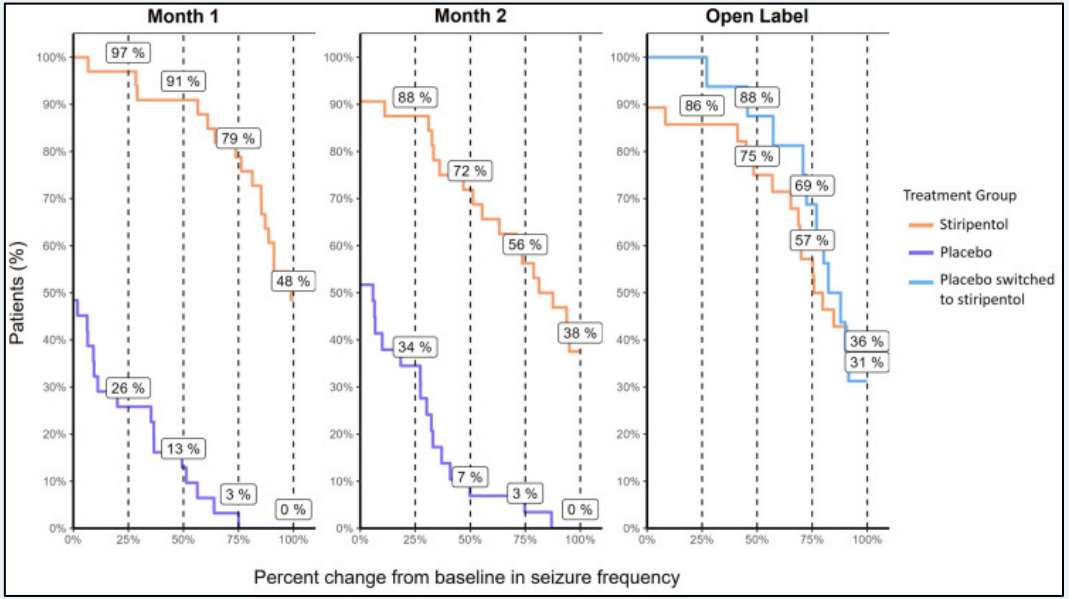


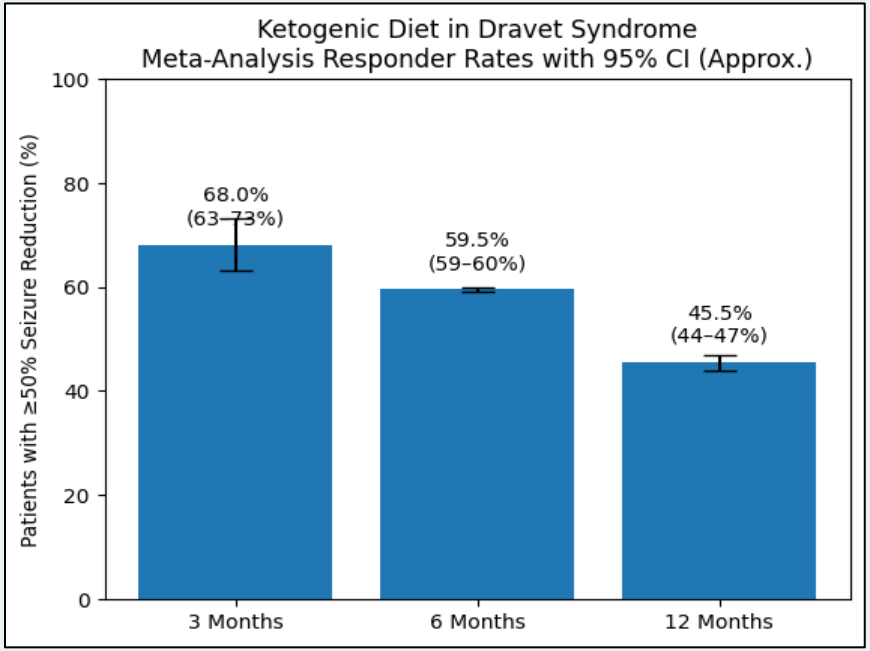
Figure reproduced without modification from: Guerrini R, et al. Additional results from two randomized, placebo-controlled trials of stiripentol in Dravet syndrome highlight a rapid antiseizure frequency efficacy with longer seizure-free periods. *Neurol Ther.* 2024;13:869–884 under the terms of Creative Commons CC-BY-NC 4.0 license. ©2024. The Author(s) 2024. Published by Springer Nature.

Stiripentol Safety

Adverse Effects	Stiripentol 50mg/kg/d (n=33)	Placebo (n=31)
Nausea	15%	3%
Vomiting	9%	0
Decreased appetite	46%	10%
Weight decreased	27%	6%
Somnolence	67%	23%
Agitation	27%	16%
Aggression	9%	0
Dysarthria	12%	0

1. Guerrini R, et al. *Neurol Ther.* 2024;13:869–884.
2. Garcia-Penas JJ, et al. *Neurol Ther.* 2025;14:27-43.

Ketogenic Diet



- Meta analysis of 7 studies
- Responder rates defined as ≥50% achieved seizure reduction
- 6 studies reported most common adverse events:
  - GI symptoms, changes in lipid profile, weight loss
- Rare adverse events included:
  - Lethargy, irritability, urinary stones, abnormal liver function, and fatigue

Wang YQ, et al. *Seizure*. 2020;81:36-42.

Multidisciplinary Care

Comorbidity	Recommended Multidisciplinary Treatment
Seizures	Maintenance of antiseizure medications, appropriate seizure action plan, epilepsy evaluation
Cognition and Behavior	Early intervention referral, individualized education plan, evaluate for ADHD, behavioral therapy
Appetite and Feeding	Swallow evaluation, dietician assessment, gastroenterology referral
Sleep Disturbances	Ask about sleep, if needed refer to sleep specialist
Gait Abnormalities	Physical therapy and rehabilitation medicine evaluation
Endocrine	Monitor stature, endocrine referral with growth concerns
Parkinsonism	Levodopa trial

Ziobro J, et al. *Curr Treat Options Neurol*. 2018;20(12):52

Dravet Syndrome Foundation Transition Guide

- The Guide reviews
  - Clinical manifestation of DS
  - Avoidance of seizure triggers
  - Vaccines
  - Guardianship and other social considerations
  - Treatment
  - Medications to avoid
  - Emergency seizure protocol

1. Andrade D, et al. *Epilepsy Res*. 2021;177:106743.
2. Dravet Syndrome Foundation. Transition Guide. 2021. Accessed March 16, 2026. https://dravetfoundation.org/new-dravet-syndrome-transition-guide-2021-10-08.

Seizure Action Plan

- Each patient should have a written action plan or emergency seizure protocol
  - High risk of recurrent status epilepticus

- It should include at home or in the community rescue medication
  - With instructions when to use
  - Interval of repetition
  - When to call 911

1. Andrade D, et al. *Epilepsy Res*. 2021;177:106743.
2. Dravet Syndrome Foundation. Transition Guide. 2021. Accessed March 16, 2026. https://dravetfoundation.org/new-dravet-syndrome-transition-guide-2021-10-08.

Zorevunersen

- An investigational antisense oligonucleotide (ASO)
  - Works at the level of mRNA-splicing
  - Using the Target Augmentation of Nuclear Gene Output (TANGO) method
  - Results in alternative splicing to avoid inclusion of poison exon
  - Increasing production of functional NAV1.1
  - Administered via intrathecal injection

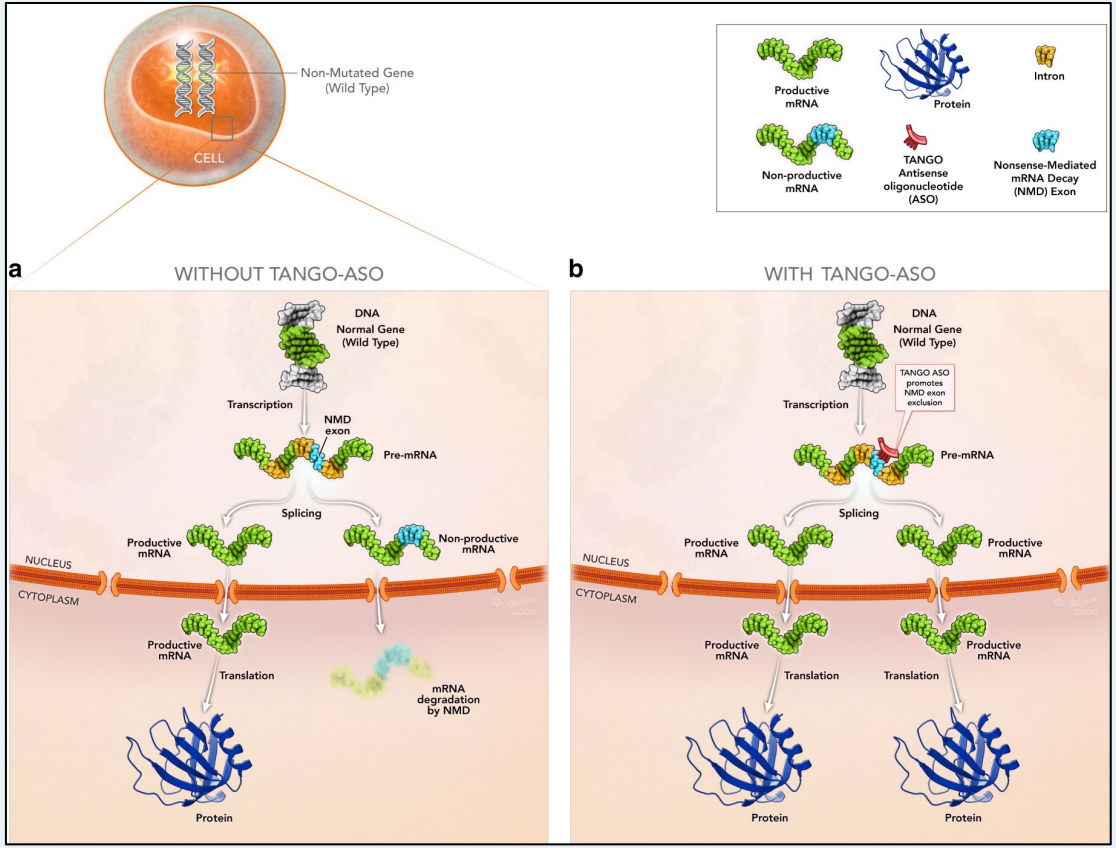


Figure reproduced without modification from: Lim KH, et al. Antisense oligonucleotide modulation of non-productive alternative splicing upregulates gene expression. *Nat Commun*. 2020;11(1):3501 under the terms of Creative Commons CC-BY 4.0 license. ©2020. The Author(s) 2020. Published by Springer Nature.

Zorevunersen Efficacy*

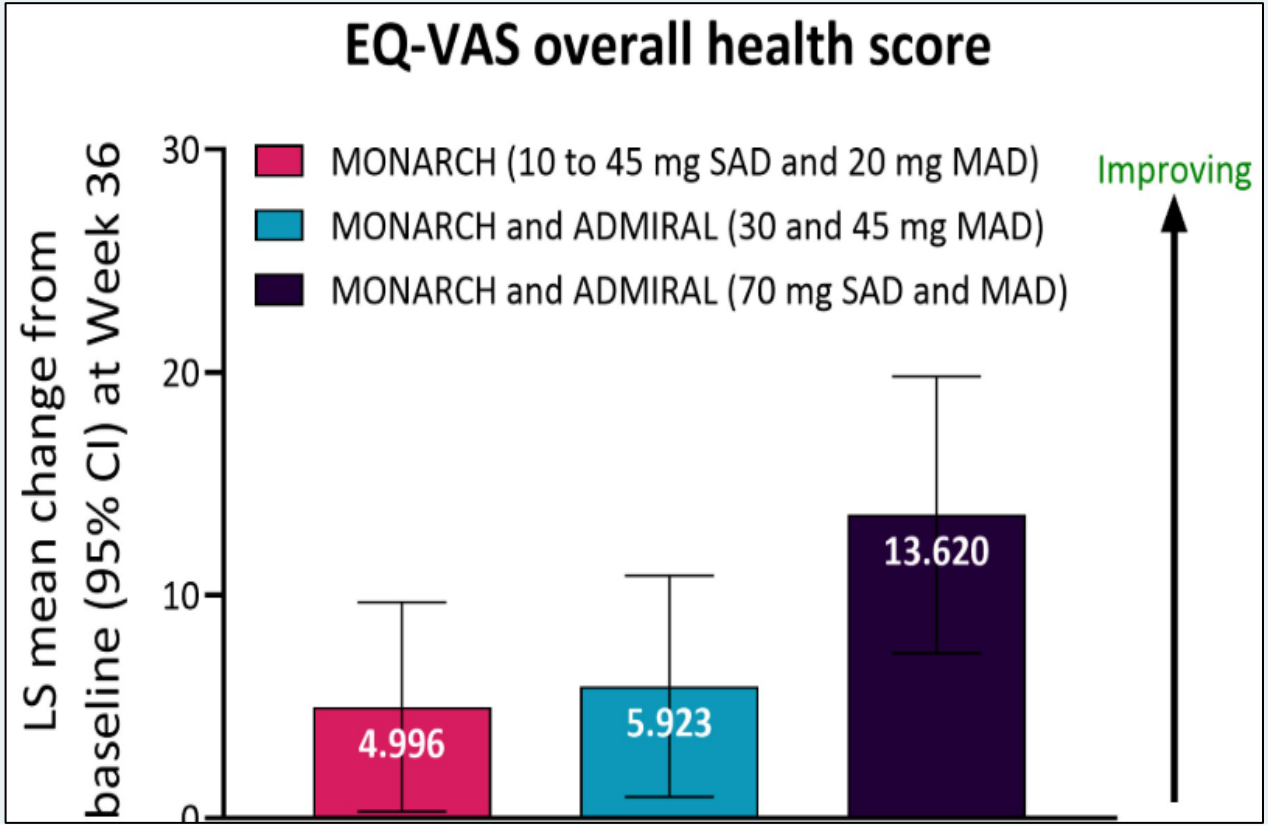
- 81 patients, age 2-18 y with DS
  - Refractory epilepsy on best available antiseizure medications
- Received single or multiple loading doses of zorevunersen ≤70 mg
- 74 patients continued with zorevunersen ≤45 mg every 4 mos
- Convulsive seizure frequency, cognition/behavior, and safety were evaluated
- Greater reduction in seizure frequency observed in those who received loading doses of 70 mg followed by maintenance dose ≤45 mg

*Data from the MONARCH, ADMIRAL, SWALLOWTAIL, LONGWING trials

Laux L, et al. *N Engl J Med*. 2026;394:969-982.

Zorevunersen Quality of Life

Quality of life ~ 9 mos after starting zorevunersen in the phase 1/2a study



Knupp K, et al. 2025 American Epilepsy Society Annual Meeting; December 5-9, 2025; Atlanta, Georgia. ABSTRACT 1.379.

Zorevunersen Safety

- Generally, well tolerated
- Most common treatment-emergent adverse event
  - Elevated CSF protein
    - 14% in phase 1/2a studies, 27% in OLE studies
    - No clinical manifestations observed
- Treatment-emergent serious adverse event
  - One patient experienced suspected unexpected serious adverse event
  - 3 deaths reported (all unrelated to zorevunersen)
    - 2 from SUDEP
    - 1 from malnutrition

1. Knupp K, et al. 2025 American Epilepsy Society Annual Meeting; December 5-9, 2025; Atlanta, Georgia. ABSTRACT 1.379.
2. Sullivan J, et al. 2025 American Epilepsy Society Annual Meeting; December 5-9, 2025; Atlanta, Georgia. ABSTRACT 2.341.

Zorevunersen: EMPEROR Trial

- Phase 3, double-blind, sham-controlled trial
- Evaluating efficacy & safety in children ages 2 to <18 y
- Randomized 1:1 to receive zorevunersen or sham procedure over 52 wks
  - Loading dose: 2 70 mg loading doses given 8 wks apart
  - Maintenance phase: 2 45 mg doses given 16 wks apart
- Primary endpoint: % change from baseline in major motor seizure frequency at week 28
- The results expected in mid-2027

Sullivan J, et al. International Epilepsy Congress. August 30- September 3, 2025; Lisbon, Portugal. ABSTRACT P358.

Clemizole Hydrochloride

- Histamine receptor antagonist
  - Modulates 5HT_2 serotonin receptors
- Demonstrated antiseizure activity in DS
- Given as oral liquid twice daily

- ARGUS phase 3 trial
  - Children age ≥ 2 y
  - Seizures not controlled on current regimen
    - Received 1:1 ratio clemizole or placebo
    - Dosing: 1-4 mg/kg twice daily, max 80 mg twice daily
    - Duration: 16 wks
  - Participants who completed ARGUS trial enrolled into 3-y OLE
  - Those in the OLE showed ~ 50% median seizure reduction compared to baseline
  - Most common treatment-emergent adverse events
    - Change in seizure presentation
    - Upper respiratory tract infection
    - Pyrexia
  - No deaths reported

OLE, open-label extension

1. Griffin A, et al. *Brain*.2017;140:669-683.
2. Ray A. 2025 American Epilepsy Society Annual Meeting; December 5-9, 2025; Atlanta, Georgia. ABSTRACT 3.353.

Bexicaserin

- A highly selective $5HT_{2c}$ agonist
  - No binding activity at $5HT_{2A}$ or $5HT_{2B}$ receptors
    - Minimizes risk of side effects (ie, hallucinogenic)
    - No risk of cardiovascular side effects
- Results from Pacific (phase 1b/2a study)
  - Individuals with DEE (n=36) who completed phase 1b/2a
  - At 18 mos, DS (n=3) showed 73% reduction in motor seizures
  - Well tolerated
- Phase 3 clinical trial ongoing
  - Individuals age ≥2 y
  - Given as capsule 3 times daily

1. Dlugos DJ, et al. *Epilepsia*. 2025;67:646-659.
2. Sylvia C, et al. 2025 American Epilepsy Society Annual Meeting; December 5-9, 2025; Atlanta, Georgia. ABSTRACT 1.564.

ETX101

- An investigational, AAV9 (adeno-associated virus serotype 9) gene therapy
- Delivers an engineered transcription factor (eTF-SCN1A) into the GABAergic inhibitory interneurons
- Enhancing transcription of the endogenous SCN1A gene
- Delivered as a single intracerebroventricular injection

1. Balestrini S, et al. *CNS Drugs*. 2026; 40(4):535-548.
2. Encoded Therapeutics. How ETX101 is expected to work [diagram]. Encoded Therapeutics Website. Accessed March 6, 2026. https://encoded.com/programs/etx101-for-dravet-syndrome/

ETX101

- POLARIS
  - Ongoing phase 1/2 trial compromising 3 open-label, dose escalation studies, ENDEAVOR (USA) WAYFINDER (AUS), AND EXPEDITION (UK)
  - Patients 6 mos to 7 y old with DS with SCN1A variant
  - On standard of care ASMs
  - Receive 1 intracerebroventricular injection
- As of June 1, 2025
  - 11 participants have received ETX101 with follow-up for up to 58 wks
  - No treatment-related serious adverse events or dose-limiting toxicities reported
  - Early efficacy data shows dose-dependent reductions in seizure burden, use of rescue medications, and an increase in seizure-free days.
    - A median reduction of 87% (range:47%-90%) in monthly countable seizure frequency from baseline observed at the highest dose tested
  - Dose escalations are ongoing

Sullivan J, et al. 2025 American Epilepsy Society Annual Meeting; December 5-9, 2025; Atlanta, Georgia. ABSTRACT 1.308.

Key Concepts

- Dravet Syndrome
  - A severe, lifelong developmental and epileptic encephalopathy
    - Normal development at onset
      - But with time, all patients develop variable degrees of developmental disabilities and other comorbidities
    - Epilepsy
      - Drug-resistant, difficult to control
  - Results from pathogenic variants in the *SCN1A* gene
    - Early genetic testing is critical
    - Initiate therapy as soon as possible

Key Concepts

- Management
  - Several Dravet syndrome-specific therapies with proven efficacy recently approved:
    - Fenfluramine, stiripentol, and cannabidiol
  - Use of ketogenic diet also an option
  - Requires a multidisciplinary approach
- Additional disease-modifying therapies are currently in the pipeline
  - Including precision genetic therapies, targeting *SCN1A* and NaV1.1
  - Shown to improve
    - Seizure frequency
    - Cognition, behavior, and overall functioning
    - Quality of life