Drugs - Electronic Supplementary Material

Pharmacotherapy for Dravet Syndrome: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

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Table e-1. Risk of bias summary

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
STICLO-France	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
STICLO-Italy	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
GWPCARE 1A	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
GWPCARE 1B	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
GWPCARE 2	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lagae et al., 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nabbout et al., 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ELEKTRA	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table e-2. Definitions of convulsive seizures in the included trials

Study	Definition of convulsive seizures
STICLO-France	Generalized tonic-clonic, clonic seizures
STICLO-Italy	Generalized tonic-clonic, clonic seizures
GWPCARE1 Part A	Tonic-clonic, tonic, clonic, atonic seizures
GWPCARE1 Part B	Tonic-clonic, tonic, clonic, atonic seizures
GWPCARE2	Tonic-clonic, tonic, clonic, atonic seizures
Lagae et al., 2019	Hemi-clonic, tonic, clonic, tonic-atonic, generalised tonic-clonic, focal with clearly observable motor signs
Nabbout et al., 2019	Hemi-clonic, tonic, clonic, tonic-atonic, generalized tonic-clonic, secondarily generalized tonic-clonic [focal to bilateral tonic-clonic], and focal with clearly observable motor signs
ELEKTRA	Generalized tonic-clonic, focal to bilateral tonic-clonic, hemi-clonic, bilateral clonic (generalized clonic), and convulsive status epilepticus seizures

Table e-3. Results of the pairwise meta-analyses for the study outcomes

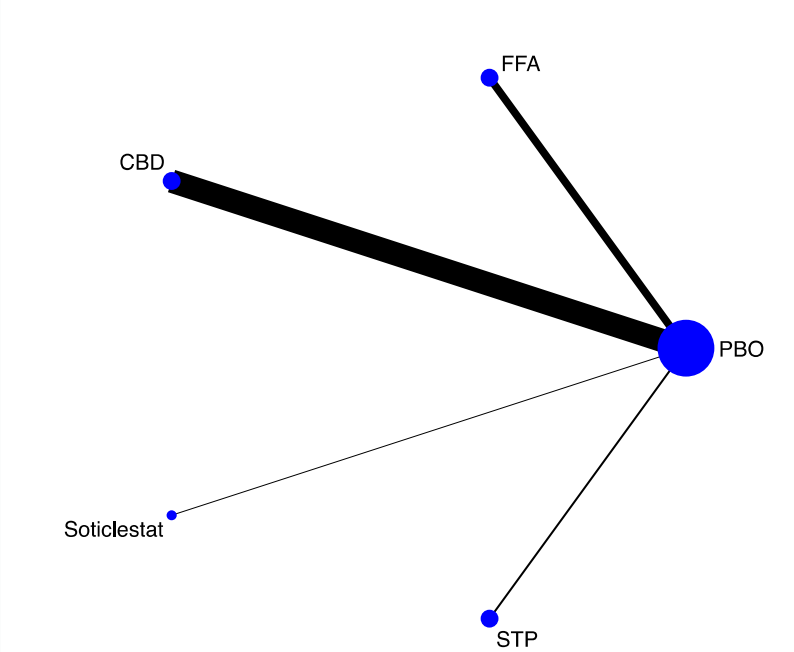
Comparison	Number of studies	Number of pooled events/participants		I^2	Odds Ratio (95% CI)	p value
		1st treatment group	2nd treatment group			
Seizure response						
STP vs. placebo	2	23/33	2/31	0.0%	31.75 (6.25-161.16)	<0.001
CBD vs. placebo	2	88/194	33/124	0.0%	2.26 (1.38-3.70)	0.001
FFA vs. placebo	2	65/122	7/84	27.4%	11.24 (4.76-26.54)	<0.001
Soticlestat vs. placebo	1	8/26	0/25	-	23.43 (1.27-423.00)	0.034
Seizure freedom						
STP vs. placebo	2	13/33	0/31	0.0%	19.86 (2.40-164.45)	0.006
CBD vs. placebo	2	7/194	1/124	0.0%	3.12 (0.53-18.45)	0.209
FFA vs. placebo	2	7/122	0/84	0.0%	4.96 (0.57-42.89)	0.146
Soticlestat vs. placebo	1	1/26	0/25	-	3.00 (0.12-77.17)	0.507
Treatment discontinuation						
STP vs. placebo	2	2/33	6/31	0.0%	0.27 (0.05-1.51)	0.138
CBD vs. placebo	3	20/221	3/131	0.0%	3.49 (1.11-10.95)	0.032
FFA vs. placebo	2	13/122	6/84	0.0%	1.65 (0.60-4.55)	0.332
Soticlestat vs. placebo	1	2/26	3/25	-	0.61 (0.09-4.01)	0.608
Treatment discontinuation for adverse events						
STP vs. placebo	2	1/33	1/31	0.0%	0.94 (0.09-9.54)	0.957
CBD vs. placebo	3	15/221	1/131	0.0%	5.18 (1.15-23.23)	0.032
FFA vs. placebo	2	7/122	1/84	0.0%	3.23 (0.50-20.96)	0.220
Soticlestat vs. placebo	1	1/26	1/25	-	0.96 (0.06-16.23)	0.977
At least one adverse event						
STP vs. placebo	1	21/21	5/20	-	121.18 (6.23-2356.89)	0.002
CBD vs. placebo	3	195/221	108/131	64.9%	1.52 (0.41-5.68)	0.189
FFA vs. placebo	2	117/122	68/84	26.7%	7.37 (2.52-21.60)	<0.001
At least one serious adverse event						
STP vs. placebo	2	2/33	3/31	0.0%	0.65 (0.12-3.61)	0.619
CBD vs. placebo	3	44/221	14/131	0.0%	1.88 (0.98-3.62)	0.057
FFA vs. placebo	2	15/122	11/84	0.0%	0.99 (0.42-2.33)	0.978

Improvement at the C-CGIC						
CBD vs. placebo	2	122/192	47/123	0.0%	2.74 (1.71-4.39)	<0.001
FFA vs. placebo	2	74/122	28/84	0.0%	3.14 (1.74-5.68)	<0.001
Soticlestat vs. placebo	1	15/26	8/25	-	2.90 (0.92-9.11)	0.069

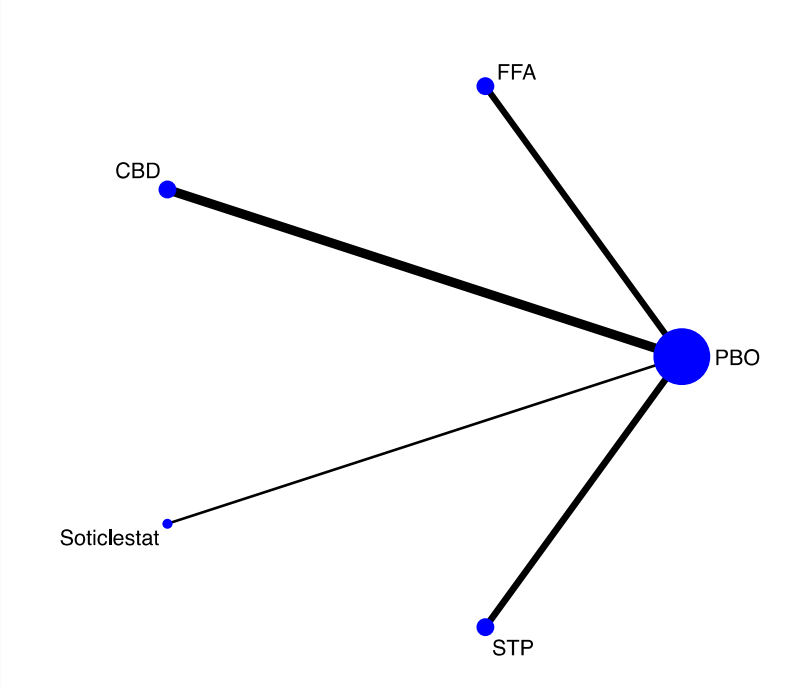
An odds ratio greater than 1 indicates increased likelihood of the outcome being achieved in the first than in the second treatment group of each comparison. Abbreviations: CBD=pharmaceutical-grade cannabidiol, C-CGIC=Caregiver-reported Clinical Global Impression of Change, FFA=fenfluramine hydrochloride, PBO=placebo, STP=stiripentol.

Figure e-1. Network meta-analysis of eligible comparisons for efficacy, tolerability, and global functioning

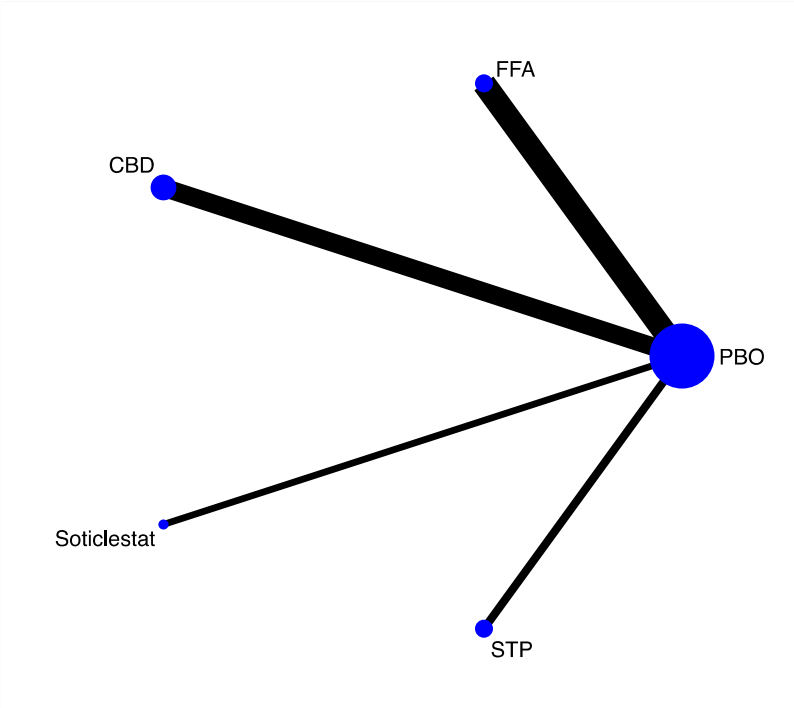
A) Seizure response



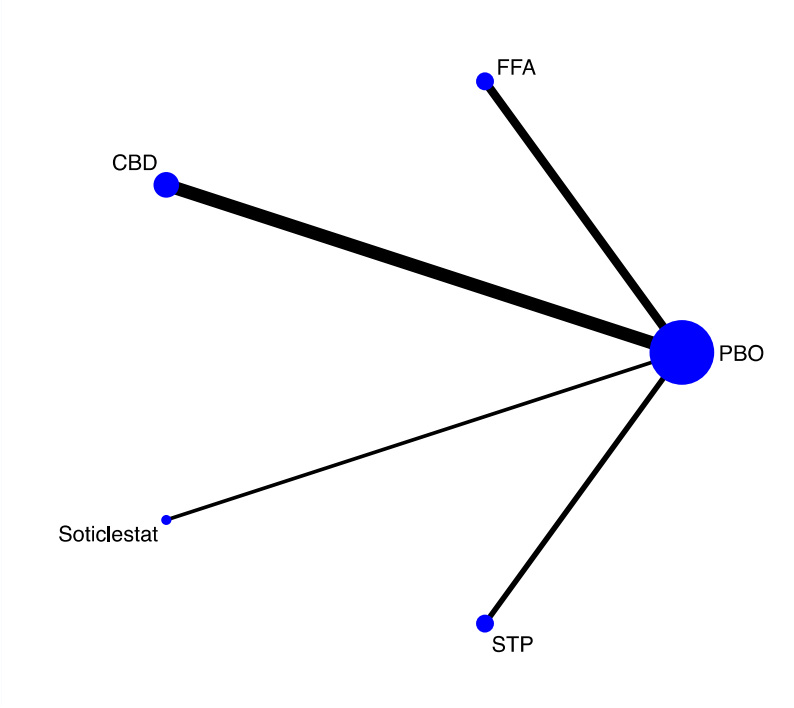
B) Seizure freedom



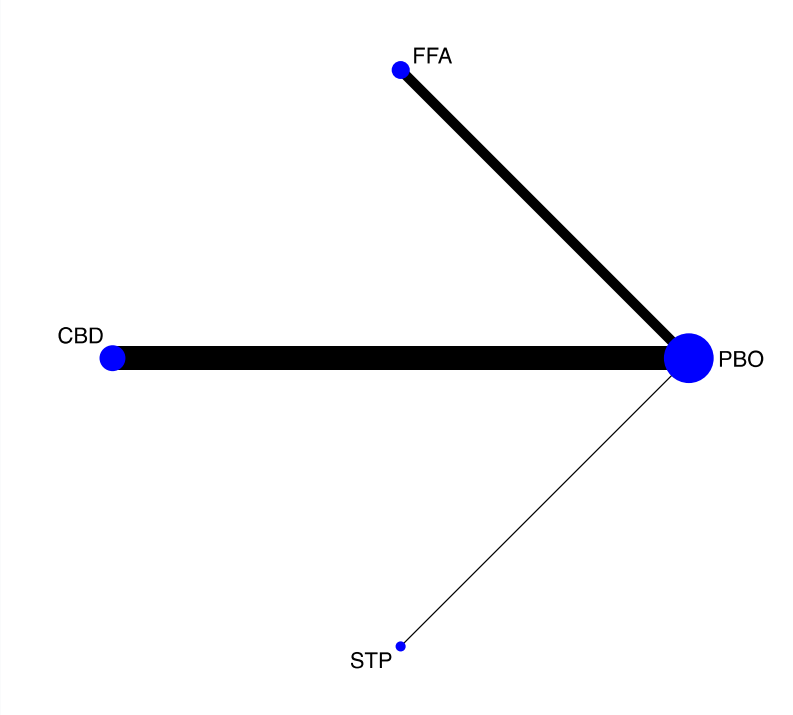
C) Treatment discontinuation



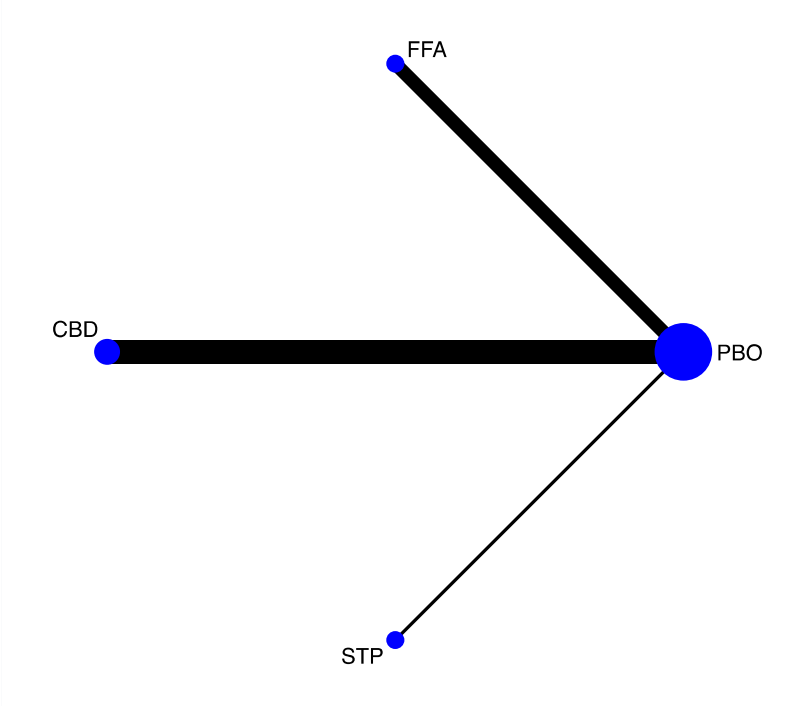
D) Treatment discontinuation for adverse events



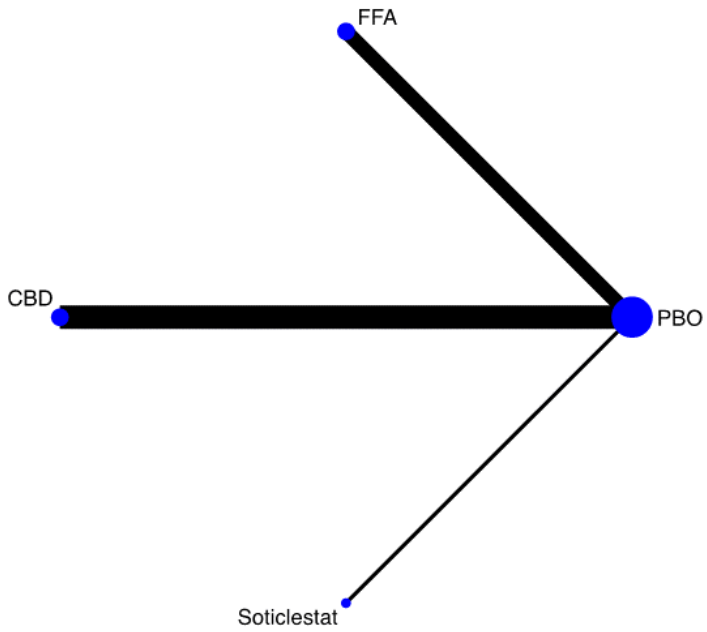
E) At least one adverse event



F) At least one serious adverse event

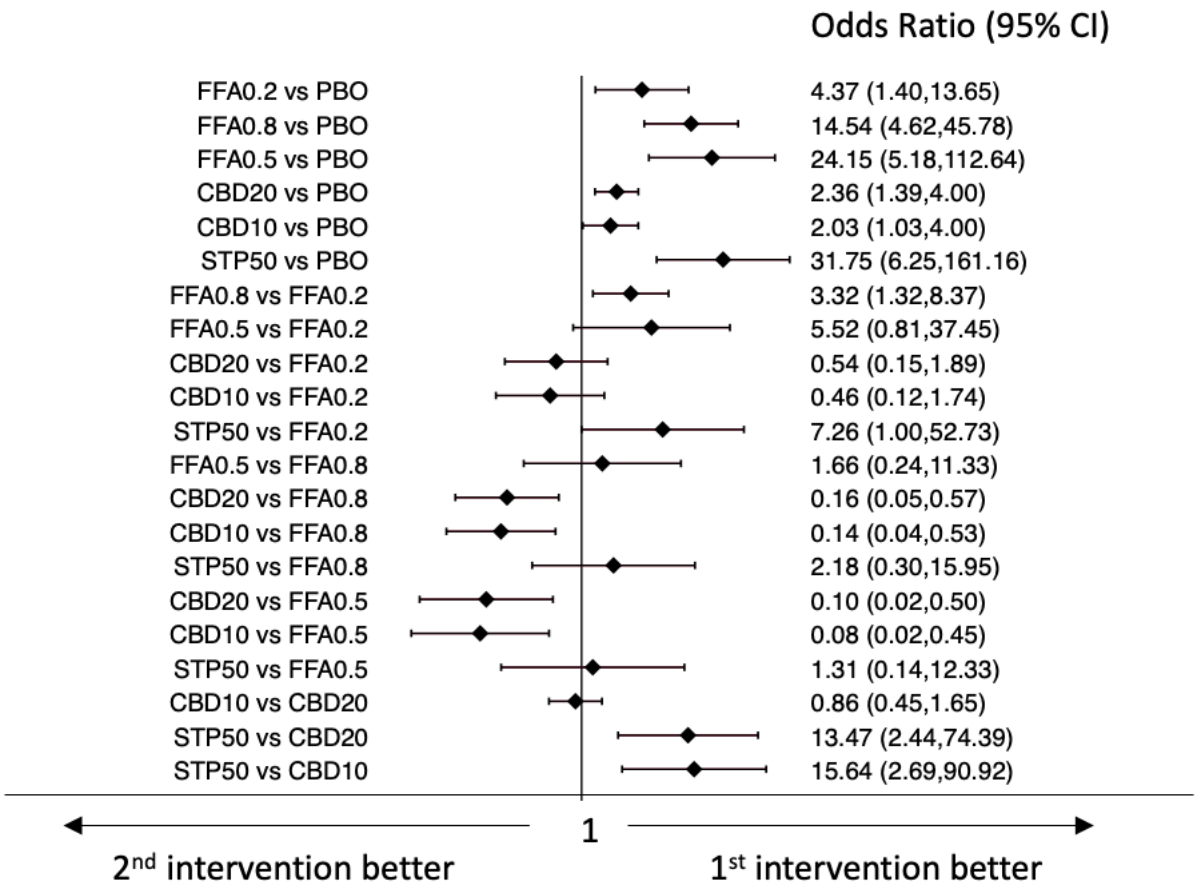


G) Improvement at the Caregiver-reported Clinical Global Impression of Change



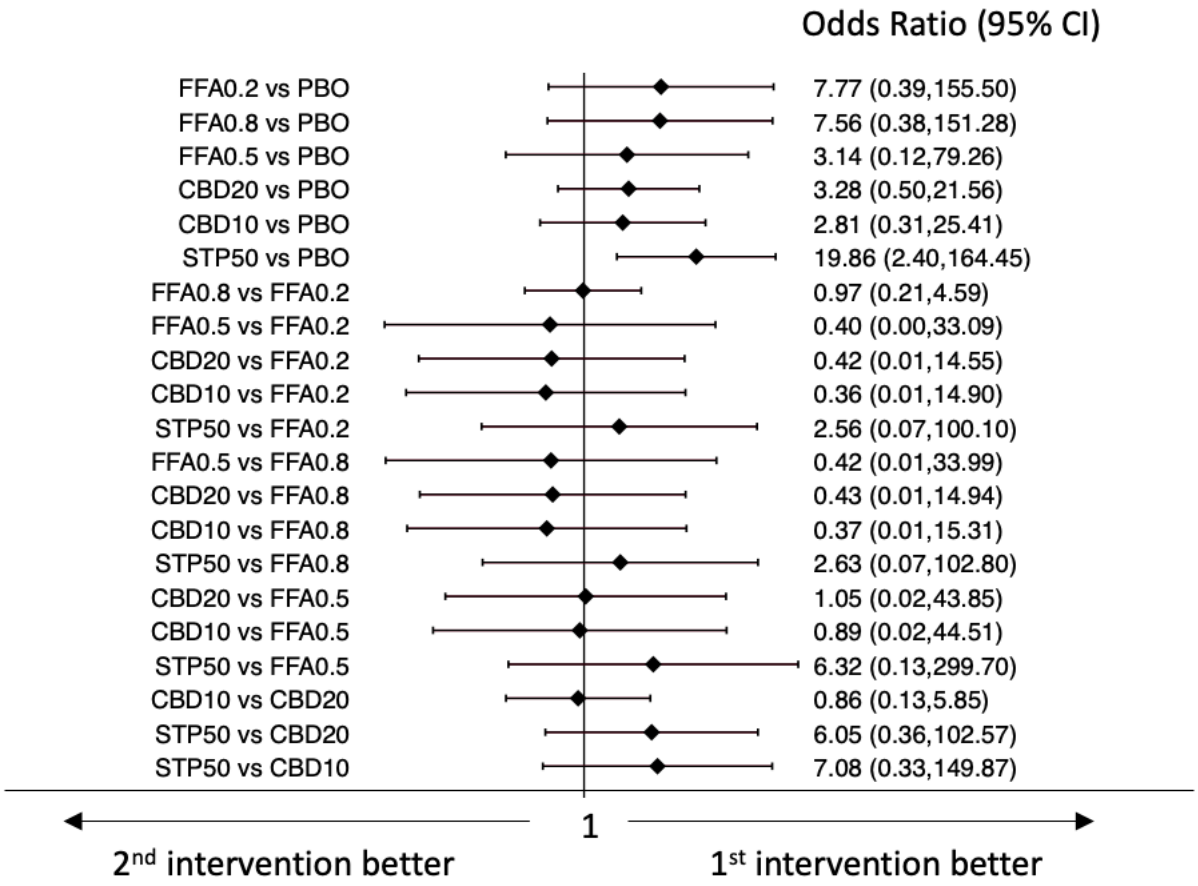
The width of the lines is proportional to the inverse of the variance of the comparison treatment effect and the size of every circle is proportional to the number of randomly assigned participants. Abbreviations: CBD=pharmaceutical-grade cannabidiol, FFA=fenfluramine hydrochloride, PBO=placebo, STP=stiripentol.

Figure e-2. Interval plot for the efficacy outcome by drug dosages: seizure response



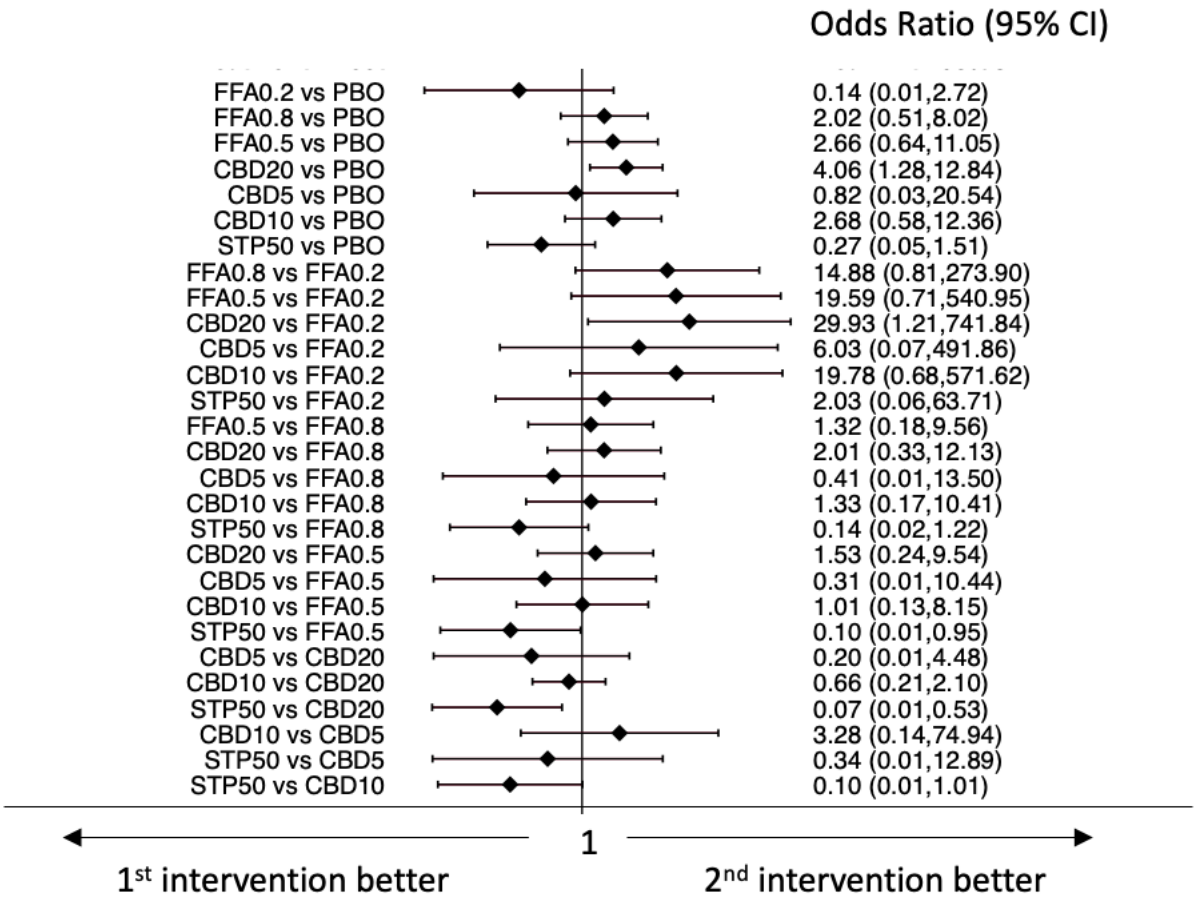
Abbreviations: CBD10=pharmaceutical-grade cannabidiol 10 mg/kg/day, CBD20=pharmaceutical-grade cannabidiol 20 mg/kg/day, CI=confidence interval, FFA0.2=fenfluramine hydrochloride 0.2 mg/kg/day, FFA0.5=fenfluramine hydrochloride 0.5 mg/kg/day, FFA0.8=fenfluramine hydrochloride 0.8 mg/kg/day, PBO=placebo, STP50=stiripentol 50 mg/kg/day.

Figure e-3. Interval plot for the efficacy outcome by drug dosages: seizure freedom



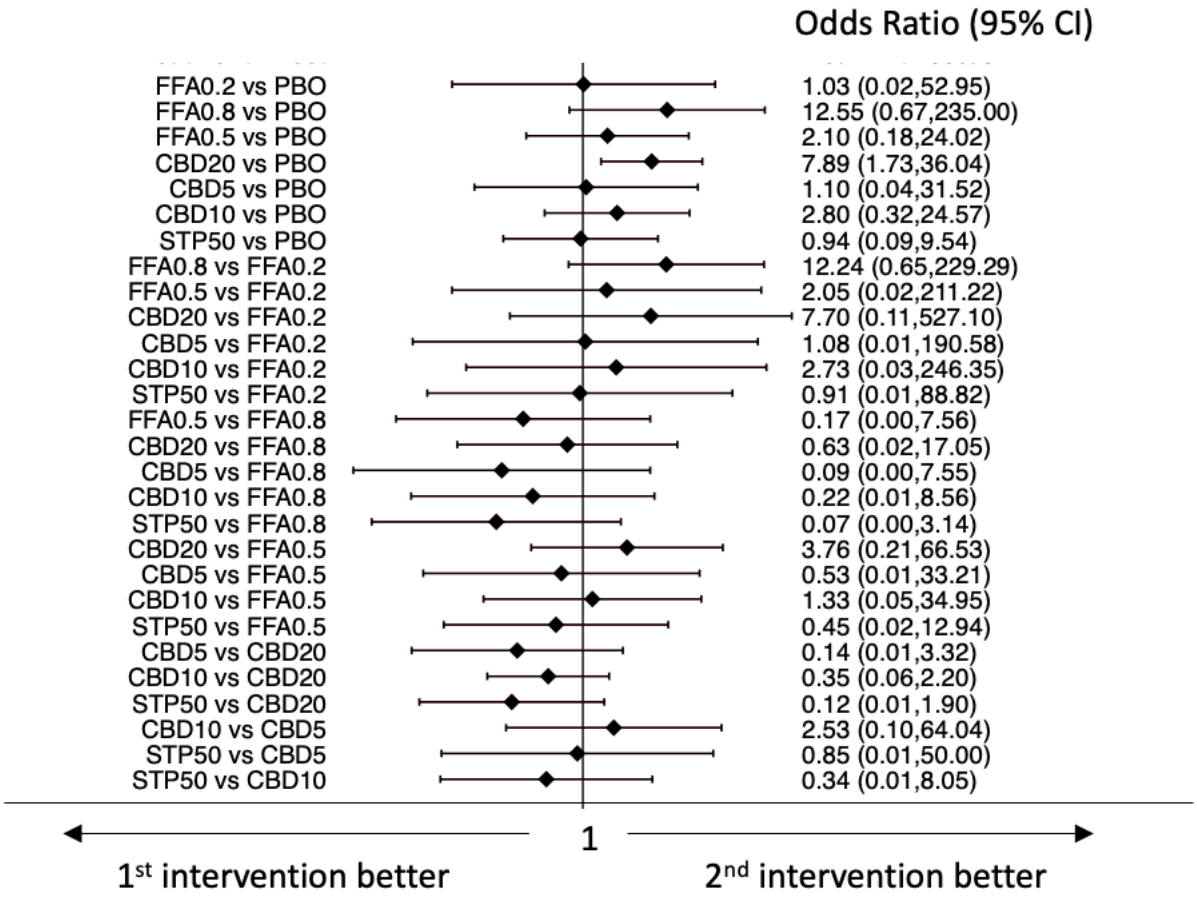
Abbreviations: CBD10=pharmaceutical-grade cannabidiol 10 mg/kg/day, CBD20=pharmaceutical-grade cannabidiol 20 mg/kg/day, CI=confidence interval, FFA0.2=fenfluramine hydrochloride 0.2 mg/kg/day, FFA0.5=fenfluramine hydrochloride 0.5 mg/kg/day, FFA0.8=fenfluramine hydrochloride 0.8 mg/kg/day, PBO=placebo, STP50=stiripentol 50 mg/kg/day.

Figure e-4. Interval plot for the tolerability outcome by drug dosages: discontinuation for any reason



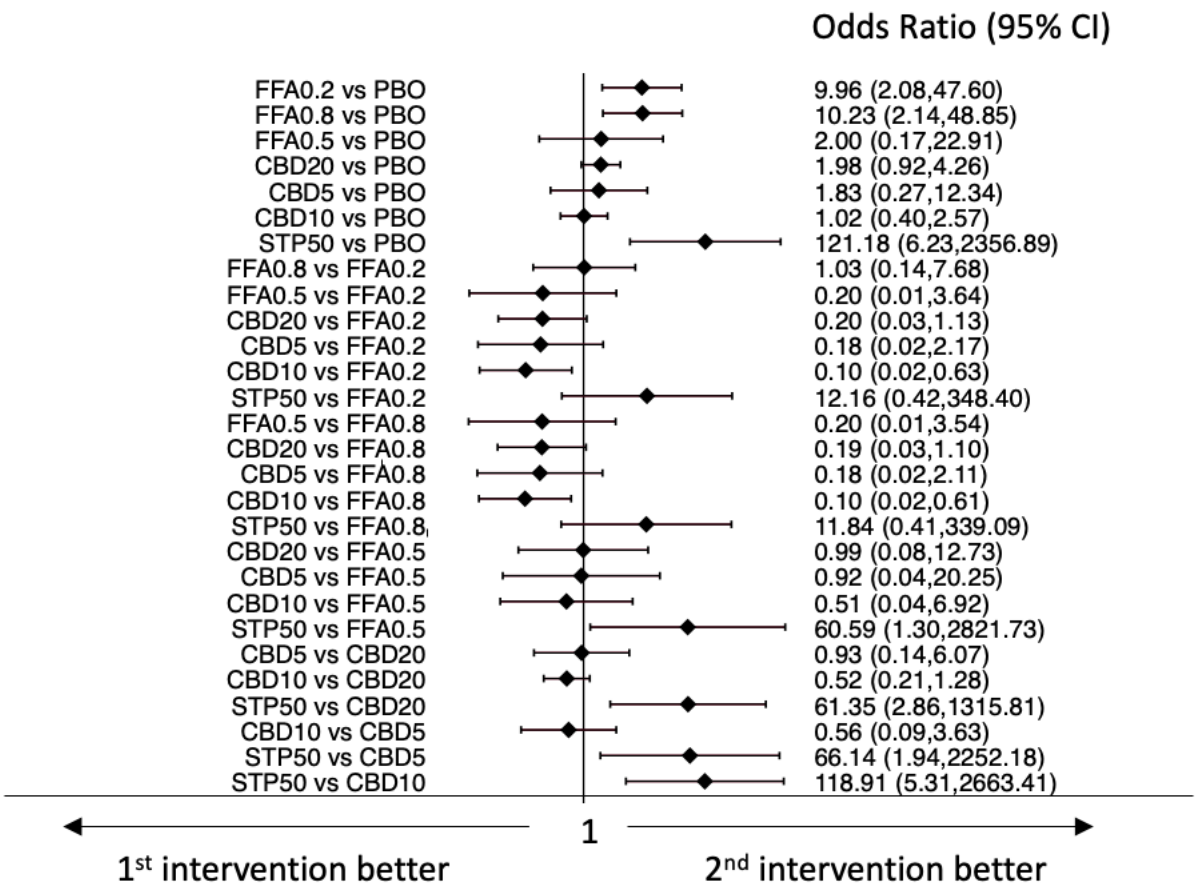
Abbreviations: CBD5=pharmaceutical-grade cannabidiol 0.5 mg/kg/day, CBD10=pharmaceutical-grade cannabidiol 10 mg/kg/day, CBD20=pharmaceutical-grade cannabidiol 20 mg/kg/day, CI=confidence interval, FFA0.2=fenfluramine hydrochloride 0.2 mg/kg/day, FFA0.5=fenfluramine hydrochloride 0.5 mg/kg/day, FFA0.8=fenfluramine hydrochloride 0.8 mg/kg/day, PBO=placebo, STP50=stiripentol 50 mg/kg/day.

Figure e-5. Interval plot for the tolerability outcome by drug dosages: discontinuation for adverse events



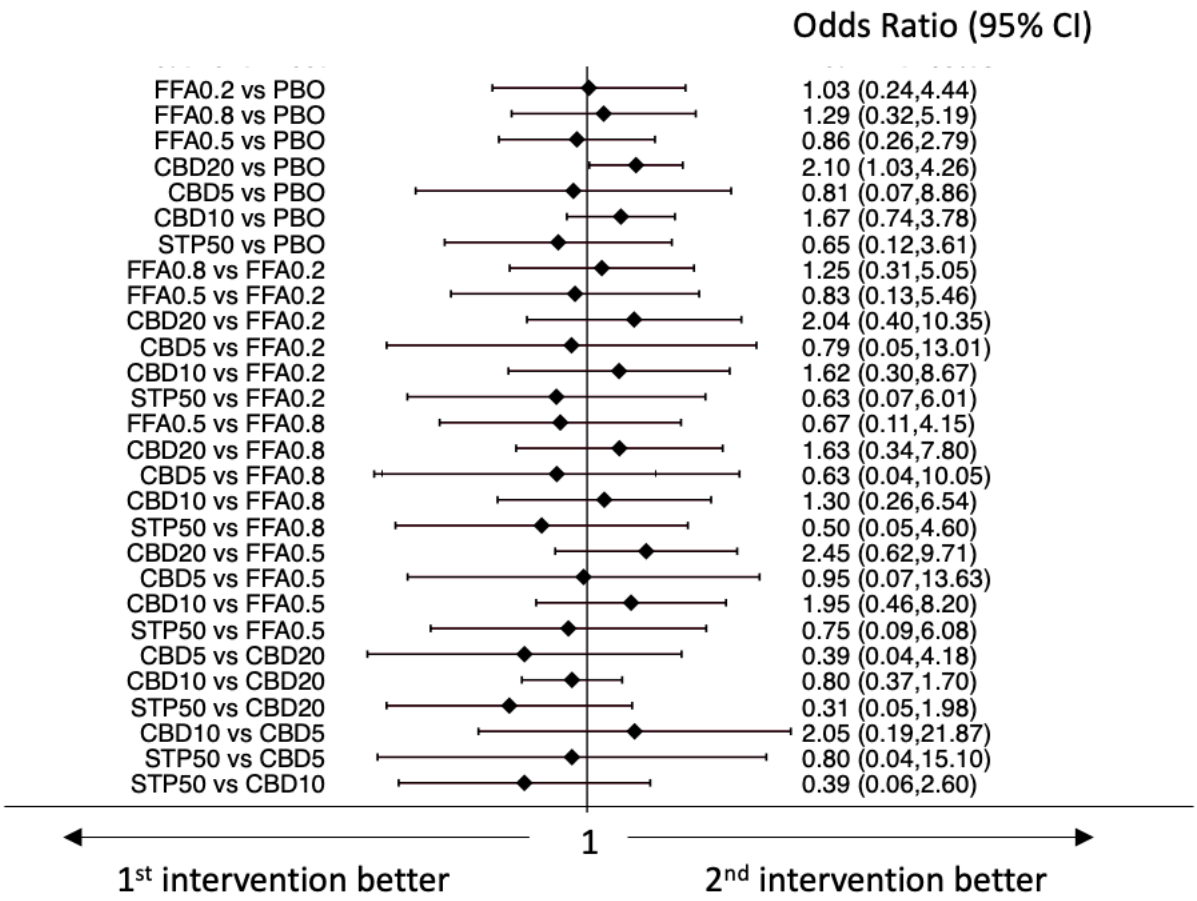
Abbreviations: CBD5=pharmaceutical-grade cannabidiol 0.5 mg/kg/day, CBD10=pharmaceutical-grade cannabidiol 10 mg/kg/day, CBD20=pharmaceutical-grade cannabidiol 20 mg/kg/day, CI=confidence interval, FFA0.2=fenfluramine hydrochloride 0.2 mg/kg/day, FFA0.5=fenfluramine hydrochloride 0.5 mg/kg/day, FFA0.8=fenfluramine hydrochloride 0.8 mg/kg/day, PBO=placebo, STP50=stiripentol 50 mg/kg/day.

Figure e-6. Interval plot for the tolerability outcome by drug dosages: occurrence of adverse events



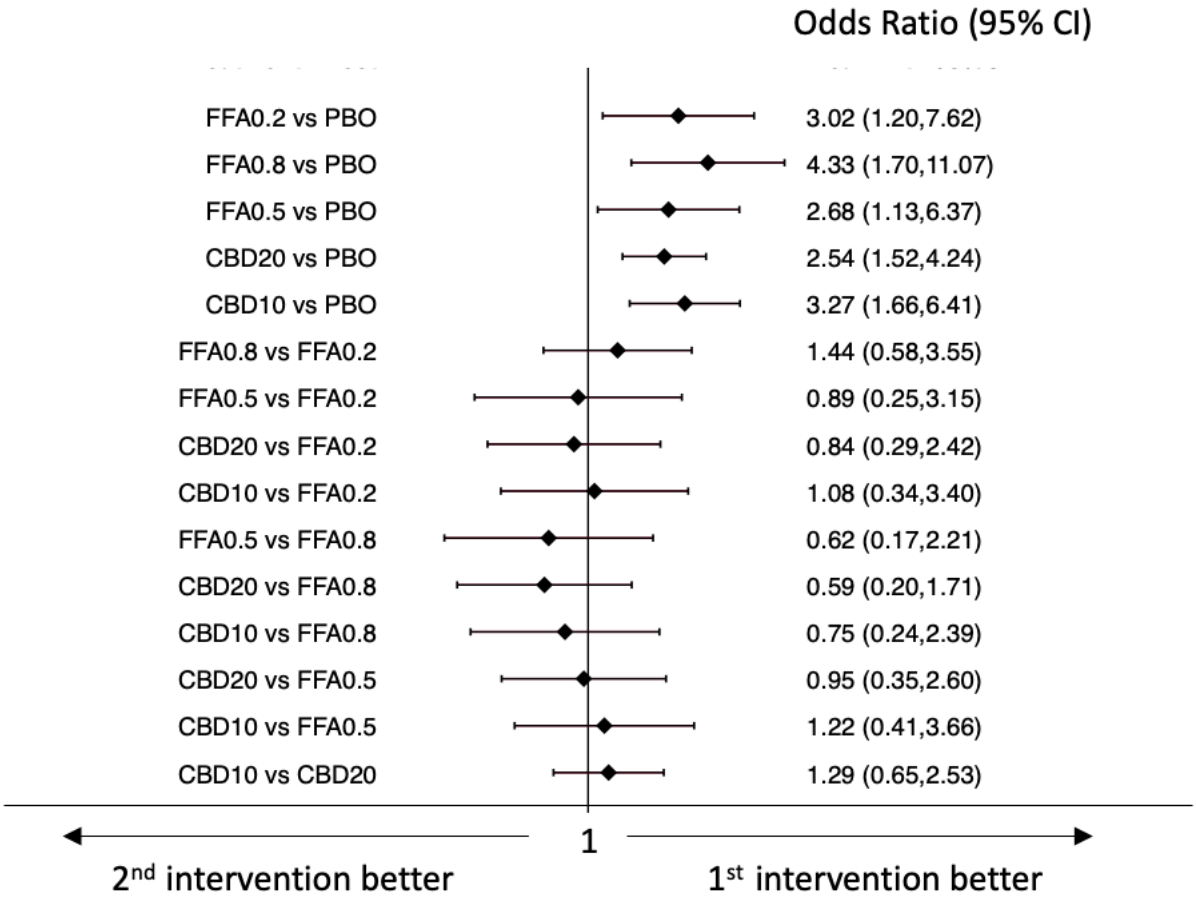
Abbreviations: CBD5=pharmaceutical-grade cannabidiol 0.5 mg/kg/day, CBD10=pharmaceutical-grade cannabidiol 10 mg/kg/day, CBD20=pharmaceutical-grade cannabidiol 20 mg/kg/day, CI=confidence interval, FFA0.2=fenfluramine hydrochloride 0.2 mg/kg/day, FFA0.5=fenfluramine hydrochloride 0.5 mg/kg/day, FFA0.8=fenfluramine hydrochloride 0.8 mg/kg/day, PBO=placebo, STP50=stiripentol 50 mg/kg/day.

Figure e-7. Interval plot for the tolerability outcome by drug dosages: occurrence of serious adverse events



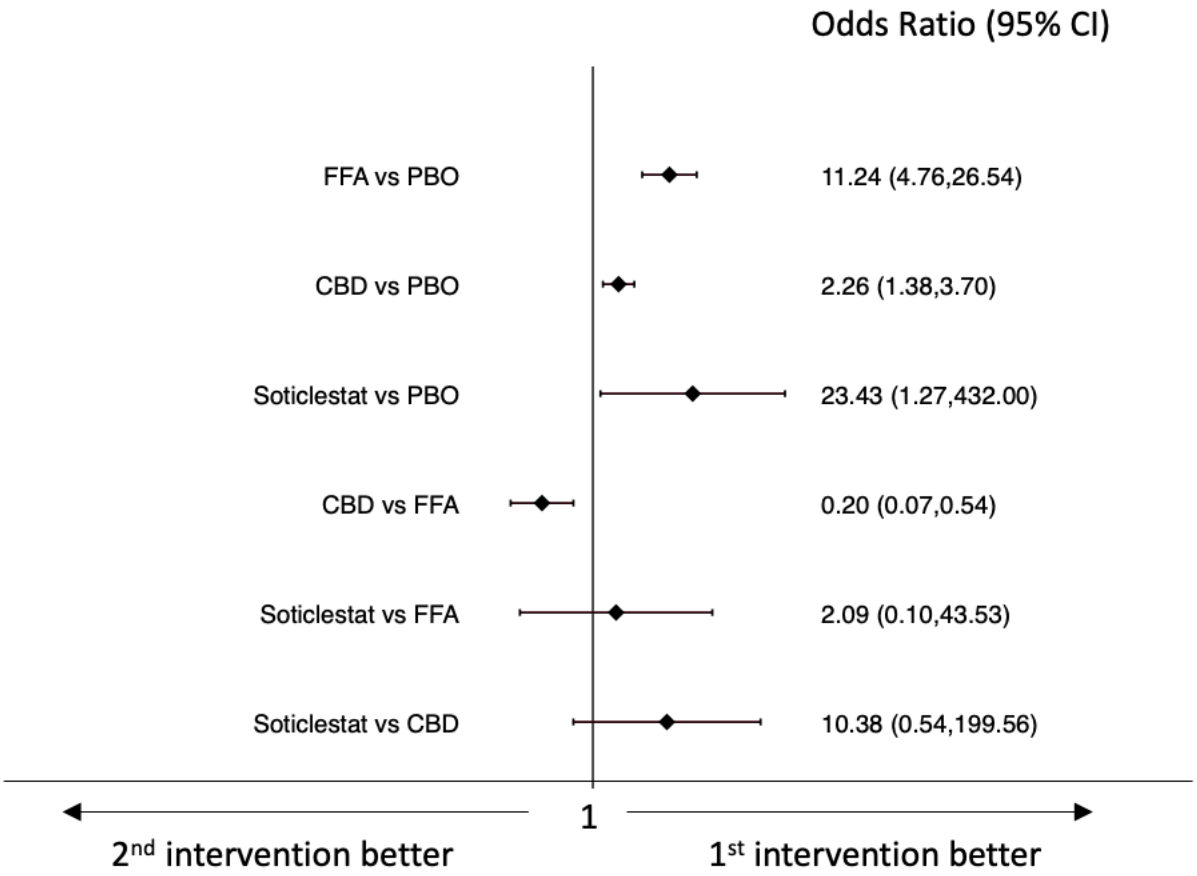
Abbreviations: CBD5=pharmaceutical-grade cannabidiol 0.5 mg/kg/day, CBD10=pharmaceutical-grade cannabidiol 10 mg/kg/day, CBD20=pharmaceutical-grade cannabidiol 20 mg/kg/day, CI=confidence interval, FFA0.2=fenfluramine hydrochloride 0.2 mg/kg/day, FFA0.5=fenfluramine hydrochloride 0.5 mg/kg/day, FFA0.8=fenfluramine hydrochloride 0.8 mg/kg/day, PBO=placebo, STP50=stiripentol 50 mg/kg/day.

Figure e-8. Interval plot for the global functioning outcome by drug dosages: improvement at caregiver-reported Clinical Global Impression of Change



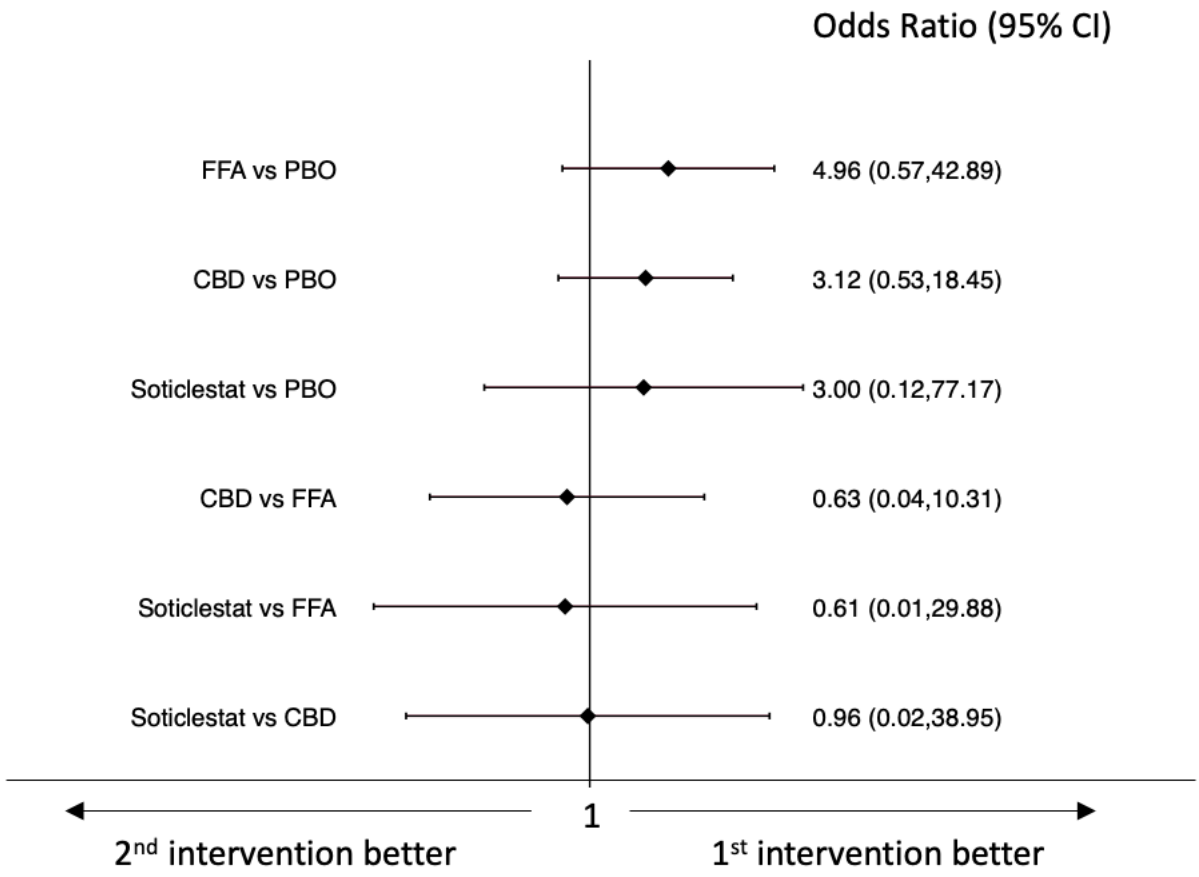
Abbreviations: CBD10=pharmaceutical-grade cannabidiol 10 mg/kg/day, CBD20=pharmaceutical-grade cannabidiol 20 mg/kg/day, CI=confidence interval, FFA0.2=fenfluramine hydrochloride 0.2 mg/kg/day, FFA0.5=fenfluramine hydrochloride 0.5 mg/kg/day, FFA0.8=fenfluramine hydrochloride 0.8 mg/kg/day, PBO=placebo.

Figure e-9. Interval plot for the efficacy outcome in trials with a maintenance period of at least 12 weeks: seizure response



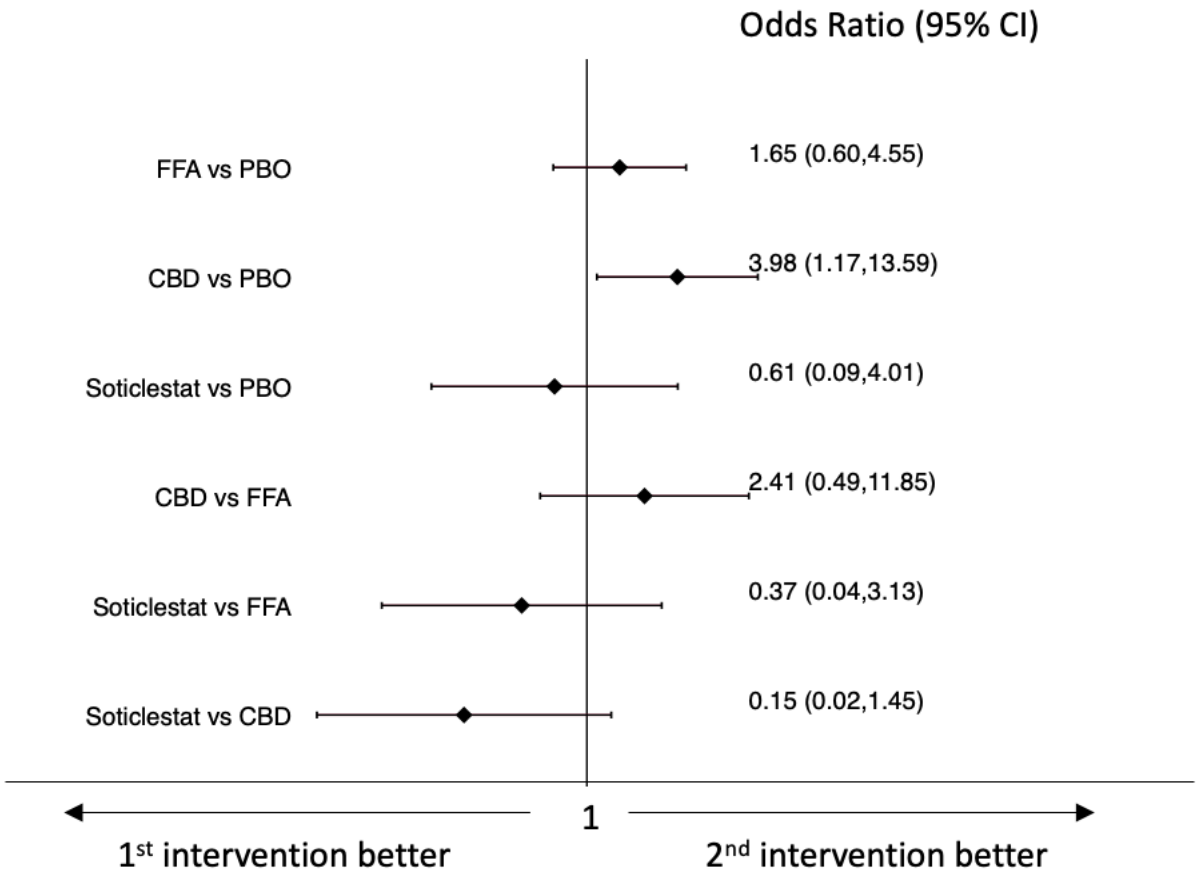
Abbreviations: CBD=pharmaceutical-grade cannabidiol, CI=confidence interval, FFA=fenfluramine hydrochloride, PBO=placebo.

Figure e-10. Interval plot for the efficacy outcome in trials with a maintenance period of at least 12 weeks: seizure freedom



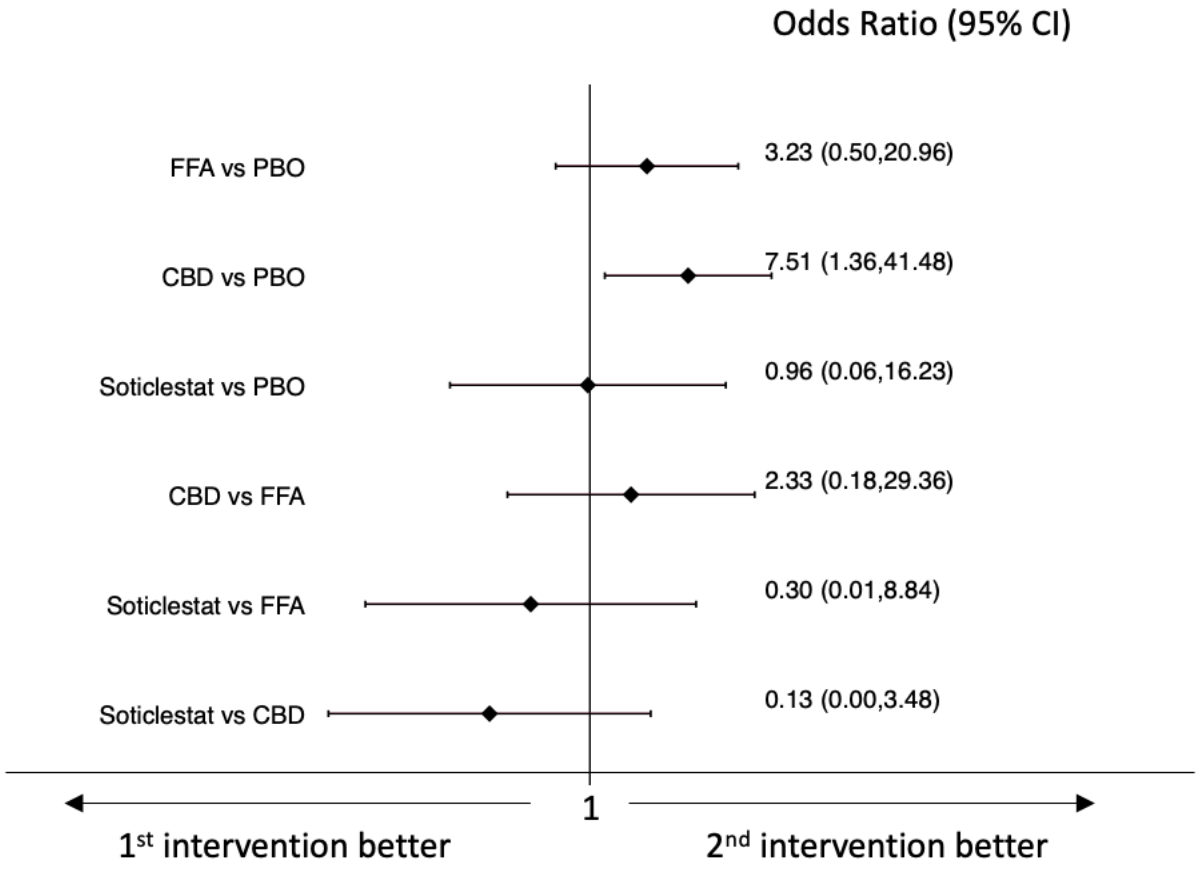
Abbreviations: CBD=pharmaceutical-grade cannabidiol, CI=confidence interval, FFA=fenfluramine hydrochloride, PBO=placebo.

Figure e-11. Interval plot for the tolerability outcome in trials with a maintenance period of at least 12 weeks: discontinuation for any reason



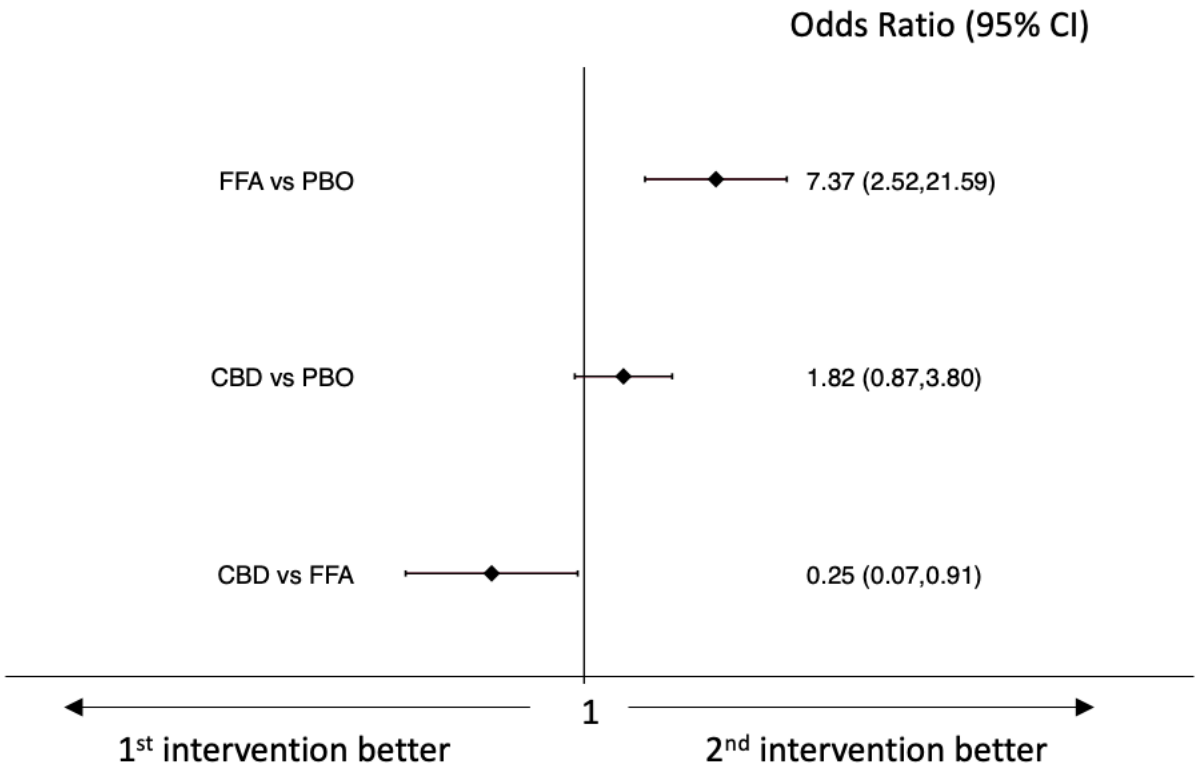
Abbreviations: CBD=pharmaceutical-grade cannabidiol, CI=confidence interval, FFA=fenfluramine hydrochloride, PBO=placebo.

Figure e-12. Interval plot for the tolerability outcome in trials with a maintenance period of at least 12 weeks: discontinuation for adverse events



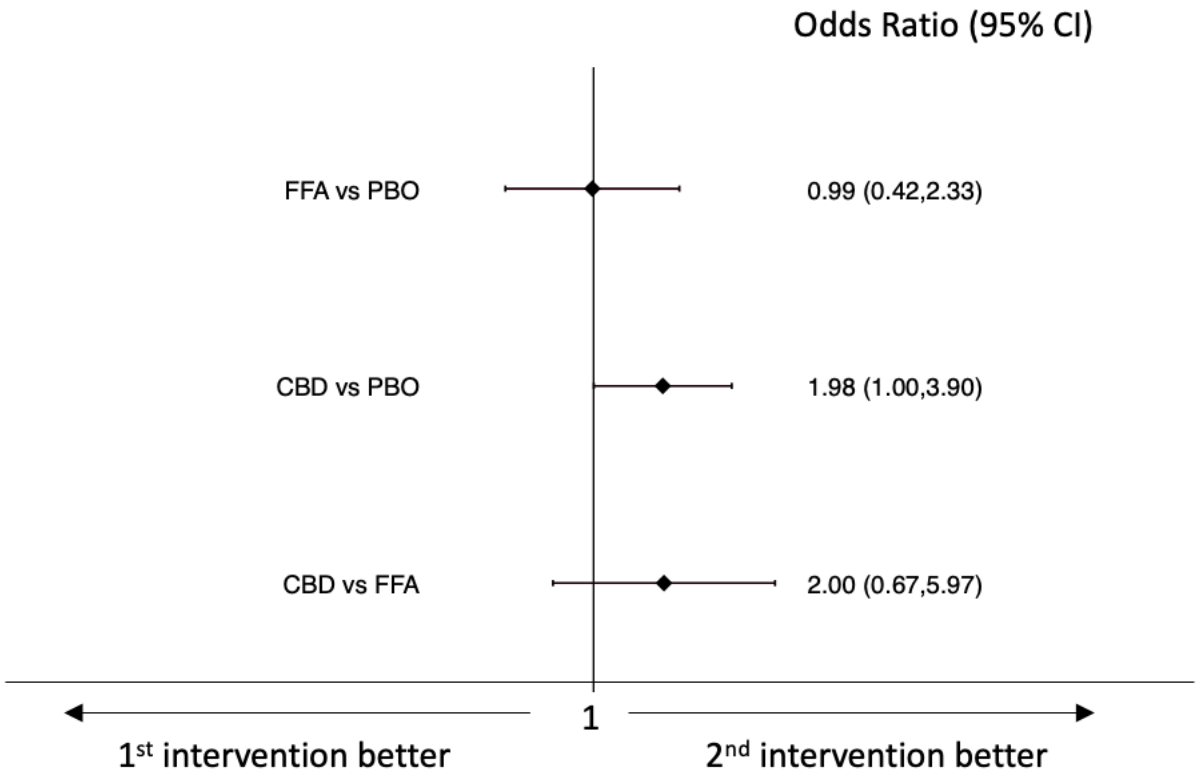
Abbreviations: CBD=pharmaceutical-grade cannabidiol, CI=confidence interval, FFA=fenfluramine hydrochloride, PBO=placebo.

Figure e-13. Interval plot for the tolerability outcome in trials with a maintenance period of at least 12 weeks: occurrence of adverse events



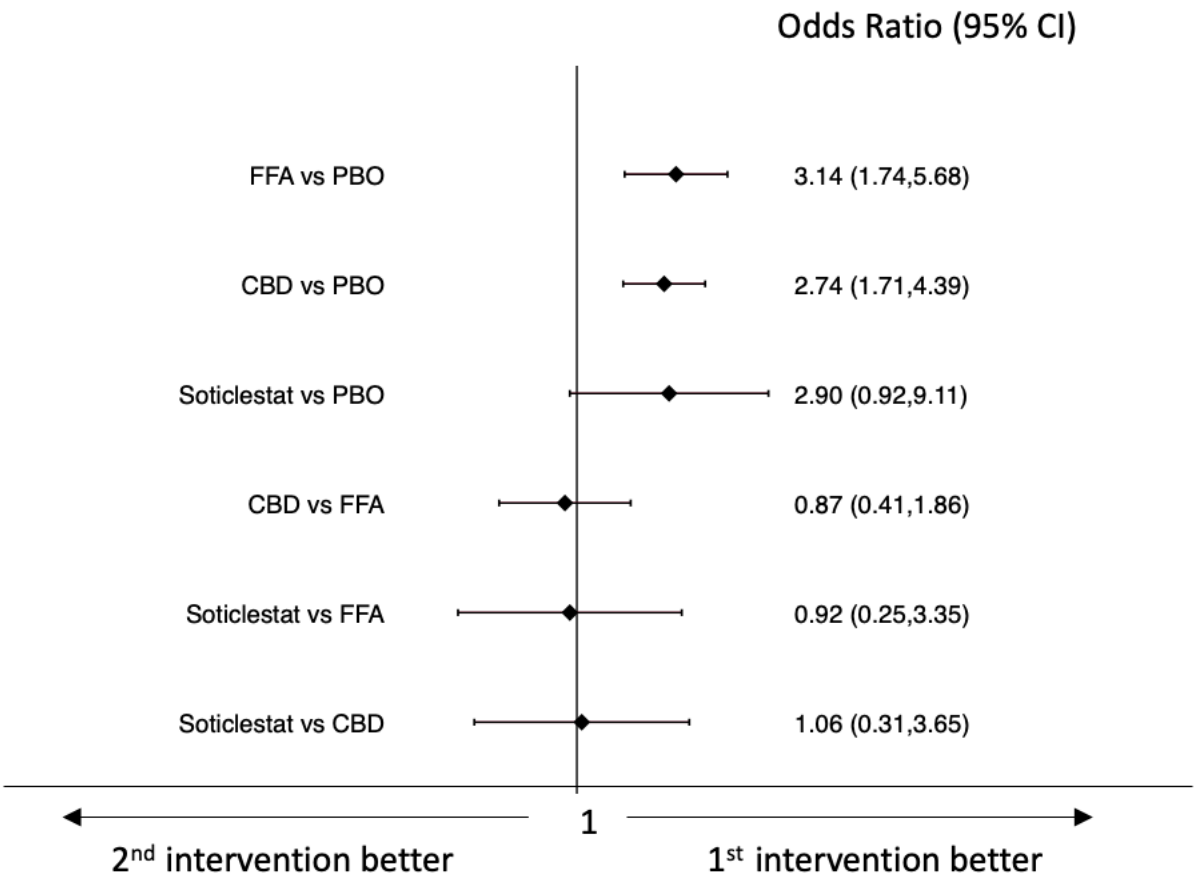
Abbreviations: CBD=pharmaceutical-grade cannabidiol, CI=confidence interval, FFA=fenfluramine hydrochloride, PBO=placebo.

Figure e-14. Interval plot for the tolerability outcome in trials with a maintenance period of at least 12 weeks: occurrence of serious adverse events



Abbreviations: CBD=pharmaceutical-grade cannabidiol, CI=confidence interval, FFA=fenfluramine hydrochloride, PBO=placebo.

Figure e-15. Interval plot for the global functioning outcome in trials with a maintenance period of at least 12 weeks: improvement at caregiver-reported Clinical Global Impression of Change



Abbreviations: CBD=pharmaceutical-grade cannabidiol, CI=confidence interval, FFA=fenfluramine hydrochloride, PBO=placebo.

Appendix I. Search strategy

PubMed search strategy

The strategy was based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials.[e-1]

#1 random* OR placebo OR trial* OR group* [Title/Abstract]
#2 "Randomized Controlled Trial"[Publication Type]
#3 "Controlled Clinical Trial"[Publication Type]
#4 ((#1) OR #2) OR #3
#5 "Animals"[Mesh] NOT"Humans"[Mesh]
#6 #4 NOT #5
#7 severe myoclonic epilepsy in infancy OR Dravet syndrome [Title/Abstract]
#8 epilep* OR seizure [Title/Abstract]
#9 #7 AND #8
#10 #6 AND #9

EMBASE search strategy

('severe myoclonic epilepsy in infancy'/exp OR 'severe myoclonic epilepsy in infancy' OR 'dravet syndrome') AND ('epilepsy'/exp OR epilepsy OR 'seizure, epilepsy and convulsion'/exp OR 'seizure, epilepsy and convulsion') AND 'randomized controlled trial'/de NOT medline

CENTRAL search strategy

(severe myoclonic epilepsy in infancy OR Dravet syndrome) AND (epilep* OR seizure) in Title, Abstract, Keywords

ClinicalTrials.gov search strategy

severe myoclonic epilepsy in infancy OR Dravet syndrome | epilepsy OR seizure | Interventional Studies

Appendix II. Assessment of the confidence in the network estimates by outcome

Seizure response

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
				Mixed evidence				
CBD vs PBO	2	No concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
FFA vs PBO	2	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Moderate
PBO vs SOTICLESTAT	1	No concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
PBO vs STP	2	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
				Indirect evidence				
CBD vs FFA	--	No concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
CBD vs SOTICLESTAT	--	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
CBD vs STP	--	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
FFA vs SOTICLESTAT	--	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
FFA vs STP	--	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
SOTICLESTAT vs STP	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low

Seizure freedom

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
				Mixed evidence				
CBD vs PBO	2	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
FFA vs PBO	2	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
PBO vs SOTICLESTAT	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
PBO vs STP	2	Some concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
				Indirect evidence				
CBD vs FFA	--	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
CBD vs SOTICLESTAT	--	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
CBD vs STP	--	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
FFA vs SOTICLESTAT	--	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
FFA vs STP	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
SOTICLESTAT vs STP	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low

Discontinuation for any reason

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
				Mixed evidence				
CBD vs PBO	3	No concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
FFA vs PBO	2	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
PBO vs SOTICLESTAT	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
PBO vs STP	2	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
				Indirect evidence				
CBD vs FFA	--	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
CBD vs SOTICLESTAT	--	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
CBD vs STP	--	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
FFA vs SOTICLESTAT	--	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
FFA vs STP	--	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
SOTICLESTAT vs STP	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low

Discontinuation for adverse events

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
				Mixed evidence				
CBD vs PBO	3	No concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
FFA vs PBO	2	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
PBO vs SOTICLESTAT	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
PBO vs STP	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
				Indirect evidence				
CBD vs FFA	--	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
CBD vs SOTICLESTAT	--	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
CBD vs STP	--	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
FFA vs SOTICLESTAT	--	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
FFA vs STP	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
SOTICLESTAT vs STP	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low

Occurrence of adverse events

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
				Mixed evidence				
CBD vs PBO	3	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
FFA vs PBO	2	No concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
PBO vs STP	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
				Indirect evidence				
CBD vs FFA	--	No concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
CBD vs STP	--	No concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
FFA vs STP	--	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate

Occurrence of serious adverse events

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
				Mixed evidence				
CBD vs PBO	3	No concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Moderate
FFA vs PBO	2	No concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
PBO vs STP	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
				Indirect evidence				
CBD vs FFA	--	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
CBD vs STP	--	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
FFA vs STP	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low

Improvement at caregiver-reported Clinical Global Impression of Change

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
				Mixed evidence				
CBD vs PBO	2	No concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
FFA vs PBO	2	No concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
PBO vs Soticlestat	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
				Indirect evidence				
CBD vs FFA	--	No concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
CBD vs Soticlestat	--	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low
FFA vs Soticlestat	--	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low

Rating of the confidence in the network estimates for each drug by outcome is shown. We used the web application CINeMA (https://cinema.ispm.unibe.ch/) and derived the judgment for each item and the overall confidence rating for each network estimate as described by Papakonstantinou and colleagues.[e-2] We used the *average risk of bias* to summarize risk of bias across contributions for each network estimate and derive the judgment for within-study bias. We used the *majority* criterion to assess the indirectness and judged all comparisons as with *no concerns*. For the assessment of imprecision and heterogeneity, we considered an odds ratio of 3.0 as clinically important for the outcomes. For the assessment of the confidence in the estimates for incoherence, we judged all comparisons as with *some concerns* because of the unavailability of indirect evidence. We rated overall confidence as *moderate* if at least one domain was judged as *some concerns* but no domains were judged as *major concerns*, and as *low* if one single domain was judged as *major concerns*. Abbreviations: CBD=pharmaceutical-grade cannabidiol, FFA=fenfluramine hydrochloride, PBO=placebo, STP=stiripentol.

e-Reference

e-1 Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 (updated September 2009). The Cochrane Collaboration, 2009. Available from www.cochranehandbook.org.

e-2 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, Salanti G. CINeMA: an approach for assessing confidence in the results of a network meta-analysis. PLoS Med. 2020;17:e1003082.