Poster #279

Comparative Effectiveness of Fenfluramine Versus Cannabidiol in Dravet Syndrome: A Numbers Needed to Treat Indirect Comparison Analysis

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Overview

QUESTION

How many patients with Dravet syndrome (DS) need to be treated with fenfluramine (FFA) for one patient to reach clinically meaningful or profound seizure reduction? How does this differ from the number of patients who need to be treated with cannabidiol (CBD)?

INVESTIGATION

- A systematic literature search for published randomized controlled trials (RCTs) of FFA or CBD in patients with DS was updated
  - Doses of FFA compared to placebo:
    - 0.4 mg/kg/d with concomitant stiripentol (STP, max: 17 mg/d)[1]
    - 0.2 or 0.7 mg/kg/d without concomitant STP (max: 26 mg/d)[2,3]
  - Doses of CBD compared to placebo[4,5]
    - 10 or 20 mg/kg/d irrespective of concomitant clobazam (CLB) use
    - 10 or 20 mg/kg/d with concomitant CLB use
- Bayesian network meta-analyses (NMAs) of the 5 RCTs were used to estimate the odds ratio (OR) of achieving ≥25%, ≥50% (clinically meaningful), and ≥75% (profound) reduction in monthly convulsive seizure frequency (MCSF) for FFA vs placebo and CBD vs placebo
- Numbers-needed-to-treat (NNTs) were found using the NMA-adjusted responder rates and ORs

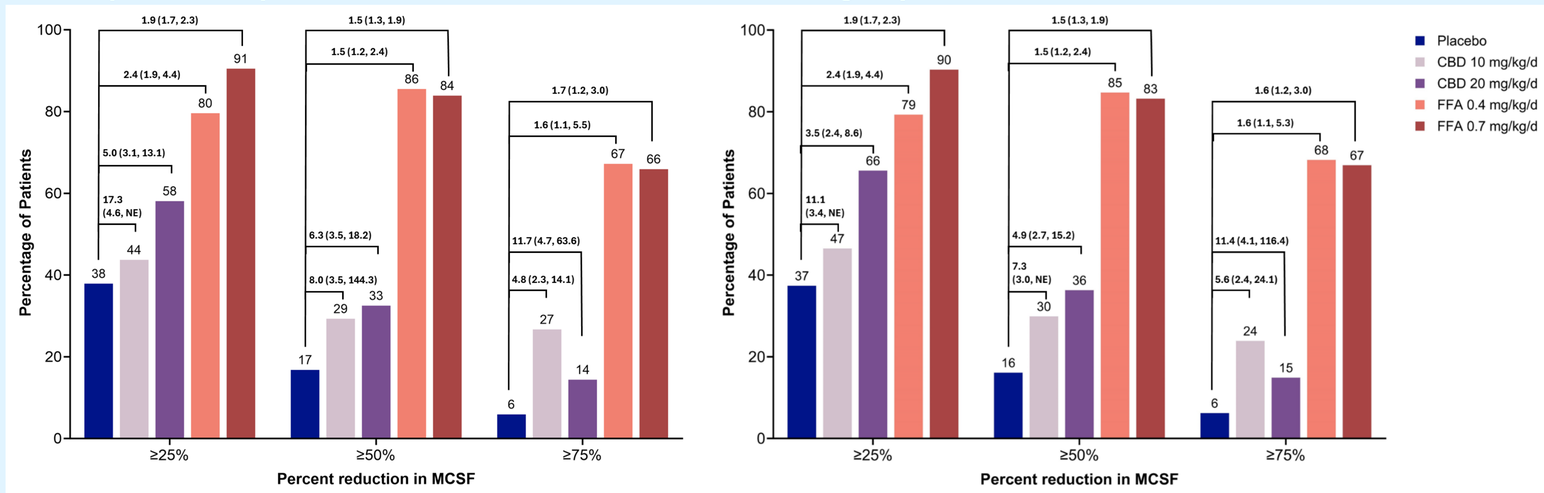
CONCLUSIONS

- The NNT vs placebo to achieve clinically meaningful reduction in MCSF was 1.5 for patients treated with either dose of FFA
- The NNT vs placebo to achieve clinically meaningful reduction in MCSF was 6.3-8.0 for patients treated with CBD irrespective of CLB use, and 4.9-7.3 for patients treated with CBD with concomitant CLB use
- The lower NNT vs placebo seen with FFA treatment reflects an advantage over CBD in terms of efficacy

RESULTS

- Responder rates were numerically higher in patients with active treatment than with placebo treatment
- NNTs were higher with CBD (irrespective of CLB use and with concomitant CLB use) compared to FFA (**Fig 1**)

Figure 1. NMA-Adjusted Responder Rates for Reductions in MCSF by Analysis



Note: Values above comparison bars indicate NNT (credible interval) for CBD vs placebo and for FFA vs placebo.
CBD, cannabidiol; FFA, fenfluramine; MCSF, monthly convulsive seizure freedom; NE, not estimable; NMA, network meta-analysis; NNT, number-needed-to-treat.

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Background

- Dravet syndrome (DS), a developmental and epileptic encephalopathy, presents with treatment-resistant seizures, including convulsive seizures
  - High convulsive seizure frequency increases risk of premature death
  - Standard antiseizure medications (ASMs) used to treat seizures associated with DS are stiripentol (STP), clobazam (CLB), and valproate (VPA)
- Fenfluramine (FFA) and cannabidiol (CBD) are the most recently FDA- and EMA-approved adjunctive treatments for DS
  - There are no direct comparisons of FFA and CBD
- The recommended starting maintenance and maximum doses:
  - FFA: 0.2 and 0.7 mg/kg/d, respectively (max daily dose: 26 mg/d[6])
  - CBD: 10 and 20 mg/kg/d[7], respectively
- Drug-drug interactions:
  - FFA: metabolism affected by STP (max daily dose: 17 mg/d)
  - CBD: bidirectional pharmacokinetic interactions with CLB (CLB dose reduction recommended)
- Numbers-needed-to-treat (NNTs) provide an important metric to assist clinicians in making informed decisions when considering new treatments for patients by comparing treatments to a single placebo value[8]
  - Indirect comparisons can be made using network meta-analyses (NMAs)
- A previous analysis[9] demonstrated that NNTs for FFA to achieve monthly convulsive seizure frequency (MCSF) reduction vs placebo were 1.8-3.5 (≥50%; clinically significant) and 1.9-4.9 (≥75%; profound)

Objective

- To indirectly compare MCSF-reduction efficiency for FFA/CBD using NNT, vs placebo

Methods

- A systematic literature review, initially conducted up to Jun 2020, updated Nov 2021
  - Updated Jul 2024 to confirm; no further studies identified
  - Systematic searches for English-language published randomized controlled trials (RCTs) of FFA and CBD at licensed doses conducted in PubMed and Embase
  - Detailed search strategies have previously been described[10]
- The intent-to-treat populations from the studies were included and presented

Table 1. Studies Included in the Literature Review

Study name	Publication	Treatment groups	Concomitant use of ASM with PK interaction
Study 1	Lagae et al, *Lancet.* 2019[3]	Placebo FFA, 0.2 mg/kg/d FFA, 0.7 mg/kg/d Max daily dose: 26 mg/d	No STP
Study 3	Sullivan et al, *Epilepsia.* 2023[2]		
Study 2	Nabbout et al, *JAMA Neurol.* 2020[1]	Placebo FFA, 0.4 mg/kg/d Max daily dose: 17 mg/d	Concomitant STP
GWPCARE1B	Devinsky et al, *NEJM.* 2017[4]	Placebo CBD, 20 mg/kg/d	Irrespective of concomitant clobazam
GWPCARE2	Miller et al, *JAMA Neurol.* 2020[5]	Placebo CBD, 10 mg/kg/d CBD, 20 mg/kg/d	

Licensed maintenance regimens of FFA and CBD were included in the meta-analysis; therefore, while FFA 0.2 mg/kg/d was tested in the included studies, the dose group was not included in the meta-analysis.
ASM, antiseizure medication; CBD, cannabidiol; FFA, fenfluramine; PK, pharmacokinetic; STP, stiripentol.

- Doses recommended for DS were utilized for this analysis:
  - FFA[6]: 0.4 mg/kg/d with concomitant STP (FFA 0.4) and 0.7 mg/kg/d without concomitant STP (FFA 0.7)
  - CBD[7]: 10 or 20 mg/kg/d irrespective of concomitant CLB use (CBD10, CBD20) and 10 or 20 mg/kg/d with concomitant CLB use (CBD10+CLB, CBD20+CLB)
    - The CBD+CLB population was identified by a previous publication[11]
- Repeated treatment dose groups were pooled across studies
  - FFA 0.7: Studies 1 and 3
  - CBD20, CBD20+CLB: GWPCARE1B and GWPCARE2
- Placebo groups were pooled across all studies to produce a placebo for the network

Outcomes

- NMAs were used to estimate the odds ratios (ORs) of achieving ≥25%, ≥50%, and ≥75% reduction in MCSF
  - Treatment vs baseline period; active treatment vs placebo rate for the network
  - Placebo rate for the network: weighted average of placebo across the studies
  - NMAs were conducted using the MetaInsight web-based tool[12] using fixed effects given the shape of the network
- The OR of achieving a specified reduction in MCSF for each treatment group vs network placebo rate and the assumed control risk (ACR) of the network placebo were used to recalculate treatment responder rates
  - NNTs were determined for each responder rate vs the network placebo rate using the following equation:

NNT = 1/|ACR-((ORxACR)/(1-ACR+ORxACR))|

Results

Participants

- Study design, baseline characteristics and demographics were similar across studies (**Table 2**) with a few numerical differences in baseline characteristics:
  - Study 2: Concomitant CLB rate higher (94.3% vs 56.3-65%) and concomitant levetiracetam rate lower (12.6% vs 22-28.2%) vs other studies
  - Study 2 and GWPCARE2: Concomitant VPA rate higher (70.2-88.5%) vs other studies (57.7-59%)
  - Study 1: Median baseline MCSF higher (20.7-27.3) vs other studies (10.4-17)

Table 2. Comparison of Study Design, Baseline Characteristics, and Demographics Across RCTs

	Study 1	Study 3	Study 2	GWPCARE1B	GWPCARE2
Treatment groups	FFA, no STP (max, 26 mg/d): 0.2 or 0.7 mg/kg/d Placebo		0.4 mg/kg/d FFA with STP (max, 17 mg/d) Placebo	20 mg/kg/d CBD irrespective of CLB Placebo	CBD irrespective of CLB: 10 or 20 mg/kg/d Placebo
Study design	Phase 3 placebo-controlled RCT				
Baseline	6 weeks			4 weeks	
Titration	2 weeks		3 weeks	2 weeks	
Maintenance	12 weeks				
Study centers	38	48[a]	28	23	38
Year(s)	2016-2017	2017-2020	2016-2018	2015	2015-2018
Key inclusion criteria	• Diagnosed with DS • 2-18y old • ≥1 stable ASM • ≥4 convulsive seizures per 4-week period during 12 weeks prior to screening • ≥6 convulsive seizures during the baseline period with ≥2 in the first and last 3 weeks			• Diagnosed with DS • 2-18y old • ≥1 stable ASM • ≥4 convulsive seizures during the baseline period	
Endpoint definitions					
Reduction in convulsive seizures	Percent change in MCSF between baseline and combined titration and maintenance period in patients who received active treatment vs placebo				
Responder rates	Proportions of participants achieving ≥25%, ≥50%, or 75% reduction in MCSF during the combined titration and maintenance period vs baseline				
Serious TEAEs	Reported over the combined titration and maintenance period				
Study size	119[b]	142[b]	87	120[c]	198[c]
Age (years), Mean ± SD	9.0 ± 4.7	9.3 ± 4.7	9.1 ± 4.8	9.8 ± 4.8	9.3 ± 4.4
Sex: male, n (%)	64 (53.8)	73 (51.4)	50 (57.5)	62 (51.7)	94 (47.5)
Geographic regions, n (%)					
United States	70 (58.8)	50 (35.2)	22 (25.3)	72 (60)	93 (47)
Rest of the world	49 (41.2)	92 (64.8)	65 (74.7)	48 (40)	105 (53)
Number of ASMs, Median (range)					
Previous	NR			4 (0-26)	4 (0-19)
Concomitant	2 (0-5)	NR		3 (1-5)	3 (1-5)
Concomitant ASMs[d], n (%)					
CLB	70 (59)	80 (56.3)	82 (94.3)	78 (65)	126 (63.6)
Valproate, all forms	71 (59)	82 (57.7)	77 (88.5)	71 (59)	139 (70.2)
STP	0	0	87 (100)	51 (42)	71 (35.9)
Levetiracetam	26 (22)	40 (28.2)	11 (12.6)	33 (28)	54 (27.3)
Topiramate	30 (25)	38 (26.8)	21 (24.1)	31 (26)	46 (23.2)
Baseline MCSF, Median (range)					
FFA 0.4	--	--	14 (3-213) n=43	--	--
FFA 0.7	20.7 (4.8-124) n=40	13 (2.7-2701) n=48	--	--	--
CBD10	--	--	--	--	14 (IQR: 6-31) n=66
CBD10+CLB	--	--	--	--	13.1 (4-238.4) n=45
CBD20	--	--	--	12.4 (3.9-1717) n=61	9 (IQR: 6-21) n=67
CBD20+CLB	--	--	--	10.4 (3.9-661.2) n=80	
Placebo n=256	27.3, (3.3-147.3) n=40	12.7, (4.0, 229) n=48	10.7, (3-163) n=44	14.9 (3.7-718) n=59	17 (IQR: 7-51) n=65
Placebo+CLB	--	--	--	17 (3, 448.9) n=79	
Full study population[e]	24.1 (2.2-623.5)	NR		13 (3.7-1717)	12 (IQR: 6-33)

[a]The number of sites includes overlap with Study 1—the difference between the two studies is time.
[b]Full study size, including patients treated with FFA 0.2 mg/kg/d.
[c]Full study size, irrespective of concomitant CLB use.
[d]All concomitant ASMs included in original publications are listed.
[e]The full study population in Studies 1 and 3 includes FFA 0.2 mg/kg/d, which is not included in the analysis.
ASM, antiseizure medication; CBD, cannabidiol; CLB, clobazam; DS, Dravet syndrome; FFA, fenfluramine; IQR, interquartile range); MCSF, monthly convulsive seizure frequency; NR, not reported; RCT, randomized controlled study; STP, stiripentol; TEAE, treatment-emergent adverse event.

Responder rates

- Responder rates were numerically higher in patients with active treatment than with placebo treatment (**Fig 2**)

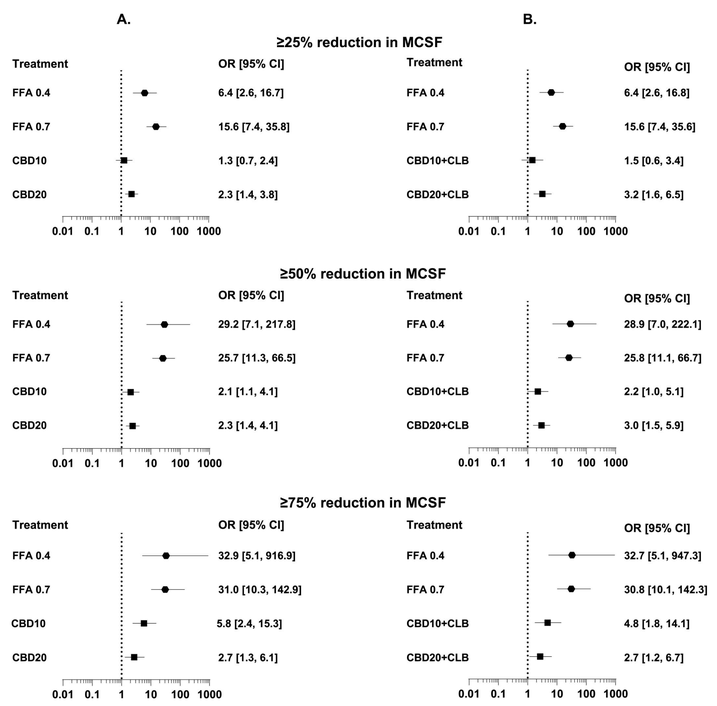
NNTs (Fig 1)

- To achieve one ≥50% MCSF reduction event vs placebo:
  - NNT is 4-5 times higher with CBD vs FFA treatment
  - NNT is 1.5-3 times higher with CBD+CLB vs FFA treatment
- To achieve one ≥75% MCSF reduction event vs placebo:
  - NNT is 3-7 times higher with CBD vs FFA treatment and with CBD+CLB vs FFA treatment

Limitations:

- NNTs for this analysis were calculated in the context of RCTs, where patient selection criteria may not completely represent the real-world patient population
- There were minor differences in study design, noted in the results
- Concomitant use of CLB and valproate was higher in Study 2 than in other studies, while concomitant use of levetiracetam was lower in Study 2 than in other studies
  - Further, concomitant treatment was required for some treatment groups analyzed:
    - All patients in Study 2 were treated with concomitant STP
    - All CBD+CLB patients were treated with concomitant CLB

Figure 2. Pairwise ORs vs Placebo for Achieving ≥25%, ≥50%, and ≥75% Reductions in MCSF A) Responder Rates Using Populations Irrespective of Concomitant CLB Use and B) Responder Rates Using Subgroup of CBD Trial Population With Concomitant CLB Use



Comparing the odds ratio for achieving reduction in MCSF for each active treatment vs the network placebo rate. The dotted line represents the network placebo rate. The x-axis is CBD, cannabidiol; CLB, clobazam; CBD10, cannabidiol 10 mg/kg/d irrespective of concomitant clobazam use; CBD10+CLB, cannabidiol 10 mg/kg/d with concomitant clobazam use; CBD20, cannabidiol 20 mg/kg/d irrespective of concomitant clobazam use; CBD20+CLB, cannabidiol 20 mg/kg/d with concomitant clobazam use; CI, confidence interval; FFA 0.4, fenfluramine 0.4 mg/kg/d; FFA 0.7, fenfluramine 0.7 mg/kg/d; MCSF, monthly convulsive seizure frequency; OR, odds ratio.

Conclusions

- In an indirect comparison, NNT vs placebo for patients with DS treated with FFA is numerically lower than for those treated with CBD over 14-15 weeks
  - Previous studies have suggested that differences in NNTs between treatments of ±0.5 are clinically meaningful[13]
  - Differences in NNTs vs placebo between FFA and CBD range from 3.1 (FFA 0.4 vs CBD10, ≥75% reduction) to 15.4 (FFA 0.7 vs CBD10, ≥25% reduction)
- For one patient with DS to achieve a clinically meaningful reduction in MCSF vs placebo:
  - Two patients would need to be treated with FFA0.4 or FFA 0.7
  - Approximately 6 patients would need to be treated with CBD20
- A lower NNT for a treatment vs placebo reflects an advantage in effectiveness, translating into fewer non-responders and reduced associated burden on patients, their families, and the healthcare system

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Disclosures

CA: Employee of HEOR Value Hub, contracted by UCB Pharma during the study.
SK, VT: Employees of UCB Pharma.

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