Update on Anti-Seizure Medications

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COMPREHENSIVE EPILEPSY CENTER

Jonathan J. Halford, MD
Professor of Neurology
Medical University of South Carolina
Charleston, SC

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Disclosures

- Consultant: Takeda Pharmaceuticals, Jazz Pharma
- Investigator for clinical trials funded by:
  - GW Pharma
  - Takeda Pharmaceuticals,
  - Cerevel Pharmaceuticals
  - Epitel Inc
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Topics

- SANAD II
- Cenobamate
- Risk of arrhythmia with lamotrigine
- Lennox-Gastaut Syndrome and Dravet Syndrome
- Cannabadiol
- Fenfluramine

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The Need for New Anti-seizure Medications

- In the USA, approximately 3 million people live with epilepsy.
- Of those, about one-third continue to experience seizures despite taking one or more antiseizure medications(ASMs).
- Many ASMs are poorly tolerated, have significant drug-drug interactions, and/or have undesirable long-term toxicity problems
- This gap in therapy suggests a need for additional therapeutics with novel mechanisms of action.

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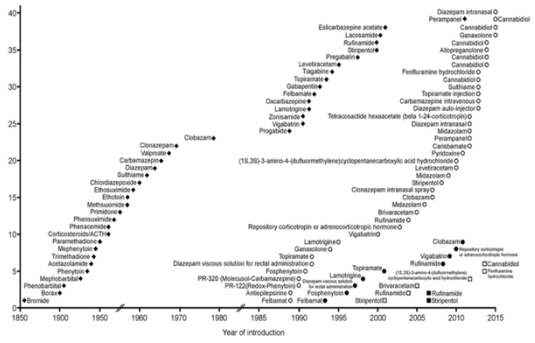

Döring JH, Lampert A, Hoffmann GF, Ries M. Thirty years of orphan drug legislation and the development of drugs to treat rare seizure conditions: a cross sectional analysis. PLoS One. 2016 Aug 24;11(8):e0161660.

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SANAD II Trials
(Study of Standard and New Antiepileptic Drugs II)

- European trials evaluating response to first line treatment in newly diagnosed focal, generalized, or unclassified epilepsy
- Randomized, controlled, un-blinded studies designed to assess the long-term effectiveness of newer and older anti-seizure medications and cost-effectiveness
- Age 5 and older and included 2 years follow-up
- For focal epilepsy, lamotrigine was chosen as the medication to beat as it had been identified in the SANAD I trial as the medication of choice for focal epilepsy: more effective, better tolerated and more cost effective than carbamazepine, oxcarbazepine, gabapentin or topiramate.

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SANAD II Trials – Focal Epilepsy

- Levetiracetam was found to be inferior to lamotrigine and zonisamide regarding the time to achieve long term (one and two year) seizure remission and time to first breakthrough seizure.
- Levetiracetam and zonisamide were found more likely to fail than lamotrigine due to poor seizure control and adverse reactions.
- Adverse reactions were more frequent in the levetiracetam (44%) and zonisamide (45%) groups as compared to lamotrigine (33%).
- Initial advised doses: lamotrigine 50 mg QAM and 100 mg QHS, levetiracetam 500 mg BID, and zonisamide 100 mg BID.
- Final doses: lamotrigine 100mg BID, levetiracetam 750mg BID, zonisamide 250mg/day

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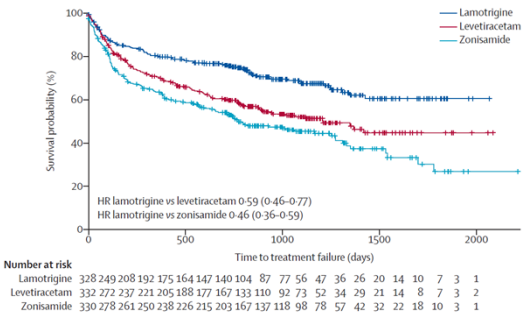
SANAD II Trials – Focal Epilepsy



Number at risk

Lamotrigine	328	249	208	192	175	164	147	140	104	87	77	56	47	36	26	20	14	10	7	3	1
Levetiracetam	332	272	237	221	205	188	177	167	133	110	92	73	52	34	29	21	14	8	7	3	2
Zonisamide	330	278	261	250	238	226	215	203	167	137	118	98	78	57	42	32	22	18	10	3	1

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SANAD II Trials
Generalized and Unclassified Epilepsy

- Valproate was chosen as the standard treatment as it had outperformed topiramate and lamotrigine in the SANAD I trial.
- In SANAD II, levetiracetam was shown to be inferior to valproate in the time to achieve long term (one and two year) seizure remission.
- A smaller proportion of patients in levetiracetam (24%) achieved immediate 12 month seizure freedom as compared to valproate (33%).
- There was no difference in treatment failure due to side effects or adverse events
- Initial advised doses: levetiracetam 500mg BID, valproate 500mg BID
- Final dose: levetiracetam 750-1000mg BID, valproate ~500mg BID

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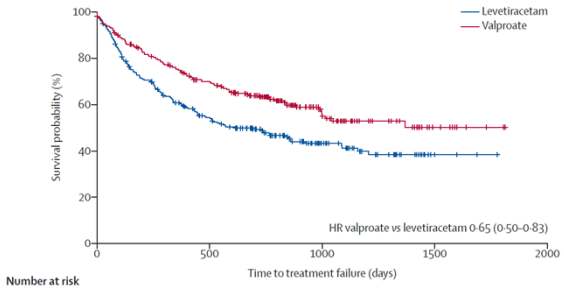
SANAD II Trials
Generalized and Unclassified Epilepsy



Number at risk

Levetiracetam	260	228	210	193	176	166	151	136	104	72	56	36	28	23	19	10	4	3	2	0
Valproate	260	209	177	155	137	123	111	97	77	65	46	39	27	22	15	3	2	1	0	..

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Levetiracetam: Is the Honeymoon Over?

- Pros: can be started quickly, low rate of allergic reactions, no drug-drug interactions, linear pharmacokinetics, broad spectrum
- Cons:
  - **Inferior Efficacy**. A prior randomized trial and a Cochrane review had already found levetiracetam to be inferior to Carbamazepine and Lamotrigine in the treatment of focal epilepsy and to valproic acid in the treatment of generalized epilepsy regarding time to achieve 12-month seizure remission.
  - **Frequent psychiatric side effects**. Levetiracetam is associated with an increased risk of behavioral side effects and neuropsychiatric symptoms in up to 13% of adults. These side effects include mood disorders, irritability, agitation, hostility, suicidal ideations and psychosis.

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Primary Generalized Gemetoc Epilepsy

- Limited number of anti-seizure drug therapeutic options
  - Valproate
  - Levetiracetam
  - Zonisamide
  - Topiramate
  - Lamotrigine
  - Lacosamide

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New data on teratogenicity of zonisamide and topiramate

- In **preclinical studies**, zonisamide causes developmental abnormalities in mice, rats, dogs and is embryo-lethal to monkeys, when given in the first trimester at doses similar to human dosing schedules
- In a recent registry, there were 112 cases of first trimester exposure to **zonisamide**, including 26 monotherapy cases. There were 3 major malformations for a rate of **13.0**%.
- In a recent large cohort study, in same-aged children of mothers with epilepsy exposed to **topiramate** and valproate monotherapy, 4.3%and 2.7%, respectively, had **autism**, and 3.1% and 2.4%had **intellectual disability**. The ajdusted risk for these after topiramate exposure were 2.8-3.5 and after valproate exposure were 2.4-2.5 (95%CI, 1.7-3.7). (Bjock, JAMA Neurology, 2022)

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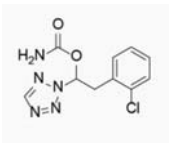
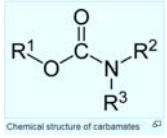
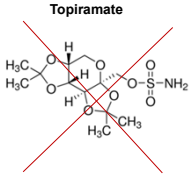
Carbamates

Cenobamate





Topiramate



Felbamate

Carisbamate

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Cenobamate Versus Other ASMs in Epilepsy Animal Models

	MES	6 Hz, 22 mA	6 Hz, 32 mA	6 Hz, 44 mA	s.c. PTZ	s.c. BIC	s.c. PIC
CBM	5.9	5.3	3.2	3.5	2.0	<0.8[a]	1.7
FBM	6.2	16.8	3.2	0.9	1.7	<0.9	2.0
LCM	6.0		1.3	1.8	<1.1	<0.5	<0.9
CBZ	5.8	4.2	1.8	1.8	<0.9	<0.9	2.5
LTG	5.6	1.6	0.5	0.7	<0.4	<0.8	<0.8
PHT	7.6		<0.9	0.8	<1.02	<1.02	<1.02
TPM	12.8		<0.8			<0.5	<0.5
VPA	1.5	6.7	2.9	1.4	1.8	0.7	1.5
PB	4.0		3.1	1.3	3.3	1.2	1.7

0.4 — 16.8

Protective Index (PI) = (median toxic dose/median effective dose); Heat map demonstrates relative PIs of ASMs in different antiseizure tests in rat and mouse epilepsy models. Red: lowest relative PI; green: largest relative PI)

Guignet M, Campbell A, White HS. Cenobamate (XCOPRI): Can preclinical and clinical evidence provide insight into its mechanism of action? Epilepsia. 2020 Nov;61(11):2329-39.

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Mechanisms of Action cenobamate

1. Acts on voltage-gated sodium channels (VGSCs) by **blocking persistent sodium currents (I_{NaP})**, and increasing inactive sodium channel states
2. **Positive allosteric modulator of $GABA_A$ receptors** independently from the benzodiazepine binding site.

- Every sodium channel blocker ASM likely has unique characteristics that differentiate it from a clinical perspective:
  - carbamazepine, felbamate, and lamotrigine primarily target the transient sodium current (I_{NaT})
  - phenytoin on is one of the few that predominately acts on I_{NaP} but it also has effects on I_{NaT} too
  - lacosamide also acts on VGSCs, but stabilizes their slow-inactivated state

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Pharmacokinetics cenobamate

- Metabolism
  - Inhibits CYP2C19, leading to increased phenytoin and phenobarbital levels
  - Phenobarbital and phenytoin increase cenobamate levels
  - Induces CYP3A4 and CYP2B6 (may require higher doses of a few medications)
  - Linear pharmacokinetics
- Elimination
  - 88% renal (6% unmetabolized)
  - 5% biliary
- Protein Binding
  - 60% protein bound
- Rapidly (T_{max}=1-4 hr) and largely absorbed (88% bioavailability)

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Pharmacokinetics cenobamate

- Half-life
  - ~ 50-60 hours at typical doses
  - Steady state attained in ~ 2 weeks
  - Non-linear pharmacokinetics
  - → once per day administration
- Safety Pharmacology and Toxicity Studies
  - Animal models show mainly CNS side effects
  - Reproductive: weakly teratogenic at very high doses
  - Genotoxicity: none detected
  - Carcinogenicity: none detected

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Drug-drug Interactions cenobamate

- Cenobamate induces CYP2C19, induces CYP2C8, and can inhibit or induce CYP2B6 and 3A4

→ increased phenytoin and phenobarbital plasma exposures by 84% and 37%(cut phenytoin dose by 50%)

→ reduce lamotrigine plasma concentrations by 21–52%

→ increases N-desmethylclobazam concentrations (but clobazam dose by 50%)

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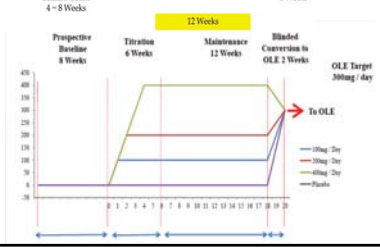
Cenobamate Phase II Trials

YKP3089-C013

YKP3089-C017



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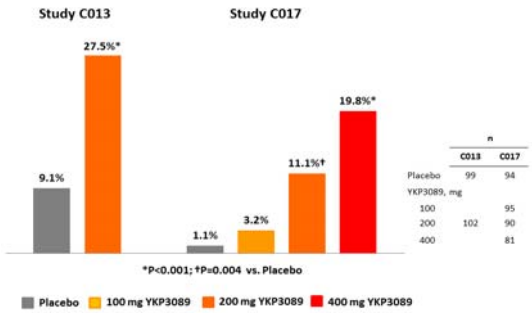
Seizure Free Rates Among Maintenance Phase Completers Cenobamate



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ASM dose	Treatment duration, wk[a]	ASM seizure freedom rate	Placebo seizure freedom rate
Cenobamate 200 mg/d	6	28.3%	8.8%
Cenobamate 100 mg/d	12	4.0%	1.0%
Cenobamate 200 mg/d	12	11.0%	1.0%
Cenobamate 400 mg/d	12	21.0%	1.0%
Eslicarbazepine 800 mg/d	12-14	4.1%	2.0%
Eslicarbazepine 1200 mg/d	12-14	8.2%	2.0%
Ezogabine 600 mg/d	8-12	2.8%	1.2%
Ezogabine 900 mg/d	8-12	4.0%	1.2%
Ezogabine 1200 mg/d	8-12	2.0%	0.0%
Lacosamide 200 mg/d	12	2.2%	1.2%
Lacosamide 400 mg/d	12	2.6%	0.8%
Levetiracetam 1000 mg/d	12-14	4.0%	0.5%
Levetiracetam 2000 mg/d	12-14	2.1%	0.9%
Levetiracetam 3000 mg/d	12-14	7.8%	0.5%
Perampanel 8 mg/d	13	3.0%	0.9%
Perampanel 12 mg/d	13	3.1%	0.8%
Topiramate 200 mg/d[b]	8-12	6.0%	2.2%
Topiramate 400 mg/d[b]	8-12	8.7%	0.0%
Vigabatrin 3000 mg/d	12	7.4%	0.7%
Zonisamide 1.5-20 mg/kg/d	8-12	6.0%	1.0%

Halford JJ, Edwards JC. Current State of Seizure Freedom as an Outcome in Epilepsy Treatment Clinical Trials. Acta Neurologica Scandinavica 2020; 142:91-107.

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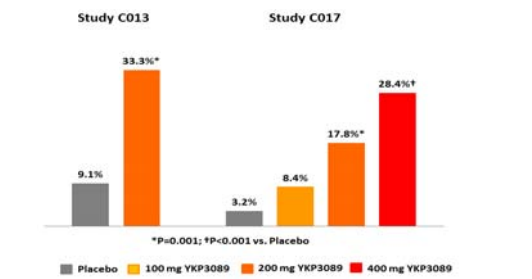
90% Responder Rates Among Maintenance Phase Completers



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Adverse Events from Phase II Trials

- Most common AEs were dose-related and included somnolence, dizziness, fatigue, diplopia, and gait disturbance.
- Hypersensitivity reactions occurred in 3/600 (442 from double-blind + 158 open-label extension) patients including one case of DRESS syndrome.
  - Two of the cases were associated with rapid titration

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DRESS Syndrome

- DRESS (drug rash with eosinophilia and systemic syndrome)
  - Severe idiosyncratic drug reaction
  - Long latency period (usually 2-8 weeks after drug initiation)
  - No tested treatment
    - It has been reported that earlier drug withdrawal improves prognosis
    - Supportive treatment
    - Corticosteroids
  - Clinical manifestations:
    - fever, rash, lymphadenopathy, eosinophilia
    - Wide range of mild to severe systemic presentations: liver enzyme elevation, renal dysfunction, heart dysfunction, toxic epidermal necrolysis, gastrointestinal symptoms, pneumonia

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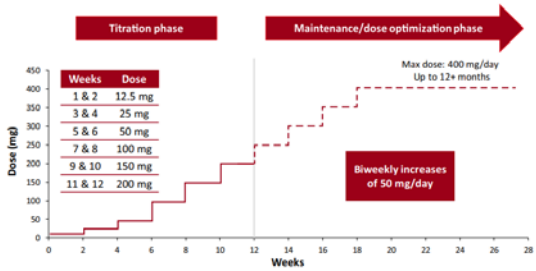
Cenobamate Phase III Study



Sperling MR, … , Halford JJ, … et al. Cenobamate (YKP3089) as adjunctive treatment for uncontrolled focal seizures in a large, phase 3, multicenter, open-label safety study. Epilepsia. 2020 Jun;61(6):1099-108.

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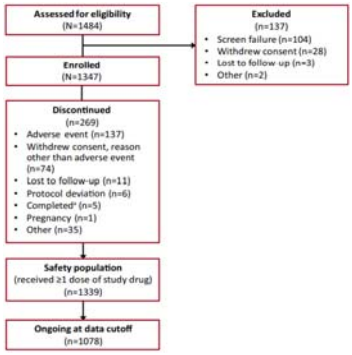
Cenobamate Phase III Study



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Cenobamate Phase III Study Results

	Cenobamate patients, n = 1339
Any TEAE	1128 (84.2)
TEAEs leading to discontinuation	147 (11.0)
Treatment-related TEAEs	935 (69.8)
Serious TEAEs	108 (8.1)
TEAEs ≥5%	
Somnolence	376 (28.1)
Dizziness	316 (23.6)
Fatigue	222 (16.6)
Headache	152 (11.4)
Viral upper respiratory tract infection	98 (7.3)
Upper respiratory tract infection	82 (6.1)
Nausea	80 (6.0)
Diplopia	78 (5.8)
Balance disorder	74 (5.5)

Abbreviation: TEAE, treatment-emergent adverse event.

- Only 12 subjects (1%) developed a rash.
- Only one subject discontinued the study because of rash. This was a 53-year-old woman who experienced mild facial erythema with swelling and pruritus following the second dose of cenobamate 12.5 mg. She was afebrile, and symptoms resolved upon discontinuation of the study drug.

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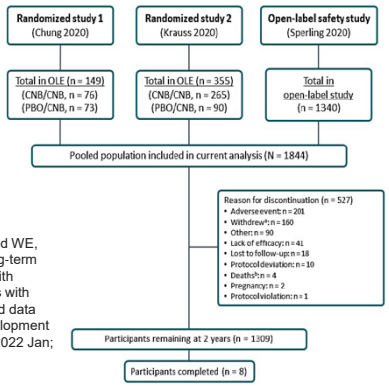
Cenobamate Open-label Data



Sander JW, Rosenfeld WE, Halford JJ, et al. Long-term individual retention with cenobamate in adults with focal seizures: Pooled data from the clinical development program. Epilepsia. 2022 Jan; 63(1):139-49.

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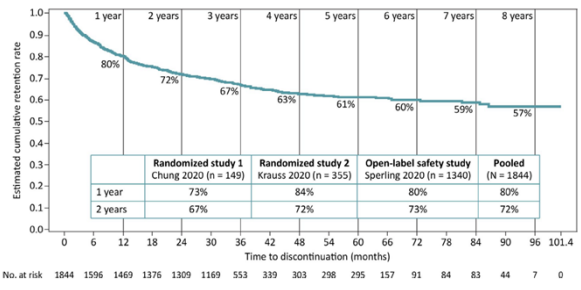

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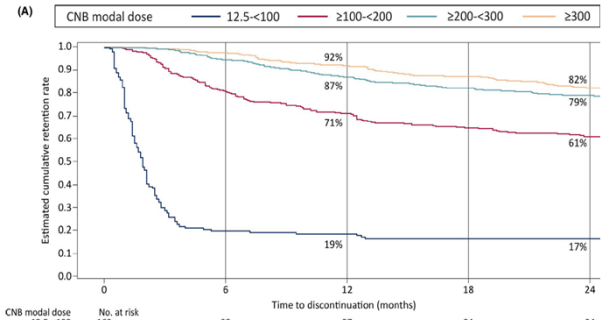

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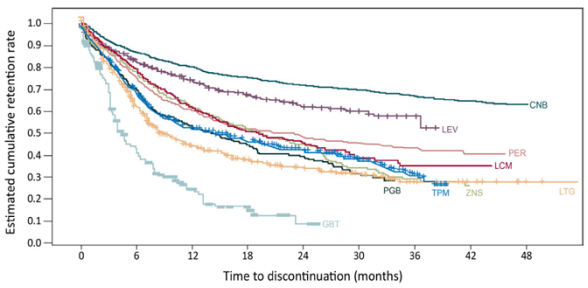

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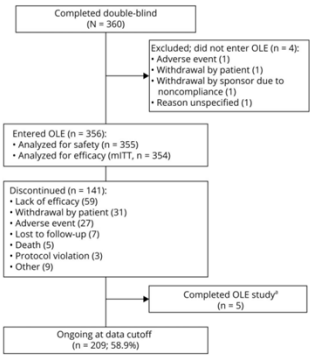
Cenobamate 4-Year Open Label Data



Klein P et al. Long-term Efficacy and Safety From an Open-Label Extension of Adjunctive Cenobamate in Patients With Uncontrolled Focal Seizures. Neurology. 2022 Sep 6;99(10): e989-98.

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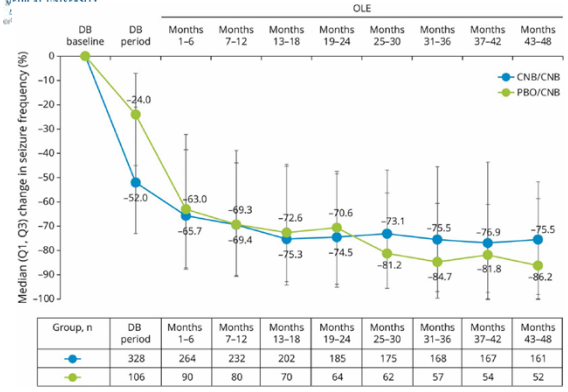
Cenobamate 4-Year Open Label Data



Group, n	DB period	Months 1–6	Months 7–12	Months 13–18	Months 19–24	Months 25–30	Months 31–36	Months 37–42	Months 43–48
CNB/CNB	328	264	232	202	185	175	168	167	161
PBO/CNB	106	90	80	70	64	62	57	54	52

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Cenobamate Open Label Data

Difficult to compare across studies because of different methodologies and study durations but:

	100% seizure reduction for observed patients	100% seizure reduction for ITT	Years
Cenobamate (Xcopri)	16.4	10.2	3-4
Briviracetam (Briviact)		3.0	2
Perampanel (Fycompa)	0 – 12.8	0 – 0.8	1-4
Lacosamide (Vimpat)	1.1 – 3.1	0.3 – 2.3	1-4

Klein P et al. Long-term Efficacy and Safety From an Open-Label Extension of Adjunctive Cenobamate in Patients With Uncontrolled Focal Seizures. Neurology. 2022 Sep 6;99(10): e989-98.

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Lamotrigine Cardiac Conduction Warning

- In 2021, the FDA added who warning paragraphs to the US Label for lamotrigine:
- In vitro testing showed that lamotrigine exhibits class IB antiarrhythmic activity at therapeutically relevant concentrations.
- Avoid the use of lamotrigine in patients who have:
  - cardiac conduction disorders (eg, second- or third-degree heart block)
  - ventricular arrhythmias
  - cardiac disease or abnormality (eg, myocardial ischemia, heart failure, structural heart disease, Brugada syndrome, or other sodium channelopathies).
- Concomitant use of other sodium channel blockers may increase the risk of proarrhythmia.
- Lamotrigine dose not slow ventricular conduction in normal individuals.

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Table 2. Effects of antiseizure medications on cardiac electrophysiology.

Anti-seizure medication	Experimental studies	Studies in healthy volunteers: Effect on PR interval	Studies in healthy volunteers: Effect on QT interval	Clinical studies/case reports
Brivaracetam	ND	-	-	NC
Cannabidiol^	+	-	-	NC
Carbamazepine	-	ND	ND	+++
Cenobamate*	ND	?	+	ND
Clobazam	ND	-	-	NC
Clonazepam	ND	ND	ND	±
Phenytoin	++	ND	ND	+++
Phenobarbital	++	ND	ND	++
Primidone	ND	ND	ND	+
Valproate	ND	ND	ND	-
Eslicarbazepine acetate	-	+	-	NC
Fenfluramine	ND	ND	ND	+
Gabapentin**	-	-	-	NC
Lacosamide	ND	+	-	++
Lamotrigine	++	+	-	+++
Levetiracetam	ND	-	-	+
Perampanel	ND	-	-	-
Pregabalin	ND	ND	ND	++
Rufinamide	ND	ND	ND	++
Topiramate	-	ND	ND	-
Vigabatrin	ND	-	-	NC
Zonisamide	ND	ND	ND	NC

Zaccara G, Lattanzi S, Brigo F. Cardiac adverse effects of antiseizure medications. Expert Opinion on Drug Safety. 2022 May 4;21(5):641-52.

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Lennox-Gastaut Syndrome

- Childhood-onset epileptic encephalopathy
- Onset usually between 2 to 5 years of age
- Multiple types of medically-intractable seizures: tonic, atypical absence, myoclonic, tonic-clonic drop, generalized tonic-clonic, focal

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Lennox-Gastaut Syndrome Treatment

- There are no head-to-head antiseizure medication trials.
- The best clinical evidence supports treatment with clobazam, cannabidiol (CBD), fenfluramine, topiramate, lamotrigine, and rufinamide.
- Low-level evidence supports the use of felbamate, levetiracetam, and zonisamide.
- **Valproate** is often used as first-line therapy (but is not indicted in females with childbearing potential unless all other alternatives are ineffective or not tolerated). **Lamotrigine** is often added as the second-line approach. The addition of **rufinamide** is often the third-line approach.
- Treatment considerations also include CBD, CBD-clobazam, and topiramate.
- Fenfluramine (oral solution, twice a day [BID]) was FDA-approved for LGS in March 2022 and is available through a risk-mitigation program.
- Carbamazepine and other sodium channel ASDs can precipitate drop attacks

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Lennox-Gastaut Syndrome Treatment (cont'd)

- There is some evidence (case series) for the use of the ketogenic diet.
- There is good data supporting the adjunctive use of vagus nerve stimulation (VNS).
- Surgical treatment with corpus callosotomy (targeting drop attacks) or lesional epilepsy surgery (in patients with

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Dravet Syndrome

- Onset birth to one year (typically between 5-8 months).
- The first seizure is usually a unilateral or bilateral tonic-clonic seizure triggered by fever, vaccination, or bathing
- Characteristics include:
  - Lifelong epilepsy
  - Multiple seizure types: GTC, myoclonic, tonic, absence, focal, non-convulsive status epilepticus
  - Developmental delay
  - Motor system problems: ataxia, tremor, dysarthria, spasticity, hyperreflexia
  - Behavioral problems: ADD, autistic traits, irritability, aggressiveness

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Dravet Syndrome Treatments

- DS treatments include:
  - Avoiding seizure triggers: There is anecdotal evidence for antipyretics for fever and avoiding flashing lights (via the use of sunglasses and high refresh-rate LCD screens).
  - Antiseizure medication: Patients usually require 2 or more drugs.
    - First-line treatment: valproate and clobazam
    - Second-line treatment: topiramate, stiripentol, levetiracetam, CBD, and fenfluramine
  - Avoiding sodium channel antiseizure medications (ASMs) such as carbamazepine and analogues, lamotrigine, and phenytoin
  - The ketogenic diet

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Developmental and Epileptic Encephalopathies Challenges in Care

- Discussions about guardianship or power of attorney (Who has the legal right to make decisions?)
- Changes in insurance status as the patient ages
- Loss of services with the end of special education
- Engagement with other types of care providers
  - Social worker
    - Guardianship, care home placement
  - Dietician
    - Ketogenic diet
  - Orthopedics
    - Progressive hip disease

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Challenges in Care (cont'd)

- Finding the right balance between seizure control and sedation
  - There is a bias toward sedation in patients with aggression and behavioral problems.
  - Many patients cannot report side effects.
  - Oversedation can lead to immobility.
  - Often, antiseizure medications continue to be added the patient's regimen, without assessing which ones work, until the patient is on 4 to 5 medications.

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CBD Pharmacology

- Oral bioavailability: low ~13-19%
- Not very water soluble (lipophilic; dissolved in oil)
- Oral C_{max}: within 1-4 hours (~2 hours)
- Protein binding: high (~90%)
- Volume distribution: very high (lipophilic)
- Linear pharmacokinetics

Taylor L et al. A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects. CNS Drugs (2018) 32:1053–1067

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CBD Pharmacology

- Half life: ~1-2 hours for single-dose oral CBD, possibly 2-5 days after chronic oral CBD – and we don't know about minor metabolite 7-OH-CBD which is active
- Extensive first-pass hepatic metabolism and major metabolite 7-COOH-CBD (inactive) is excreted via kidney
- Drug-drug interactions: many
  - Inhibits CYP2C family of isoenzymes -- can elevate blood levels of clobazam and 7-OH-CBD metabolite
- Can cause liver toxicity, especially when used with valproate

Taylor L et al. A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects. CNS Drugs (2018) 32:1053–1067

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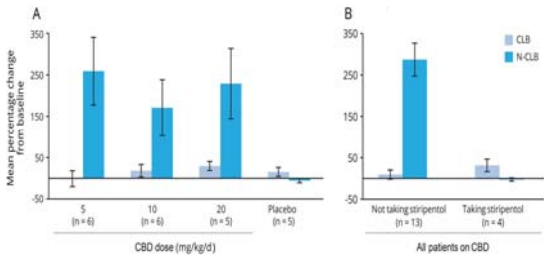
CBD/clobazam Interaction – Dravet Patients



Devinsky O et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology 2018; e1-e8.

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Recent Controlled Treatment Studies in Epilepsy with CBD

Dravet Syndrome (pediatric studies; Greenwich Biosciences; Epidiolex)

- Two positive double-blind placebo controlled studies
- Open label long term data looks good (so far) after ~3 years

Lennox-Gastaut Syndrome (adult and pediatric; Greenwich Biosciences; Epidiolex)

- One positive pediatric double-blind placebo controlled study
- One positive adult double-blind placebo controlled study (adult)
- Open label long term data looks good (so far) after ~3 years

Tuberous Sclerosis Complex (adult and pediatric; Greenwich Biosciences; Epidiolex)

- One positive double-blind placebo controlled study: 224 subjects (age 1-65) who had medication refractory TSC-related focal and generalized seizures

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Inclusion Criteria (LGS)

- Diagnosis of Lennox-Gastaut Syndrome
- Slow spike-wave (less than 3 per second) on EEG
- More than one type of generalized seizure, including drop seizures for at least 6 months
- Medication refractory (having failed at least 2 previous drugs) and on 1-4 concomitant AEDs
- Having at least 2 drop seizures per week during 4 week baseline period

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Inclusion Criteria (Dravet)

- Diagnosis of Dravet Syndrome
- Slow spike-wave (less than 3 per second) on EEG
- More than one type of generalized seizure, including drop seizures for at least 6 months
- Medication refractory (having failed at least 2 previous drugs) and on 1-4 concomitant AEDs
- Having at least 2 drop seizures per week during 4 week baseline period

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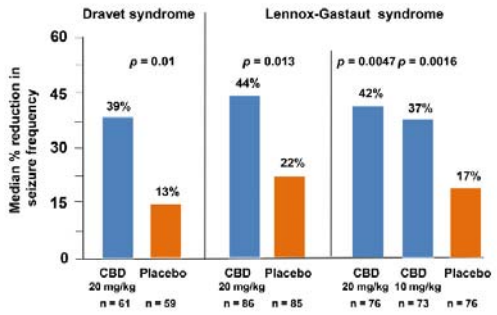
CBD Efficacy Results



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Adverse Effects / Lennox-Gastaut Syndrome

AE summary

Patients in safety analysis set		N=366
All-causality AEs, n (%)		337 (92)
Treatment-related AEs, n (%)[a]		211 (58)
AEs leading to withdrawal, n (%)[a]		35 (10)
Serious AEs, n (%)		94 (26)
Treatment-related serious AEs, n (%)[a]		23 (6)
AEs reported in >10% of patients, n (%)	All cause	Treatment related*
Diarrhea	98 (27)	59 (16)
Somnolence	86 (23)	50 (14)
Convulsion	78 (21)	20 (5)
Pyrexia	69 (19)	1 (<1)
Decreased appetite	65 (18)	40 (11)
Vomiting	65 (18)	9 (2)
Upper respiratory tract infection	53 (14)	2 (1)

[a]As determined by investigator assessment. *Includes all patients with AE listed as one of the reasons for withdrawal.
AE=adverse event.

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Adverse Effects / Dravet Syndrome

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)

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CBD Product Basics

- Purified CBD oil with concentration of 100 mg/mL
- Delivered in glass bottles of 100 mL
- Inactive ingredients include dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose (no gluten)
- Comes with two 5 mL syringes to dose (can get 1 mL syringes)
- Stored at room temperature
- Open bottle should be disposed of after 12 weeks

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CBD Product Basics

Dosing

- Week 1 → 5 mg/kg/day div BID (2.5 mg/kg BID)
- Week 2 → 10 mg/kg/day div BID (5 mg/kg BID) –
- Pending tolerability and effectiveness, can titrate to 15 mg/kg/day div BID for 1 week and then to 20 mg/kg/day div BID (max dose)

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Fenfluramine

- Derivative of amphetamine which causes the release of serotonin (5-HT) by disrupting vesicular storage of the neurotransmitter and inhibiting its reuptake
- It was formerly marketed at a higher dose as an appetite suppressant in the treatment of obesity (combined with phentermine) but was discontinued in the US in 1997 due to cardiovascular valvulopathy (7x increased risk of heart valve problems requiring surgery) and pulmonary hypertension
- The mechanism by which it works for epilepsy is unknown. The mechanism may be increased activity in the serotonergic system which increases GABA signaling coupled with positive allosteric modulation effects at sigma-1 receptors which decreases glutamate signaling.

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Fenfluramine Clinical Trials

Epilepsy Syndrome	Subject Number	Duration	Arms
Lennox-Gastaut Syndrome	263	14 weeks	1:1:1 Placebo, 0.2 mg/kg and 0.7 mg/kg
Dravet Syndrome (- stiripental)	119	14 weeks	1:1:1 Placebo, 0.2 mg/kg and 0.7 mg/kg
Dravet Syndrome (+ stiripentol)	87	15 weeks	1:1 Placebo, 0.4 mg/kg

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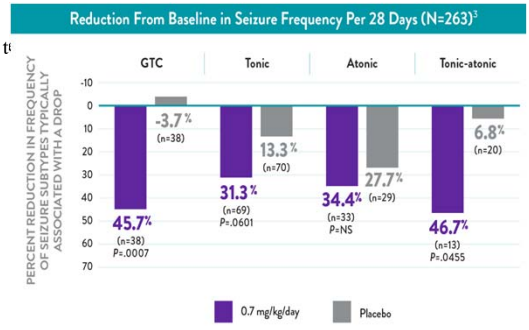
Fenfluramine (Fintepla) Results in LGS



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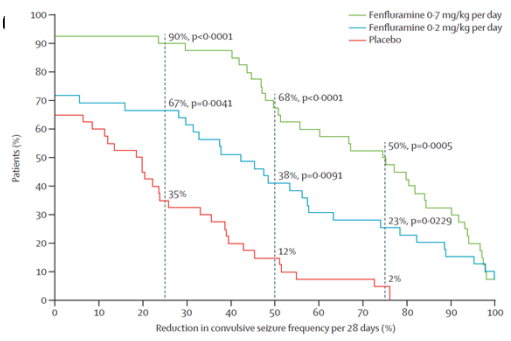
Fenfluramine (Fintepla) in Dravet Syndrome



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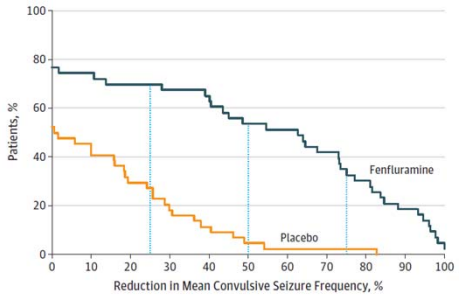
Fenfluramine (Fintepla) in Dravet Syndrome



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Fenfluramine Dosing

- Fenfluramine is an oral solution (2.2 mg/mL). The starting and initial maintenance dose is 0.1 mg/kg given twice daily, which can be increased weekly as needed and tolerated.
- For patients not on concomitant stiripentol, the recommended maintenance dose of fenfluramine is 0.35 mg/kg twice daily, not to exceed a total daily dose of 26 mg.
- For patients who are taking concomitant stiripentol, the maximum daily maintenance dose of fenfluramine is 0.2 mg/kg twice daily, not to exceed a total daily dose of 17 mg.

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Fenfluramine Adverse Effects

- Decreased Appetite (36%)
- Asthenia (≤24%)
- Drowsiness (≤26%) fatigue (≤24%) lethargy (≤26%) sedated state (≤26%)
- Malaise (≤24%)
- Drooling (≤13%)
- Fever (15%)

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Fenfluramine (Fintepla) Cardiac Surveillance

- Fenfluramine treatment has also been associated with a risk of cardiac valve injury and pulmonary hypertension.
- In the US, fenfluramine is available only through a risk evaluation and mitigation strategy (REMS) program. Evaluation with echocardiography is required before treatment, every six months during treatment, and once three to six months after treatment to monitor for valvular heart disease and pulmonary hypertension.
- In current trials in patients receiving fenfluramine for Dravet syndrome, trace aortic insufficiency and mitral valve insufficiency, considered to be within the normal physiologic range, have commonly been observed; no cases of valvular heart disease were observed in studies for Dravet syndrome or Lennox-Gastaut syndrome up to 3 years duration.

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Changing What's Possible

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