COLLEGE OF PHARMACY
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EVIDENCE REVIEW:

Experimental Controlled Trials on the Treatment of Epilepsy with Cannabis-based Products

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FEBRUARY 11, 2025

I have no conflicts of interest to disclose

BRIEF EVIDENCE REPORT OBJECTIVE & METHODS

- **Objective:**
  - Summarize recent experimental evidence for the use of cannabis- or cannabinoid-based products (CBPs) in people with epilepsy (PWE)
  - Assist the CRRB with updating guidance
- **Methods:**
  - Searched for SRs of experimental controlled trials (ECTs) or ECTs (eg, RCTs) published since 2018
  - Included ECTs of any design with:
    - PWE, or people with persistent seizures
    - Administered CBPs (natural or synthetic) for any duration, with comparisons between different CBPs[#] or with a non-cannabinoid treatment
    - Any outcome
  - Excluded if: 1) published as abstract only; 2) single-arm before-after trials; 3) only presented *post-hoc* results; 4) insufficient clinical research standards/merit*
  - Summarized select results from ECTs
  - Extracted ROB ratings from an SR,[1] when available

[#] Excluded trials *only* with comparisons between 2 doses of an identical CBP product (eg, CBD 10 mg vs CBD 20 mg, without placebo)

*Per Utah law: required US-based trials to be IRB approved or conducted by the US government; and international trials to have reported similar standards (eg, following the Declaration of Helsinki) and be considered to have reasonable scientific merit[2]

Abbreviations: CBP, cannabis- or cannabinoid-based product; CRRB, Utah Cannabis Research Review Board; ECT, experimental controlled trial; IRB, Institutional Review Board; PWE, people with epilepsy; RCT, randomized controlled trial; ROB, risk of bias; SR, systematic review

INCLUDED TRIALS

Current CRRB guidance addresses 3 of 8 included Epidiolex trials

- Including: 1 RCT in people with DS[8] and 2 RCTs in people with LGS[6,7]

15 ECTs in PWE

Included 11 RCTs

Excluded 4 trials[3-6] due to insufficient clinical research standards

- Published 1978-1990/92
- Total of 48 participants
- Oral CBD 200-300 mg/day vs placebo
- See report Appendix A for results

CBD (as Epidiolex) in children and adults with LGS (N=2)[7,8]

CBD (as Epidiolex) in children with DS (N=3)[9-11]

CBD (as Epidiolex) in children and adults with TSC (N=1)[12]

CBD (as Epidiolex) DDI trials in adults with epilepsy (N=2)[13,14]

Oral CBD (N=1)[15] or **TD CBD** (N=1)[16] in adults with focal epilepsy

Oral CBDV (N=1)[17] in adults with focal epilepsy

Abbreviations: CBD, cannabidiol; CBDV, cannabidivarin; CBP, cannabis or cannabinoid-based product; DS, Dravet syndrome; ECT, experimental controlled trial; LGS, Lennox-Gastaut syndrome; PWE, people with epilepsy; RCT, randomized controlled trial; ROB, risk of bias; TD, transdermal; TSC, tuberous sclerosis complex

OVERVIEW OF TRIAL AND PARTICIPANT CHARACTERISTICS

- 11 double-blinded, placebo-controlled RCTs published from 2017–2023

- Studied CBPs: Oral pure CBD solution (Epidiolex; N=8),[7-14] liposomal oral CBD (N=1),[15] CBD transdermal gel (N=1),[16] CBDV oral solution (N=1)[17]
  - Each administered as an adjunct to other anti-seizure therapies
  - Treatment durations: 8-16 weeks in efficacy trials; 3-4 weeks in PK/safety trials

- Randomized a total of 1,404 PWE (867 [61.8%] received a CBP)

- Trial populations varied by trial, *generally* including PWE who were:
  - Drug-resistant or treatment-refractory
  - Variable ages:
    - pediatric (N=3 trials in people with DS), mixed adult and pediatric (N=3 trials in people with LGS or TSC), or adults (N=5)
  - Lacking significant non-epileptic comorbidities
  - Little to no detail provided about prior cannabis-related treatment(s)

Abbreviations: CBD, cannabidiol; CBDV, cannabidivarin; CBP, cannabis or cannabinoid-based product; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; PK, pharmacokinetic; PWE, people with epilepsy; RCT, randomized controlled trial; TSC, tuberous sclerosis complex

CBD (EPIDIOLEX) FOR DRAVET SYNDROME (DS): OVERVIEW

Trial and design	Population (total/completed n)	Approx. tx. length
Devinsky et al (2017)[9] *Efficacy-focused*, parallel, DB, PC RCT	• **Children** aged 2-18 years (median 9.1 years; 52% male) with **DS and drug-resistant seizures, including ≥4 convulsive* seizures over the 4-week BL** (n=120/108) • **Taking ≥1 ASD** (mean 2.9), and allowed to continue other stable therapies • Median of 12.4 (CBD) or 14.9 (placebo) *convulsive* seizures/month at BL • Excluded if: taking felbamate for <1 year	14 weeks
Miller et al (2020)[10] *Efficacy-focused*, parallel, DB, PC RCT	• **Children** aged 2-18 years (mean 9.3 years; 47.5% male) with **DS and insufficient seizure control, including ≥4 convulsive* seizures over the 4-week BL** (n=199/190) • **Taking ≥1 ASD** (median 3), and allowed to continue other stable therapies • Median of 9 or 14 (CBD groups) or 17 (placebo) *convulsive* seizures/28-days at BL • Excluded if: taking felbamate for <1 year	14 weeks

*Convulsive seizures = tonic-clonic, tonic, clonic, and atonic seizures

Abbreviations: Approx., approximate; ASD, anti-seizure drug; BL, baseline; CBD, cannabidiol; DB, double-blinded; DS, Dravet syndrome; PC, placebo-controlled; RCT, randomized controlled trial; Tx, treatment;

CBD (EPIDIOLEX) FOR DRAVET SYNDROME (DS): OVERVIEW

Trial and design	Population (total/completed n)	Approx. tx. length
Devinsky et al (2018)[11] *Safety/PK-focused*, parallel, DB, PC RCT	• **Children** aged 4-10 years (mean 7.6 years; 47% male) with **DS and insufficient seizure control, including ≤ 4 convulsive seizures over the 4-week BL** (n=34/32) • Taking a mean of 2.6 ASDs; allowed to continue other stable therapies	3 weeks

Abbreviations: Approx., approximate; ASD, anti-seizure drug; BL, baseline; DB, double-blinded; DS, Dravet syndrome; PC, placebo-controlled; PK, pharmacokinetic; RCT, randomized controlled trial; Tx, treatment;

CBD (EPIDIOLEX) FOR DS: SELECT EFFICACY RESULTS

Outcome	Devinsky (2017)[9]		Miller (2020)[10]		
	CBD 20mg/kg/day	PBO	CBD 10 mg/kg/day	CBD 20 mg/kg/day	PBO
% reduction from BL in convulsive seizures*	**38.9%#**	**13.3%#**	**48.7%**	**45.7%**	**26.9%**
	Adj. median diff. vs PBO: –22.8 (–41.1 to –5.4)Ŧ; P=0.01		**vs PBO: 29.8% (8.4%–46.2)Ŧ; P=0.01**	**vs PBO: 25.7% (2.9%–43.2)Ŧ; P=0.03**	
% participants with ≥50%↓in convulsive seizures	43%	27%	**43.9%**	**49.3%**	**26.2%**
	OR 2.0 (0.93 to 4.30)Ŧ; P=0.08		**vs. PBO: P=0.03**	**vs. PBO: P=0.007**	
% caregivers rating condition improved from BL (CGIC)	**62%**	**34%**	**68.2%**	**60.6%**	**41.5%**
	vs. PBO: P=0.02		**vs. PBO: P<0.001**	**vs. PBO: P=0.03**	

Key: green/bold, efficacy favors CBD over PBO (statistically); grey, efficacy favors neither CBD or PBO (statistically)

***Primary outcome.** For Devinsky et al, the % change from the 4-week BL was calculated *per 28-days* of the 14-week treatment period. Miller et al calculated the percentage change over the entire 14-week period vs BL.

Median change; Ŧ 95% confidence interval (CI)

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Abbreviations: Adj., adjusted; BL, baseline; CBD, cannabidiol; CBP, cannabis- or cannabinoid-based product; CGIC, Caregiver Global Impression of Change; CI, confidence interval; diff, difference; DS, Dravet syndrome; PBO, placebo; OR, odds ratio;

CBD (EPIDIOLEX) FOR LENNOX-GASTAUT SYNDROME (LGS): OVERVIEW

Trial and design	Population (total/completed n)	Approx. tx. length
Thiele et al (2018)[8] *Efficacy-focused*, parallel, DB, PC RCT	• **Children and adults** aged 2-55 years (mean ~15 years; 51.5% male) with **LGS* and treatment-refractory seizures, including ≥2 drop[#] seizures *per week* over the 4-week BL** (n=171/156) • **Taking 1-4 ASD** (median 3), and allowed to continue other stable therapies • Median of 71.4 (CBD) or 74.7 (placebo) *drop* seizures/month at BL • Excluded if: taking felbamate for <1 year; had taken a corticotrophin in the prior 6 months	14 weeks
Devinsky et al (2018)[7] *Efficacy-focused*, parallel, DB, PC RCT	• **Children and adults** aged 2-55 years (mean ~15 years; 57.3% male) with **LGS*, treatment-refractory seizures,[18] and ≥2 drop seizures *per week* over the 4-week BL** (n=225/212) • **Taking 1-4 ASD** (median 3), and allowed to continue other stable therapies • Median of 86.9 or 85.5 (CBD groups) or 80.3 (placebo) *drop* seizures/month at BL • Excluded if: taking felbamate for <1 year; had taken a corticotrophin in the prior 6 months	14 weeks

*LGS per clinical criteria: 1) documented history of slow spike-and-wave EEG, and 2) ≥1 type of generalized seizure, including drop seizures, for ≥6 months. [#]Drop seizures = "…an epileptic seizure (atonic, tonic, or tonic-clonic) involving the entire body, trunk, or head that leads or could lead to a fall, injury, or slumping in a chair" (Devinsky et al, page 1889)[6]

Abbreviations: Approx., approximate; ASD, anti-seizure drug; BL, baseline; CBD, cannabidiol; DB, double-blinded; EEG, electroencephalogram; LGS, Lennox-Gastaut Syndrome; PC, placebo-controlled; RCT, randomized controlled trial; Tx, treatment;

CBD (EPIDIOLEX) FOR LGS: SELECT EFFICACY RESULTS

Outcome	Thiele (2018)[8]		Devinsky (2018)[7]		
	CBD 20mg/kg/day	PBO	CBD 10 mg/kg/day	CBD 20 mg/kg/day	PBO
Median % reduction from BL in drop seizures per 28-days*	43.9%	21.8%	37.2%	41.9%	17.2%
	Adj. median difference vs PBO#:				
	–17.2 (–30.3 to –4.1)∓; P=0.0135		19.2 (7.7 to 31.2)∓; P=0.002	21.6 (6.7 to 34.8)∓; P=0.005	
% participants with ≥50%↓in drop seizures	44%	24%	36%	39%	14%
	vs PBO: P=0.0043		vs. PBO: P=0.003	vs PBO: P<0.001	
% patients/ caregivers rating condition improved from BL (P/CGIC)	58%	34%	66%	57%	44%
	vs. PBO: P=0.012		vs. PBO: P=0.002	vs. PBO: P=0.002	

Key: green/bold, efficacy favors CBD over PBO (statistically); grey, efficacy favors neither CBD or PBO (statistically)

***Primary outcome.** # Reported as reported by the respective publications. ∓ 95% confidence interval (CI)

Abbreviations: Adj., adjusted; BL, baseline; CBD, cannabidiol; CBP, cannabis- or cannabinoid-based product; CGIC, Caregiver Global Impression of Change; CI, confidence interval; LGS, Lennox-Gastaut syndrome; PBO, placebo; PGIC, Patient Global Impression of Change;

CBD (EPIDIOLEX) FOR TUBEROUS SCLEROSIS COMPLEX (TSC): OVERVIEW

Trial and design	Population (total/completed n)	Approx. tx. length
Thiele et al (2021)[12] *Efficacy-focused*, parallel, DB, PC RCT	• **Children and adults** aged 1-65 years (median ~11 years; 58.5% male) with **TSC* and medication-resistant epilepsy, including ≥8 TSC-associated[#] seizures over the 4-week BL** (n=224/201) • **Taking ≥1 ASD** (median 3), and allowed to continue other stable therapies • Median of 56 or 61 (CBD groups) or 54.1 (placebo) *TSC-associated* seizures/month at BL • Excluded if: epilepsy surgery within the prior 6 months; taking an oral mTOR inhibitor or taking felbamate for <1 year	16 weeks

*TSC per clinical criteria according to the 2012 International Tuberous Sclerosis Complex Consensus Conference
[#]TSC-associated seizures =countable focal seizures ± impaired awareness, focal seizures that evolve to bilateral motor seizures, generalized seizures (including tonic, clonic, atonic) – approximately 94% of seizures at BL met this criteria

Abbreviations: Approx., approximate; ASD, anti-seizure drug; BL, baseline; CBD, cannabidiol; DB, double-blinded; mTOR, mechanistic target of rapamycin; PC, placebo-controlled; RCT, randomized controlled trial; Tx, treatment;

CBD (EPIDIOLEX) FOR TSC: SELECT EFFICACY RESULTS

Outcome	Thiele (2021)[12]		
	CBD 25 mg/kg/day	CBD 50 mg/kg/day	PBO
% reduction from BL in TSC-associated seizures*	48.6%	47.5%	26.5%
	percentage reduction from placebo:		
	30.1% (13.9%–43.3%)[Φ]; P<0.001	**28.5% (11.9%–42.0%)[Φ]; P=0.002 (nominal)**	
% participants with ≥50%↓in TSC-associated seizures	36%	40%	22%
	vs PBO: NR		
% patients/ caregivers rating condition improved from BL (P/CGIC)	**69%**	62%	**39%**
	vs. PBO: nominal P=0.007[#]	vs. PBO: nominal P=0.06[#]	

Key: green/bold, efficacy favors CBD over PBO (statistically); grey, efficacy favors neither CBD or PBO (statistically)

***Primary outcome.** [Φ] 95% confidence interval (CI); [#] "nominal" P-values were "used descriptively"

Abbreviations: Adj., adjusted; BL, baseline; CBD, cannabidiol; CGIC, Caregiver Global Impression of Change; CI, confidence interval; NR, not reported; PBO, placebo; PGIC, Patient Global Impression of Change; TSC, tuberous sclerosis complex;

CBD (EPIDIOLEX) FOR DS, LGS OR TSC: SAFETY PROFILE

	Select Safety Results from RCTs

Pure CBD oral solution (Epidiolex) 5–50 mg/kg/day	• **AEs of any severity with incidence ≥10% in a CBD-treated group and ≥5% greater than PBO in at least 1 trial[7-12]:**
	  • Diarrhea, vomiting, fatigue, somnolence, pyrexia, decreased appetite, convulsions, lethargy, ataxia, upper abdominal pain, pneumonia, rash, abnormal behavior, increased hepatic enzyme levels
	• **Hepatic transaminase elevations:** increased incidence* at higher CBD dosages, and associated with concomitant use of valproate ± clobazam[19]
	• Most TEAEs were of **mild-to-moderate severity**[7-10,12]
	• **Increased incidence* of serious AEs** with CBD vs PBO[7-10,12]
	• **Increased incidence* of trial withdrawals due to AEs** with CBD vs PBO
	  • Devinsky 2018 (in LGS)[7]:
	  • 1.5% (CBD10) vs **7.3% (CBD20) vs 1.3% (PBO)**
	  • Miller 2020 (in DS)[10]:
	  • 0% (CBD10) vs **7.5% (CBD20) vs 0% (PBO)**
	  • Thiele 2021 (in TSC)[12]:
	  • **11% (CBD25) vs 14% (CBD50) vs 3% (PBO)**

*Descriptive associations without formal statistical differences

Abbreviations: AE, adverse event; CBD, cannabidiol; CBD10, CBD 10 mg/kg/day; CBD20, CBD 20 mg/kg/day; CBD25, CBD 25 mg/kg/day; CBD50, CBD 50 mg/kg/day; DS, Dravet syndrome; LGS, Lennox-Gastatut syndrome; PBO, placebo; TEAE, treatment-emergent AEs; TSC, tuberous sclerosis complex

CBD (EPIDIOLEX): LONG-TERM EFFECTIVENESS FOR DS, LGS, OR TSC

Open-label Extension Trials of RCTs*			
Epilepsy population	**Median treatment duration (range)**	**Median % reduction from BL in monthly target seizures**	**Withdrawals due to AEs**
DS (n=315; 95% of RCT completers)[20]	444 (18 to 1535) days	12-week increment ranges over **up to 156 weeks**: • Convulsive seizures: 45%-74% • Total (all types) seizures: 49%-84%	8% of total trial withdrawals
LGS (n=366; 99.5% of RCT completers)[21]	1090 (3 to 1421) days	12-week increment ranges over **up to 156 weeks:** • Drop seizures: 48%-71% • Total (all types) seizures: 48%-68%	30.2% of total trial withdrawals
TSC (n=199; 99% of RCT completers)[22]	267 (18 to 910) days	12-week increment ranges over **up to 48 weeks:** • TSC-associated seizures: 54%-68% • Total (all types) seizures: 51%-67%	5.5% of total trial withdrawals (75.4% had not completed the OLE trial)

*Per the latest known publication of results from open-label extension trials of an RCT addressed by this review; the OLE trials were **uncontrolled**, with all enrolled participants receiving Epidiolex.

Abbreviations: AE, adverse event; BL, baseline; CBD, cannabidiol; DS, Dravet syndrome; LGS, Lennox-Gastaut Syndrome; OLE, open label extension; RCT, randomized controlled trial;

CBD (EPIDIOLEX) PK DRUG-DRUG INTERACTION TRIALS

- Trials aimed to assess the effect of **CBD 20 mg/kg/day** (at steady state) on steady state exposure to the target other ASD(s)

Trial and design	Population (total/completed n)	Approx. CBD tx. length
VanLandingham et al (2020)[13] *DDI-focused*, parallel, DB, PC RCT	• **Adults** ages 18-65 years (mean 36.8 years; 50% male) with **epilepsy with ≥1 seizure within the prior 2 months** (n=20/13) • **Taking a stable dose of clobazam ≤ 20 mg/day + ≤2 other ASDs**	4.4 weeks
Ben-Menachem et al (2020)[14] *DDI-focused*, parallel, DB, PC RCT	• **Adolescents or adults** ages 16-65 years (mean 29.5 years; 65% male) with **epilepsy with ≥1 seizure within the prior 2 months** (n=34/30) • **Taking a stable dose of stiripentol or valproate + ≤2 other ASDs**	3.4 weeks

Abbreviations: Approx., approximate; ASD, anti-seizure drug; BL, baseline; CBD, cannabidiol; DB, double-blinded; DDI, drug-drug interaction; PC, placebo-controlled; PK, pharmacokinetic; RCT, randomized controlled trial; Tx, treatment;

CBD (EPIDIOLEX) PK DDI TRIALS: SELECT RESULTS

Trial	ASD/ metabolite	Geometric LS Mean Ratio* of ASD PK Parameter	
		C_{max}	AUC_{tau}
VanLandingham (2020)[13]	Ratio at end of treatment (day 33) vs pre-treatment (day 1)		
	Clobazam (CLB)	**PBO:** 1.1 (0.4–2.7)[φ] **CBD**: 1.1 (0.8–1.2)[φ]	**PBO**: 1.0 (0.7–1.5)[φ] **CBD**: 1.1 (0.9–1.2)[φ]
	N-desmethyl-clobazam (N-CLB)	**PBO**: 1.2 (0.6–2.2)[φ] **CBD**: **2.2 (1.4–3.5)**[φ]	**PBO**: 1.0 (0.8–1.3)[φ] **CBD**: **2.6 (2.0–3.6)**[φ]
Ben-Menachem (2020)[14]	Ratio at ASD steady state + CBD steady state vs. ASD steady state alone		
	Stiripentol (STP)	1.17 (1.03–1.33)[φ]	1.30 (1.09–1.55)[φ]
	Valproate (VPA)	0.87 (0.79–0.95)[φ]	0.83 (0.75–0.92)[φ]
	4-ene-VPA	0.77 (0.66–0.90)[φ]	0.70 (0.62–0.80)[φ]

Key: green/bold – investigators concluded the PK change was meaningful; grey – investigators concluded the effect was likely not clinically meaningful.

***Co-primary outcome.** [φ] = 90% confidence interval; if the 90% CI fell between 0.5–2.0, investigators concluded there was a lack of meaningful change in the PK parameter.

Abbreviations: 4-ene-VPA, 2-propyl-4-pentenoic acid; ASD, anti-seizure drug; AUC_{tau}, area under the concentration-time curve over the dosing interval; CBD, cannabidiol; Cmax, maximum observed plasma concentration; DDI, drug-drug interaction; LS, least squares; PBO, placebo; PK, pharmacokinetic;

OTHER CBD FORMULATIONS FOR FOCAL EPILEPSY: OVERVIEW

Trial and design	Population (total/completed n)	Studied CBP	Approx. tx. length
Ebadi et al (2023)[15] *Efficacy-focused*, parallel, DB, PC RCT	• **Adults** ≥18 years (median 28.8 years; 33.3% male) with **drug-resistant frontal lobe focal epilepsy** (n=27/NR) • Continued other usual anti-seizure therapies during trial • Mean BL (monthly?*) seizure frequency: 86.5 (CBD); 34 (PBO) • Excluded if: taking clobazam, eslicarbazepine, topiramate, or zonisamide	**Liposomal CBD** (99.5% pure) 210 mg per day	8 weeks
O'Brien (2022)[16] *Efficacy-focused*, parallel, DB, PC RCT	• **Adults** aged 18-70 years (mean 39.2 years; 45.2% male) with **drug-resistant focal seizures for ≥ 2 years, with ≥ 3 observed seizures per month** (n=188/174) • **Taking ≤3 ASD**, and allowed to continue other stable therapies • Median past-month seizure frequency: 11.5 • Excluded if: taking clobazam, ethosuximide, felbamate, or vigabatrin	**CBD transdermal gel** 195 mg or 390 mg per day (in divided doses applied twice daily)	12 weeks

*Ebadi et al reported insufficient details about how seizure frequency was assessed and how the liposomal CBD product was administered.

Abbreviations: Approx., approximate; ASD, anti-seizure drug;; CBD, cannabidiol; CBP, cannabinoid/cannabis-based product; DB, double-blinded; NR, not reported; PBO, placebo; PC, placebo-controlled; RCT, randomized controlled trial; Tx, treatment;

OTHER CBD FOR FOCAL EPILEPSY: SELECT EFFICACY RESULTS

RCT	Select Efficacy Results			
Ebadi (2023)[15]	**Mean change** from BL to 8 weeks in **monthly seizure frequency***	**Liposomal CBD**	**PBO**	
		–45.58	–9.33	
		Favors CBD: significant change from BL with CBD (P=0.009), but not PBO (P>0.999)		
	• No differences in changes in seizure severity			
	• **CBD treatment associated with improved QoL[#] at 8 weeks** (but not 4 weeks) vs baseline			
O'Brien (2022)[16]	Median (IQR) percentage change from BL in seizure rate per 28 days	**TD CBD 195 mg**	**TD CBD 390 mg**	**PBO**
		18.4 (–65 to 91)	12.0 (–117 to 79.5)	8.70 (–199 to 100)
		No significant LS mean difference from placebo* (P=0.89 for CBD 195 mg and P=0.32 for CBD 390 mg)		
	• No significant between group differences in secondary outcomes, including the 50% responder rate			
	• In the uncontrolled OLE trial, ≥60% of participants who continued CBD therapy had a ≥50% reduction in seizures by month 6			

Key: green/bold, efficacy favors CBD over PBO (statistically); grey, efficacy favors neither CBD or PBO (statistically)

***Primary outcome.** [#] Assessed using the validated quality of life in epilepsy 31 questions (QOLIE-31) scale in Persian; only assessed among participants without "cognitive problems" (excluded 4 participants)

Abbreviations: BL, baseline; CBD, cannabidiol; IQR, interquartile range; LS, least squares; OLE, open label extension; PBO, placebo; RCT, randomized controlled trial; TD, transdermal; QoL, quality of life;

OTHER CBD FORMULATIONS FOR FOCAL EPILEPSY: SELECT SAFETY RESULTS

	Select Safety Results from RCTs
Liposomal CBD 210 mg per day[15]	• Limited details reported; *apparently*, no significant differences vs placebo • Types of reported AEs generally were similar to Epidiolex, *possibly* except for the AEs (unknown incidence): • Dry mouth, blurred vision, urinary retention, HR/BP changes

Transdermal CBD gel 195 mg (~2.6 mg/kg/day) or 390 mg (~5.3 mg/kg/day)[16]	• TEAEs:
	  • 51.6% (CBD 390 mg); 49.2% (CBD 195 mg); 41.3% (PBO)
	  • Mostly mild-moderate severity
	• AEs causing treatment discontinuation:
	  • 3.2% (CBD 390 mg); 4.7% (CBD 195 mg); 1.6% (PBO)
	• Serious AEs:
	  • 6.5% (CBD 390 mg); 1.6% (CBD 195 mg); 4.8% (PBO)
	• No significant increases (≥3x ULN) in hepatic transaminases after up to 18 months of exposure to transdermal CBD during the open-label trial

Abbreviations: AE, adverse event; BP, blood pressure; CBD, cannabidiol; HR, heart rate; TEAEs, treatment-emergent AEs; PBO, placebo; ULN, upper limit of normal;

CANNABIDIVARIN (CBDV) FOR FOCAL EPILEPSY: OVERVIEW

Trial and design	Population (total/completed n)	Studied CBP	Approx. tx. length
Brodie et al (2021)[17] *Efficacy-focused*, parallel, DB, PC RCT	• **Adults** 18-65 years (mean 36years; 44% male) with **focal epilepsy and ≥1 seizure/week during the 4-week BL** (n=162/142) • Persistent seizures despite ≥2 ASDs • Taking 1-3 ASDs (median 3); continued other usual anti-seizure therapies during trial • BL seizure rate per 28 days: 18.1 (CBDV) or 17 (PBO)	**CBDV oral solution** 800 mg twice daily (~23 mg/kg/day)	8 weeks

Abbreviations: Approx., approximate; ASD, anti-seizure drug; CBDV, cannabidivarin; CBP, cannabinoid/cannabis-based product; DB, double-blinded; PBO, placebo; PC, placebo-controlled; RCT, randomized controlled trial; Tx, treatment;

CANNABIDIVARIN (CBDV) FOR FOCAL EPILEPSY: SELECT EFFICACY RESULTS

Outcome	Brodie et al (2021)[17]	
	CBDV 1600 mg/day	PBO
% reduction from BL in focal seizures*	40.5 (31.4–48.4)∓	37.7 (28.2–45.9)∓
	Treatment ratio, CBDV vs PBO:	
	0.95 (0.78 to 1.17); P=0.648	
% participants with ≥50%↓in focal seizures	• Details NR • Described as similar between treatment groups	
% patients rating condition improved from BL (PGIC)	61%	64%
	vs. PBO: P=0.866	

Key: grey, efficacy favors neither CBD or PBO (statistically)

***Primary outcome.** Assessed focal seizures included: focal motor seizures without impaired awareness, focal seizures with impaired awareness, and focal seizures that evolve to bilateral convulsive seizures.

∓ 95% confidence interval (CI)

Abbreviations: BL, baseline; CBDV, cannabidivarin; ; CBP, cannabis- or cannabinoid-based product; CI, confidence interval NR, not reported; PBO, placebo; PGIC, Patient Global Impression of Change;

CANNABIDIVARIN (CBDV) FOR FOCAL EPILEPSY: SELECT EFFICACY RESULTS

	Select Safety Results from RCTs

CBDV oral solution 800 mg twice daily[17]
 	
(~23 mg/kg/day)
	• TEAEs:
	  • 73% (CBDV); 48% (PBO)
	  • Mostly mild-moderate severity
	  • Most common (incidence ≥10% and ≥5% greater than PBO):
	  • Diarrhea, upper abdominal pain, somnolence
	
	• **AEs causing treatment discontinuation:**
	  • **14% (CBDV), most commonly due to diarrhea or maculopapular rash; 3% (PBO)**
	
	• Serious AEs:
	  • 4% (CBV); 1% (PBO)
	
	• Increases in hepatic transaminases to ≥3x ULN: 3.7% (CBDV); 1.2% (PBO)

Abbreviations: AE, adverse event; CBDV, cannabidivarin; TEAEs, treatment-emergent AEs; PBO, placebo; ULN, upper limit of normal;

ROB ASSESSMENT AND GENERALIZABILITY

- *Overall* ROB assessment by an SR[1] was available for **9 of 11 trials:**
  - **Low risk:** Thiele et al (2018),[8] Miller et al (2020),[10] Thiele et al (2021)[12]
  - **Unclear/some concerns:** Devinsky et al (2017),[9] VanLandingham et al (2020),[13] Ben-Menachem et al (2020)[14]
  - **High risk:** Devinsky et al (2018),[7] Devinsky et al (2018),[11] and O'Brien et al (2022)[16]

- All 9 RCTs rated as <u>low risk for</u>: bias from randomization, deviations from intended intended intervention, or missing outcome data
- <u>Increased ROB</u> arising from: outcome measurement (N=6)[7,9,11,13,14,16] and selection of the outcome reported (N=2)[7,11]

- Potential ROB concerns* for remaining 2 RCTs (Brodie et al [2021][17] and Ebadi et al [2023][15]):
  - Outcome measurement
  - Missing outcome data

- Uncertain generalizability to medical cannabis formulations available to Utah patients

*Select concerns. No formal ROB assessment was performed.

Abbreviations: RCT, randomized controlled trial; ROB, risk of bias; SR, systematic review;

EXPERT OPINION STATEMENTS FROM US ORGANIZATIONS

- Epilepsy Foundation (2019)[23]
  - For patients with uncontrolled seizures despite conventional therapies, medical cannabis/"CBD oil" treatment could be considered
  - Consider consultation with an epilepsy specialist →
    - determine if possible/available evidence-based treatments have been tried

- American Epilepsy Society *position statement* (2022)[24]
  - Addresses the lack of robust evidence for using cannabis-related therapies other than CBD to treat epilepsy
  - Encourages PWE to work with their epilepsy specialist to explore and make informed decisions about treatment options

Abbreviations: CBD, cannabidiol; PWE, people with epilepsy;

CURRENT UTAH CRRB GUIDANCE FOR EPILEPSY

Includes 1 formal (ie, graded) conclusion[25]:

"With the exception of CBD/Epidiolex, there is *insufficient evidence* to support the conclusion that medical cannabis or cannabinoids (other than CBD) are effective or ineffective treatments for various types of epilepsy or seizure disorders."

- Summarizes descriptive and/or observational evidence not addressed by this evidence review
- Informally, provides additional guidance, including considerations for using medical cannabis in the treatment of adult and pediatric patients

Abbreviations: CBD, cannabidiol; CRRB, (Utah) Cannabis Research Review Board;

CONSIDERATIONS FOR UPDATES TO CRRB GUIDANCE FOR EPILEPSY

- Graded statement about effectiveness for epilepsy or seizure disorders:
  - **Option 1: maintain the current recommendation**
    - Current statement generally reflects the body of experimental controlled trial evidence, but lacks detail
  - **Option 2: modify the current recommendation** to include more detail, *for example*:
    - Consider creating separate recommendations for CBD as Epidiolex and other cannabinoid/cannabis-related products
      - There is substantial evidence* to support the conclusion that high-dose oral pure CBD solution (as the FDA-approved pharmaceutical preparation, Epidiolex) *as an adjunct* to other anti-seizure treatments is an effective treatment for seizures in children with Dravet syndrome and children or adults with Lennox-Gastaut syndrome or tuberous sclerosis complex
      - Insufficient evidence* for CBD formulations other than Epidiolex or other cannabis- or cannabinoid-based formulations

*Based on NASEM LOE categories (refer to extra slides for details).[26]

Abbreviations: CBD, cannabidiol; CRRB, Utah Cannabis Research Review Board; LOE, level of evidence; NASEM, National Academies of Sciences, Engineering, and Medicine

CONSIDERATIONS FOR UPDATES TO CRRB GUIDANCE FOR EPILEPSY

- Additional considerations for <u>elaboration in guidance</u>:
  - Discuss/review non-graded recommendations/guidance to ensure continued agreement
    - Current guidance also highlights observational evidence excluded from this review[25]
      - See report section 5.1 for examples of excluded uncontrolled, single-arm clinical trials
  - Elaborate about the characteristics of available RCTs, particularly those not not addressed by current guidance
    - Guidance addresses 1 RCT of Epidiolex for people with DS and both RCTs among people with LGS, but no trials among people with TSC
    - Consider updating information about DDIs
      - May refer to Epidiolex prescribing information[19]
    - May consider updating dosing guidance based on the most recent Epidiolex prescribing information

Abbreviations: CBD, cannabidiol; CRRB, Utah Cannabis Research Review Board; DDIs, drug-drug interactions; DS, Dravet syndrome; LGS, Lennox-Gastaut Syndrome; RCT, randomized controlled trial; TSC, tuberous sclerosis complex;

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Extra slides

NATIONAL ACADEMIES LOE RATINGS*[26]

Conclusive Evidence
"There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 7).
"For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitation of the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence" (page 7).
Substantial Evidence
"There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 7).
"For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence" (page 7).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report on cannabis.

Abbreviations: LOE, level of evidence;

NATIONAL ACADEMIES LOE RATINGS*[26]

Moderate Evidence
"There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).
"For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence" (page 8).
Limited Evidence
"There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).
"For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors" (page 8).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report on cannabis.

Abbreviations: LOE, level of evidence;

NATIONAL ACADEMIES LOE RATINGS*[26]

No or Insufficient Evidence
"There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).
"For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors" (page 8).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report on cannabis.

Abbreviations: LOE, level of evidence;

OVERVIEW OF STUDIED CANNABIS-RELATED TREATMENTS

Trial *Approx. tx length*	Studied Cannabinoid- or Cannabis-based Product (CBP) Regimen*
CBD (as Epidiolex) for Dravet Syndrome	
Devinsky et al (2017)[9] NCT02091375 *14 weeks*	CBD oral solution 20 mg/kg/day, administered in divided doses twice daily • At end of treatment, tapered by 10% of the total dose over 10 days
Devinsky et al (2018)[11] NCT02091206 *3 weeks*	CBD oral solution (with 25 or 100 mg/mL CBD) 5 mg/kg/day, or 10 mg/kg/day or 20 mg/kg/day, administered twice daily • Initiated at 2.5 mg/kg and titrated by 2.5–5 mg/kg every other day to the target dose
Miller et al (2020)[10] NCT02224703 *14 weeks*	CBD oral solution 10 mg/kg/day, or 20 mg/kg/day, administered in 2 equally divided doses • Initiated at 2.5 mg/kg/day and titrated to the target dose by day 7 (10 mg/kg dose) or day 11 (20/mg dose)
CBD (as Epidiolex) for Lennox-Gastaut syndrome	
Thiele et al (2018)[8] NCT02224690 *14 weeks*	CBD oral solution 20 mg/kg/day, administered in 2 equally divided doses (AM and PM) • Initiated at 2.5 mg/kg/day, and titrated to the target dose over 2 weeks
Devinsky et al (2018)[7] NCT02224560 *14 weeks*	CBD oral solution 20 mg/kg/day or 10 mg/kg/day, administered in 2 equally divided doses • Initiated at 2.5 mg/kg/day and increased by 2.5–5 mg/kg every other day until reaching the target dose

*According to information reported by the trial's primary publication (not supplementary information or protocol). Refer to Epidiolex prescribing information (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8bf27097-4870-43fb-94f0-f3d0871d1eec) for the FDA-approved dosage and administration instructions.

Abbreviations: CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product;Tx, treatment

OVERVIEW OF STUDIED CANNABIS-RELATED TREATMENTS

Trial *Approx. tx length*	Studied Cannabinoid- or Cannabis-based Product (CBP) Regimen*
CBD (as Epidiolex) for tuberous sclerosis complex	
Thiele et al 9 (2021)[12] NCT02544763 *16 weeks*	CBD oral solution 25 mg/kg/day or 50 mg/kg/day, administered in 2 equally divided doses • Initiated at 5 mg/kg/day and and titrated to the target dose by day 9 (25 mg/kg dose) or day 29 (50 mg/kg dose) • Per kg of body weight • Primarily due to AEs, only 67% of patients in the 50 mg/kg/day group achieved that dose; the modal dosage at the end of the treatment period was 36 mg/kg/day (per supplementary information)[27]
CBD (as Epidiolex) DDI trials	
VanLandingham et al (2020)[13] *About 4.4 weeks*	CBD oral solution 20 mg/kg/day, administered in 2 equally divided doses • Titrated to target dose over 10 days; taken immediately after the clobazam dose
Ben-Menachem et al (2020)[14] *About 3.4 weeks*	CBD oral solution 20 mg/kg/day, administered in 2 equally divided doses in AM and PM • Titrated to target dose over 10 days; taken immediately after the stiripentol or valproate dose • Patients educated to take the dose consistently with regard to food

*According to information reported by the trial's primary publication (not supplementary information or protocol), unless otherwise noted. Refer to Epidiolex prescribing information (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8bf27097-4870-43fb-94f0-f3d0871d1eec) for the FDA-approved dosage and administration instructions.

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; Tx, treatment

OVERVIEW OF STUDIED CANNABIS-RELATED TREATMENTS

Trial *Approx. tx length*	Studied Cannabinoid- or Cannabis-based Product (CBP)*
Liposomal CBD for focal epilepsy (in adults)	
Ebadi et al (2023)[15] *8 weeks*	Liquid liposomal CBD (99.5% pure CBD without THC; 40 mg/mL) 210 mg per day, from the KMT company • Initiated at 70 mg per day for 1 week, then increased to 140 mg per day for 1 week, followed by an increase to the target dose • Lacked information about the dosing frequency or weight of participants
Transdermal CBD for focal epilepsy (in adults)	
O'Brien et al (2022)[16] *12 weeks*	CBD transdermal gel (ZYN002, Zynerba Pharmaceuticals) 195 mg (~2.6 mg/kg/day) or 390 mg (~5.3 mg/kg/day), administered in equal divided doses twice daily • ZYN002 was suppled as foil-lined sachets containing 97.5 mg CBD (4.2% wt/wt) • Study drug was applied to the upper arms and shoulders
CBDV for focal epilepsy (in adults)	
Brodie et al (2021)[17] *About 8 weeks*	CBDV (50 mg/mL) oral solution 800 mg twice daily (about 23 mg/kg/day) • Initiated at 400 mg twice daily for 1 week, then increased to 600 mg twice daily and continued for 1 additional week; administered after ≥2 hours of fasting and with 30 min fasting after administration • Mean modal dose achieved was 1480 mg/day • Tapered over 12-days at trial completion

*According to information reported by the trial's primary publication (not supplementary information or protocol)

Abbreviations: CBD, cannabidiol; CBDV, cannabidivarin; CBP, cannabinoid- or cannabis-based product; Tx, treatment