Cost to Achieve Seizures Reduction or Seizure Freedom in Dravet Syndrome in the USA: An Analysis Based on NNT (NUMBER NEEDED TO TREAT) of Stiripentol, Fenfluramine and Cannabidiol

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INTRODUCTION

- Dravet syndrome (DS) is a rare and catastrophic, highly refractory developmental and epileptic encephalopathy. It is characterized by frequent, treatment-resistant convulsive seizures arising in the first years of life, followed by developmental delay and cognitive impairment, which impair patient and carer quality of life (QoL). Around 15-20% of children with DS die before reaching adulthood primarily due to status epilepticus (SE), sudden unexpected death in epilepsy (SUDEP), and accidents.
- Given the association between convulsive seizure frequency and comorbidities, quality of life, healthcare resource utilization and costs, and premature mortality described above, convulsive seizure reduction is a key goal of treatment in Dravet syndrome. Complete, sustained seizure freedom (i.e. zero convulsive seizures) is the ambition for patients with Dravet syndrome but few patients ever achieve this outcome[1].
- Recently published treatment recommendations suggest initial anti-seizure medication (ASM) with valproate or valproate and clobazam; however, as most patients' seizures are inadequately controlled with these treatments, additional add-on therapy is typically required[2]. DIACOMIT® (stiripentol)[3] , FINTEPLA® (fenfluramine)[4] and EPIDIOLEX® (cannadibiol)[5] are licensed specifically as add-on ASMs for Dravet syndrome. The most recent international consensus guidelines position DIACOMIT® and FINTEPLA® ahead of EPIDIOLEX® in the treatment pathway[2].
- The number needed to treat (NNT) is an outcome measure commonly used in clinical settings, providing a quick, short-hand approach to estimating relative efficacy of different treatments. This indicator is considered meaningful for physicians and health care decision makers because it measures the number of patients that is needed to treat to prevent one additional bad outcome (e.g. death, stroke, seizures, etc.).
- The objective of this study was to evaluate the cost implications of stiripentol, fenfluramine and cannabidiol, to achieve given level of seizure reduction or freedom, using NNT .

METHODS

- NNTs, provided in table 1, are issued from the network meta-analysis published by Guerrini et al. 2024[6]. Relative treatment effects in the NMA were assessed using absolute risk differences (RD). The RD approach enabled the use of the largest possible dataset, ensured consistency in the presentation of the comparative treatment effect estimates, and permitted calculation of the number needed to treat (NNT) with each intervention (added on to background ASMs therapy) for one more patient to achieve the outcome of interest compared with placebo (added on to background ASMs therapy): NNT = 1/|RD|[7]. NNTs were calculated for pairwise comparisons versus placebo for RD that were statistically significant to facilitate a clinical interpretation of the NMA results.
- Annual per patient costs of the three add-on therapies, based on their wholesale acquisition costs (WAC) as of January 2024, are provided in table 2. Two patient groups are considered: pediatric patients aged 9 years with an average body weight of 30kg, based on RCTs[8] and adult patients aged 18+ years with an average body weight of 60kg[9;]. The dose assumed for each of the add-on therapies is based on their approved dosing. For stiripentol, the dosing adopted in this analysis is 50mg/kg/day in pediatric patients[10] and adults[11]. For fenfluramine (used without concomitant stiripentol) this dosing is 0.7mg/kg/day (maximum 26mg per day) based on the label[12]. For cannabidiol the dosing is 20mg/kg/day[13].

Table 1. Efficacy results of pairwise comparison versus placebo[6]

Endpoints	Comparison	RCTs (N)	RD (95%CI); p-value	NNT
≥50% reduction in seizure frequency	STP vs PLB	2	RD: 0.64 (0.46; 0.81); p<0.01	NNT: 2
	FFA vs PLB	2	RD: 0.62 (0.51; 0.74); p<0.01	NNT: 2
	CBD10 vs PLB	1	RD: 0.16 (0.01; 0.31); p<0.04	NNT: 7
	CBD20 vs PLB	2	RD: 0.19 (0.08; 0.31); p<0.01	NNT: 6
≥75% reduction in seizure frequency	STP vs PLB	2	RD: 0.52 (0.34; 0.70); p<0.01	NNT: 2
	FFA vs PLB	2	RD: 0.46 (0.35; 0.57); p<0.01	NNT: 3
	CBD10 vs PLB	1	RD: 0.24 (0.12; 0.36); p<0.01	NNT: 5
	CBD20 vs PLB	2	RD: 0.11 (0.03; 0.20); p<0.02	NNT: 10
100% reduction in seizure frequency	STP vs PLB	2	RD: 0.36 (0.19; 0.53); p<0.01	NNT: 3
	FFA vs PLB	2	RD: 0.10 (0.03; 0.16); p<0.01	NNT: 10
	CBD10 vs PLB	1	RD: 0.02 (-0.03; 0.07); p=0.44	
	CBD20 vs PLB	2	RD: 0.04 (0.00;0.08); p<0.05	NNT: 25

Table 2. Annual WACs for add-on therapies in pediatric and adult patients

	Add on therapy initiated at age 9 years*			Add on therapy initiated in adulthood**		
	Stiripentol	**Cannabidiol**	**Fenfluramine**	**Stiripentol**	**Cannabidiol**	**Fenfluramine**
Dose (mg/kg/day)	50	20	0.7	50	20	0.7
Body weight (kg)	30	30	30	60	60	60
Daily dose (mg)	1500	600	21	3000	1200	26 (max)
WAC ($/mg)	0.125	0.164	24.396	0.125	0.164	24.396
Daily cost ($) per patient	187.63	98.10	512.32	375.26	196.20	634.296
Annual cost per patient ($)	68,486	35,807	186,996	136,971	71,613	231,519

*Assumed 30kg body mass

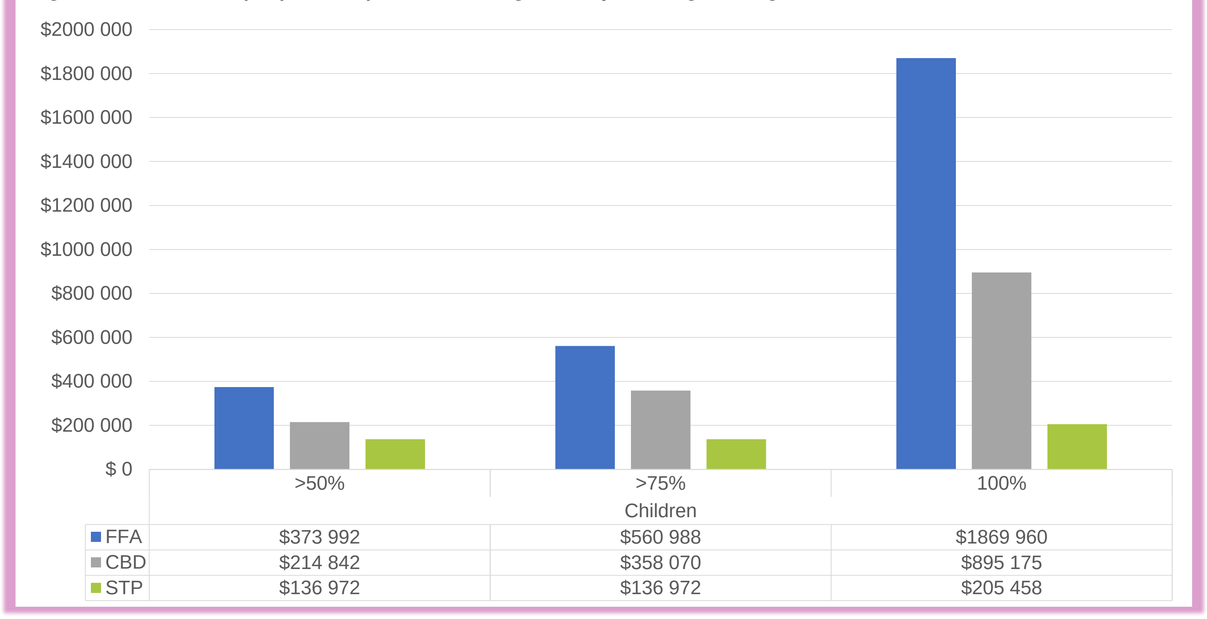
** Assumed body mass 60kg

WAC prices as of January 2024

RESULTS

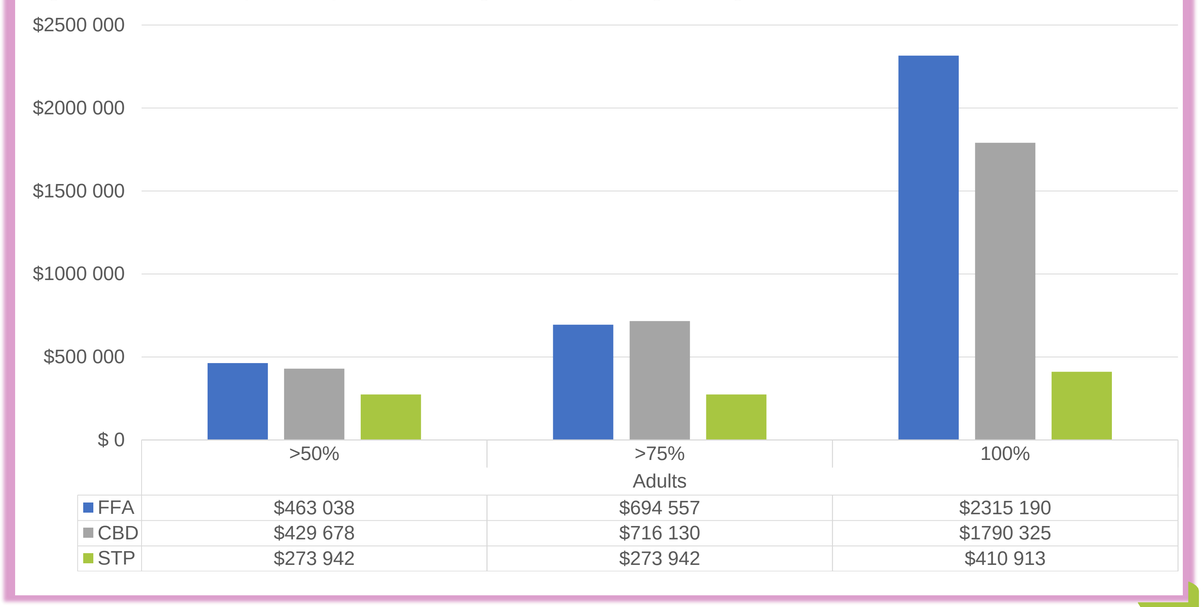
- The costs for 1 patient to achieve a ≥50% (i.e., clinically meaningful), a ≥75% (i.e., profound) and 100% reduction in monthly convulsive seizure frequency (MCSF) with each of the add on therapies are presented in Figure 1 for pediatric group and Figure 2 for adults.
- **In the pediatric group,** the annual costs per patient achieving a **clinically meaningful reduction in MCSF (50%)** are **$136,972 with stiripentol, $214,842 with cannabidiol and $373,992 with fenfluramine** and **$136,972, $358,070 and $560,988 respectively for the ≥75% (i.e., profound) reduction in MCSF endpoint.** Finally annual costs per patient achieving **seizures freedom** are **$205,458 for stiripentol, $895,175 for cannabidiol and $1,869,960 for fenfluramine.**

Figure 1. Annual costs per pediatric patient achieving clinically meaningful and greater reductions in MCSF



- **In the adult group**, for **the ≥50% (clinically meaningful) reduction in MCSF** endpoint the annual costs are **$273,942 for stiripentol, $429,678 for cannabidiol and $463,038 for fenfluramine**. The annual costs per patient achieving a **profound (≥75%) reduction in MCSF** are **$273,942, $716,942 and $694,557 for stiripentol, cannabidiol and fenfluramine respectively**. Finally annual costs per patient achieving **seizures freedom** are **$410,913 for stiripentol, $1,790,325 for cannabidiol and $2,315,190 fenfluramine**.
- In a sensitivity analysis using lower doses of the add-on therapies in all patients and assumed similar NNT, stiripentol remained the least costly per patient achieving a clinically meaningful and profound reduction in MCSF and per patient achieving convulsive seizure freedom across all patient groups.

Figure 2. Annual costs per adult patient achieving clinically meaningful and greater reductions in MCSF



DISCUSSION

- For the >50% (clinically meaningful) and >75% (i.e., profound) reduction in MCSF, and for the 100% reduction in MCSF (i.e., convulsive seizure freedom), stiripentol was numerically the most effective of the three interventions, with the lowest NNTs.
- Despite the fact that cannabidiol has a lower annual acquisition cost per patient treated than stiripentol in the US, fewer patients need to be treated with stiripentol than with cannabidiol for one patient to achieve these levels of response (≥50%, ≥75% and 100%). This results in a substantially lower annual cost with stiripentol per patient achieving a clinically meaningful and profound reduction in MCSF and convulsive seizure freedom.
- Compared with fenfluramine, stiripentol is at least as effective in achieving a clinically meaningful and profound reduction in MCSF, and is more effective in achieving seizure freedom, whilst also having lower annual acquisition costs.

CONCLUSION

Stiripentol achieves the same or better clinical outcomes at a lower cost than cannabidiol or fenfluramine. Stiripentol should be considered as a cost-effective and highly efficacious treatment for Dravet syndrome patients. These findings are observed for both pediatric and adult patient groups.

References:

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12. FDA label FINTEPLA 2020
13. FDA label EPIDIOLEX 2018

Acronyms:

ASM : Antiseizure medications
CBD : Cannabidiol
DS : Dravet syndrome
FFA : fenfluramine
MCSF : monthly convulsive seizure frequency
NNT : Number needed to treat
RCT randomized clinical trials
PLB : Placebo
WAC : Wholesaler acquisition cost

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