A Cost-Effectiveness Analysis of Fenfluramine for the Treatment of Seizures for Patients with Dravet Syndrome (DS) in the UK Setting

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AIMS AND OBJECTIVES

- Dravet syndrome (DS) is a rare epileptic encephalopathy that is diagnosed in early infancy and extends through adulthood.
- Characterised by frequent (often daily) severe convulsive seizures (CS) that increase the risk of death due to Sudden Unexpected Death in Epilepsy (SUDEP), status epilepticus (SE), and accidents; an estimated 15-20% of children with DS die before the age of 10 years old and the risk remains elevated throughout life (1).
- The high seizure frequencies experienced by patients with DS is also associated with a profound and progressive deterioration to their cognitive and physical developmental (collectively termed "comorbidities") and substantially affects their day-to-day life; with a high impact on their quality life (QoL) and a demonstrated similar level of impact to their care-givers and the broader family (2–4).
- Seizures in DS are often intractable, despite the use of combination anti-epileptic drug (AED) therapy. Complete seizure freedom is rarely possible in DS; the primary aim of treatment is to reduce the seizure burden (5). Increasing the number of seizure-free days by reducing the frequency of seizures substantially reduces the daily risk for accidental injury and death and improves the quality of life for patients and their carers.
- Cannabidiol (CBD) plus clobazam (CLO)(6), added on to standard of care (SoC) AEDs that may or may not include stiripentol (STP), is the most recent NICE recommended add-on treatment for DS accepted as a cost-effective option in the UK (7).
- Fenfluramine (FFA) is a recently licensed add-on therapy for the treatment of seizures in patients with DS aged 2 years and older. It has a different mode of action to other therapies used in DS and, in contrast to STP and CBD, which are only licensed for use in combination with CLO, can be used with or without concomitant CLO.
- An indirect treatment comparison (ITC) showed that fenfluramine (FFA) is more effective than CBD (+/-CLO) in reducing CS frequency (8).
- This work presents a novel individual-level simulation modelling approach to calculate the cost-effectiveness of FFA compared with CBD+CLO as an add-on therapy for DS patients in England.

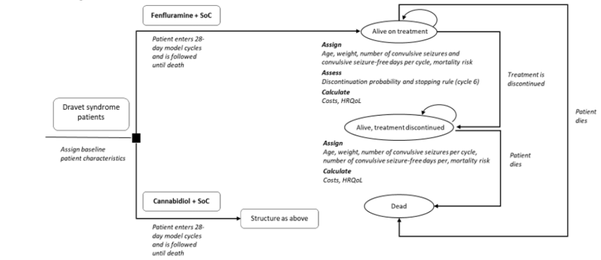
MODEL APPROACH

- A cost-effectiveness model was developed in R (version 3.5.2) to estimate the clinical and economic impact of FFA (+/-CLO) against CBD (with CLO). The endpoint was the incremental cost per QALY gained.
- An individual-level model simulated a cohort of DS patients in England, aged 2 years and older, and modelled over their lifetime. Individuals were assigned characteristics based on an analysis of patient-level data from the FFA registration trials (9) and a cohort of patients in England (DISCUSS study) (10).
- Individuals were assigned to either FFA + SoC (intervention strategy, dose-dependent on if taken with concomitant STP) or CBD + CLO + SoC (comparator strategy) in the base case. The model reflects the concomitant use of STP in the UK.
- Extensive uncertainty analyses, including scenario analyses, were done to explore the impact on model results. This took the NHS perspective, and a 3.5% discount rate was implemented based on recommendations.

MODELLING APPROACHES

- Individuals were modelled over their lifetime; seizures occur based on their seizure characteristics (**Figure 1**).

Figure 1. Schematic Diagram of the Patient-Level Simulation Model of Dravet Syndrome

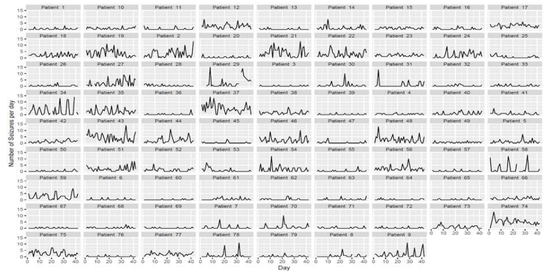


SoC, standard of care drugs; HRQoL, health-related quality of life

MODELLING CONVULSIVE SEIZURE FREQUENCY AND SEIZURE-FREE DAYS

- Individuals were assigned CS's per 28-day cycle at baseline based on individual-level data from the placebo arm of the two registration phase III FFA studies (Study 1 and Study 2 (also known as 1504) (4,11) (**Figure 2**).
- The daily number of CS's were bootstrapped from the placebo arm of the clinical trial data and used to calculate the number of seizure-free days (SFDs) per 28-day cycle.
- If an individual had at least one seizure on a single day, this was considered a seizure day, and thus if no seizures were reported on a single day, it was considered an SFD.
- Bootstrapping of the seizure histories was performed for every individual ten times to create a larger sampling population than the trial. Each bootstrapped sample was run for each individual for ten years, and those ten years repeated over a lifetime, enabling the extrapolation of CS's beyond the first 14-15 weeks (maintenance period) of the FFA registration studies.
- As there are no trial data directly comparing FFA to CBD, an ITC was used to model the impact of treatment on seizures (8), comparing FFA and CBD to a commonly adjusted placebo.
- The percentage reduction in CS's between baseline and the maintenance period compared to placebo was then applied to the simulated individuals on treatment in the model for both the comparator and intervention arm.
- Whilst an individual remained on treatment; the same treatment effect was applied to CS's and SFDs. At discontinuation, the treatment effect was removed from CS's and SFDs. In line with NICE guidance for CBD (+CLO), patients should only continue treatment if "the frequency of convulsive seizures is checked every 6 months, and … the frequency has not fallen by at least 30% compared with the 6 months before starting treatment" (8). A similar stopping rule was applied to FFA-treated patients.

Figure 2. Number of Seizures Per Individual Patient at Baseline in the Placebo Arm of the FFA Registration Studies



MODEL INPUTS & RESULTS

Summary of Key Model Inputs

Input	Value/Note
Individual characteristics*	
Gender	55% male
Age	Based on the age distribution from DISCUSS UK (9)
Weight	RCPCH and NHS Health Survey for England data (10); starting weight of 12kg - age 2, linear increase to 78kg at 25 years (constant weight thereafter)
Motor impairment	FFA registration studies (4,11)
Concomitant medication	FFA registration studies (4,11), DISCUSS UK dataset (9)
Model inputs	
Clinical parameters	
Seizure frequency and seizure-free days per 28-day period	FFA registration studies (4,11)
Mortality	SUDEP, SE, and accidental death due to seizures and background mortality; Office for National Statistics (12), Cooper et al. (13), Nilsson et al. (14)
Status Epilepticus	0.0029 probability of death per cycle due to SE, FFA registration studies (4,11)
Treatment strategy	
Discontinuation	FFA registration studies and open-label extension (4,11) (15); GWPCARE5 (16); includes discontinuation due to lack of efficacy, long-term discontinuation (FFA or CBD), and other discontinuation
Treatment stopping rule	Treatment stopping rule applied at 6-months after treatment initiation to patients that had not seen a 30% reduction in seizure frequency; Expert opinion / CBD NICE submission (7)
Treatment dosing (daily dose)	BNF/CBNF (March 2020); FFA: 0.7mg/kg/day (max 26mg/day without stiripentol) or 0.4mg/kg/day with a maximum dose of 17mg/day (with stiripentol); CBD: 12mg/kg/day
Utilities	
Individual and carer utilities	Based on data from the individuals and their carers in the FFA registration studies (4,11); regression analysis model included the following covariates: Age group (<6 years, 6-11 years, ≥12 years), 28-day frequency of the number of SFDs, motor impairment (none, ataxia, severe), Study ID (Study 1, study 1504 cohort 2). Caregiver utility is included in the base case (assume 1.8 carers/individual based on NICE CBD submission).
Time horizon, perspective and discounting	NICE reference case; lifetime horizon, NHS perspective, 3.5% discounting (base case)
Costs	
AEDs (SoC)	British National Formulary (BNF) (17); Prescription cost analysis (18)
FFA & CBD costs	FFA is based on the confidential discounted price; CBD is based on the list price (discounted price is confidential)
Healthcare Resource Use (HCRU) – ongoing costs	UK Pathway Research study (8); PSSRU 2019 (19); NHS Schedule of reference costs 2018/2019 (20)
Emergency Resources	UK Pathway Research study (8); PSSRU 2019 (19); NHS Schedule of reference costs 2018/2019 (20)

* Baseline characteristics selected based on an analysis of covariates that significantly influence Health-Related Quality of Life (confirmed in an internal modelling workshop and by a UK pathway research study (8)).

Base Case results

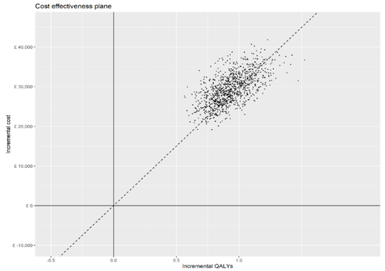
Treatment	Cost (£)	QALYs	ICER Compared to Next Most Effective AED	ICER Compared to Underlying SoC AEDs
SoC AED (trial data)	188,365	19.57	--	--
Cannabidiol (with clobazam) + SoC AED	255,759	20.54	£69,478/QALY	£69,478/QALY (Extendedly dominated by fenfluramine + SoC AED)
Fenfluramine + SoC AED	285,205	21.47	£31,638/QALY	£50,968/QALY

Uncertainty analyses results

- Probabilistic sensitivity analysis (1000 iterations) gives a mean ICER of £31,638 /QALY gained. **Figure 3** shows the incremental costs and QALYs for each model run; the hashed line indicating the NICE recommended threshold of £30,000/QALY gained.
- Increasing the dose of CBD to 15mg/kg/day or only including adult patients in the model significantly reduced the ICER (£14,355 and £8,532, respectively). Excluding carer utilities or assuming mortality in DS is equivalent to general epilepsy increased the ICER (£104,835 and £57,990, respectively); other scenarios had less of an impact on the ICER.

RESULTS AND DISCUSSIONS

Figure 3. Scatterplot of the Incremental Costs and QALYs for 1000 Model Iterations



DISCUSSION

- Results indicate that FFA is a cost-effective intervention (£31,638/QALY gained) compared to the current NICE-recommended standard of care (CBD + CLO), and FFA extendedly dominates CBD.
- The novel individual-level modelling approach allowed the model to more accurately describe the heterogeneity in DS individual characteristics, which better reflects the impact of interventions than more conventional cohort modelling approaches.
- Utility values specific to DS based on patient and carer-level trial data were used to appropriately capture the burden of seizures across heterogeneous individuals.
- In the absence of direct comparative trials, a robust ITC was conducted to determine the relative efficacy of FFA with CBD (+/-CLO). This novel individual-level simulation model indicates that the FFA may be a cost-effective add-on therapy across its licensed indication in DS.
- Results from extensive uncertainty analyses suggest that FFA would be a cost-effective intervention, irrespective of age or disease characteristics. A range of sensitivity and scenario analyses indicate the results are consistent across this heterogenous population but are limited by a small sample.
- At plausible maximum doses of CBD, FFA dominates cannabidiol. In fully incremental analyses, FFA had a lower ICER vs SoC than did cannabidiol, i.e., FFA extendedly dominated CBD (+CLO).
- Although the patient-level simulation was run accurately, it is important to note that the model relies on simulating data across an artificial lifetime and may be prone to inaccuracies.
- CONCLUSIONS: This novel patient-level simulation model, which appropriately characterises the population heterogeneity in DS, demonstrates fenfluramine provides a clinically and cost-effective alternative to existing 'add-on therapy' options for this rare, life-threatening syndrome.

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