COMPARATIVE EFFECTIVENESS OF FENFLURAMINE AND CANNABIDIOL FOR DRAVET SYNDROME: A NETWORK META-ANALYSIS

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BACKGROUND

- Fenfluramine and cannabidiol have been approved as add-on therapies **to reduce seizures in patients with Dravet syndrome (DS).**
- No direct comparative trials between these two drugs are available, and only indirect comparisons have been made by comparing each dosage against all dosages.
- However, the dosage of drugs can be determined by factors such as concomitant anti-seizure medications, the patient's clinical response, and tolerance, rather than the severity of DS or the potency of the therapy.
- Given that in real-world practice, **treatment of Cannabidiol** is individualized based on variables like concomitant medications, clinical response, and tolerance, we chose to pool all dosages to better reflect the actual clinical scenario.

OBJECTIVES

- We aimed to conduct a **network meta-analysis (NMA)** to assess the **comparative effectiveness** of pooled cannabidiol doses versus individual fenfluramine doses, reflecting real-clinical practice.

METHODS

- A systematic literature review was conducted to identify randomized controlled trials (RCTs) evaluating fenfluramine and cannabidiol for the treatment of DS patients aged 2 to 18 years (See **Figure 1**).
- Primary outcomes, placebo-adjusted reduction in **monthly convulsive seizure frequency (MCSF)** from baseline, were extracted from each study, regardless of dosage or concomitant medications such as Stiripentol and Clobazam.
- **Bayesian NMA** was performed to combine extracted data from included studies and compare their efficacy between treatments. Depending on the level of heterogeneity, an appropriate model was chosen.
- The relative effect was estimated as the **mean differences in MCSF** with 95% credible intervals (CrIs) and presented in a forest plot and league table. A surface under the cumulative ranking analysis (SUCRA) was also presented to identify the relative ranking of the comparators.
- **NMA** was performed using the BUGSnet package of R software (version 4.3.3).

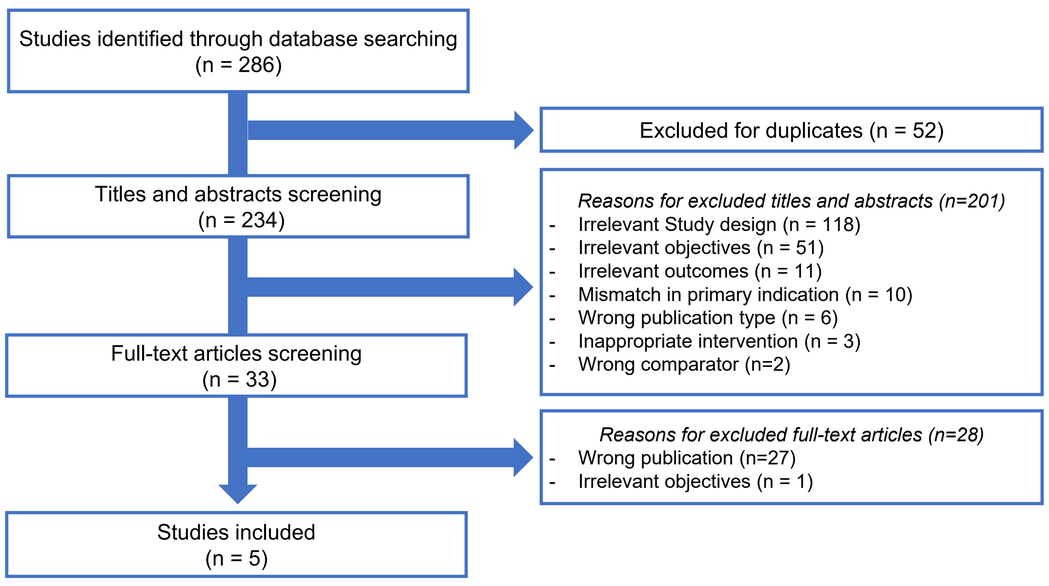


Figure 1. Study selection diagram

RESULTS

- A total of 5 studies were considered relevant for the relative efficacy of Fenfluramine 0.4mg, 0.7mg and pooled groups of Cannabidiol, with 3 studies focused on Fenfluramine and 2 studies on Cannabidiol (see **Figure 2**).
- The data show on log-transformed values, indicating that treatment **Fenfluramine 0.7mg demonstrated a greater reduction in seizures** from baseline compared to Cannabidiol (**Figure 3A**). Forest plot illustrates the mean differences in seizure reduction for each Fenfluramine dose and Cannabidiol compared to placebo (**Figure 3B**).
- The **mean difference in MCSF reduction from baseline** for Fenfluramine 0.7mg, Fenfluramine 0.4mg and Cannabidiol compared to placebo was **63.7%** (95% CrIs: 54.5–71.1), **54.0%** (95% CrIs: 35.6–67.2) and **26.1%** (95% CrIs: 13.2–37.1), respectively, indicating greater efficacy of Fenfluramine (**Table 1**).
- Fenfluramine 0.7mg had the highest SUCRA value for efficacy – probability to be the best treatment – with Fenfluramine 0.4mg in second place, cannabidiol in third, and placebo in fourth (**Figure 3C and 3D**).

Table 1. NMA results of change in MCSF

(A) NMA results of the percent change in the mean MCSF

Mean difference, % (95% CrI)

	Fenfluramine 0.7mg	Fenfluramine 0.4mg
Cannabidiol	50.8% (35.3–62.7)†	37.7% (9.5–57.2)†

(B) NMA results of the percent change in the mean MCSF compared to placebo

Intervention	Mean difference, % (95% CrI)
Fenfluramine 0.7mg vs Placebo	63.7 (54.5–71.1)†
Fenfluramine 0.4mg vs Placebo	54.0 (35.6–67.2)†
Cannabidiol vs Placebo	26.1 (13.2–37.1)†

CrI, creditable interval; MCSF, monthly convulsive seizure frequency; NMA, network meta-analysis
† Inverse transformed to the original scale

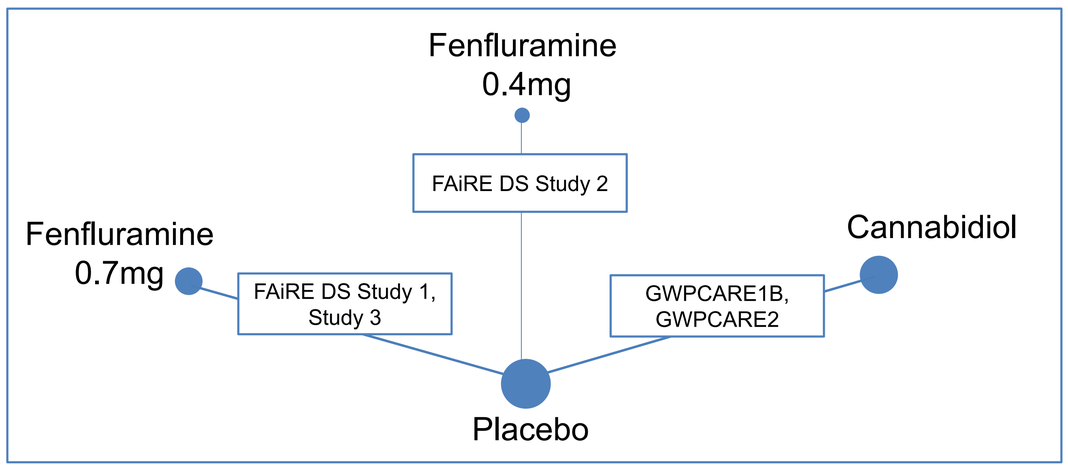


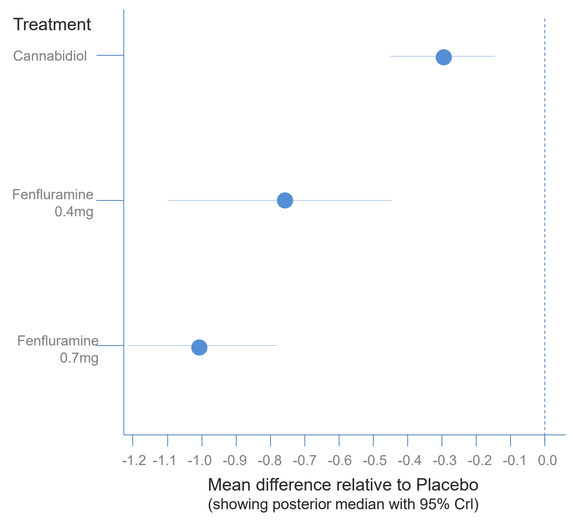
Figure 2. Network plot of DS treatments

(A) League Table

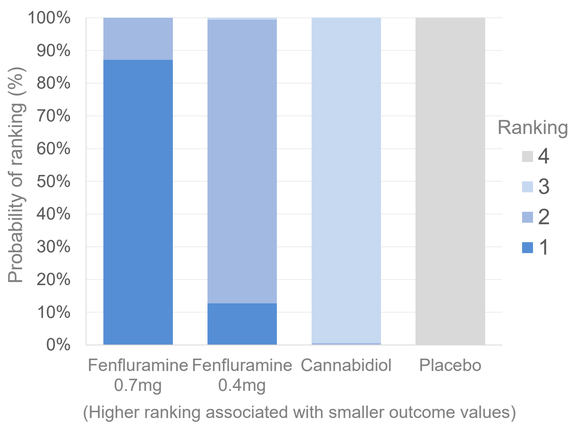
Fenfluramine 0.7mg			
-0.235* (-0.642,-0.174)	**Fenfluramine 0.4mg**		
-0.709* (-0.985, -0.435)	-0.474* (-0.848, -0.100)	**Cannabidiol**	
-1.013* (-1.240, -0.787)	-0.777* (-1.115, -0.440)	-0.303* (-0.463, -0.142)	**Placebo**

* Data are presented as log-transformed values

(B) Forest plot



(C) SUCRA value bar chart



(Higher ranking associated with smaller outcome values)

(D) SUCRA rank table

Probability Rank** / Treatment	1	2	3	4
Fenfluramine 0.7mg	87.2	12.8	0	0
Fenfluramine 0.4mg	12.8	86.6	0.63	0
Cannabidiol	0	0.63	99.4	0.01
Placebo	0	0	0.01	100

** The probability ranking reflects whether each treatment is the most effective option.

Figure 3. Comparative efficacy based on MCSF reduction

CONCLUSIONS

- The NMA indicates that each dose of Fenfluramine has greater efficacy in **reducing MCSF in patients with DS** compared to Cannabidiol.
- These findings suggest that Fenfluramine could be considered as **an optimal treatment option to control convulsive seizures** in DS patients.

References:

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