Determining the Relationship of Seizures, Seizure-Free Days and Other Predictors of Health-Related Quality of Life in Patients with Dravet Syndrome (DS) and Their Carers

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INTRODUCTION AND AIMS:

- Dravet syndrome (DS) is a rare, early onset, lifelong, epileptic encephalopathy characterised by frequent and severe convulsive seizures (1).
- The often daily seizure episodes are also associated with cognitive, motor, behavioural, and sleep impairments with a substantial impairment and burden to the health-related quality of life (HRQoL) of patients (2) as well as to their primary caregivers and the broader family members (3), with frequent seizures contributing to lower carer QoL (4). Reducing convulsive seizure frequency and increasing SFDs is therefore a primary treatment goal for patients. Studies that explored the impact of seizures on QoL in people with DS have focused on the link to seizure frequency or self-rated seizure severity (5,6).
- However, other measures of seizure presentation such as short-term periods of seizure freedom (rather than longer-term remission) or complete seizure freedom, and epidemiological factors such as age and motor impairments may also have an important impact on patients' and carers' QoL.
- This study has sought to explore the impact of increasing SFDs on patients' and carers' HR-QoL, and specifically examined and quantified the impact of clinical and epidemiological covariates to understand which factors may predict DS patient and carer HRQoL using data collected from two fenfluramine (FFA) registration trials (7,8). In Study 1, fenfluramine was added to standard of care (SoC) antiepileptic drugs (AEDs) that exclude stiripentol (STP), and in Study 1504 (also known as Study 2) fenfluramine was added to SoC that included STP.

METHODS: MEASURES AND MAPPING OF PATIENT AND CARER UTILITIES

Paediatric quality of life

- Paediatric Quality of Life Inventory (PedsQL) (9) was used to measure QoL in patients with DS.
- PedsQL has four scales that measure physical, emotional, social and school functioning (scores of 0-100; higher scores represent better QoL).
- In the FFA registration studies (7,8), 155 patients (or proxies) completed the PedsQL survey at randomisation, 2 weeks (end of titration period) and 12-13 weeks (end of maintenance period or discontinuation) – hereafter referred to as visits. Completed PedsQL data for all three visits were available for 128/155 patients.
- PedsQL data were mapped directly to EQ-5D-Y using the Khan et al. algorithm (10) to provide patient utilities. This dataset was used for subsequent statistical analyses.

Carer quality of life

- EuroQol 5 Dimensions five-level (EQ-5D-5L) was used to assess HRQoL in carers in the FFA registration studies (7,8) at two time points: randomisation (2 weeks after first assessment) and 12-13 weeks after initial visit (end of maintenance period). 185 carers completed EQ-5D-5L surveys at visit 3 and 176 completed EQ-5D-5L surveys at visits 3 and 12.
- EQ-5D-5L has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
- These carer utilities data were mapped from EQ-5D-5L onto EQ-5D-3L using the UK value set developed by van Hout et al. (11).

Statistical approach

- Two regression models were considered and applied to each dataset during the analysis:
  - A linear mixed-effects regression model
  - A panel linear fixed-effects regression model
- Both models were tested with the patient and carer datasets to assess whether a fixed or random-effects model better represented the data. The final mixed-effects model and final panel model for each dataset were statistically compared using the Hausman test, where a p-value of <0.05 would indicate that the preferred model was a mixed-effects model.
- All analyses were conducted in R (R core Team, 2019).

METHODS: MODELLING PATIENT AND CARER HRQOL

Covariate selection:

- Covariates from FFA registration studies were tested in a univariate analysis to explore the relationships between patient EQ-5D-Y and carer EQ-5D-3L scores at baseline and clinically relevant variables.
- Covariates explored were: motor impairments (categorised as: none, ataxia or severe), visit number during the trial period, 28-day frequency of seizure days and the frequency of seizure-free days (SFDs) per 28 days, and patient age group.

Mixed Effects Model:

- A univariate analysis was done to inform the selection of (candidate) covariates to understand whether any were correlated with the patient and carer HRQoL data at baseline.
- Covariates, adjusting for age and underlying comorbidities, were selected as candidate predictors based on statistical significance (assessed by p-value <0.05) in the baseline data and through clinical and epidemiological understanding.
- The same set of candidate covariates were used in both the carer and patient model.
- Data for both patients and carers were then analysed separately to assess whether there were any differences in HRQoL score between patients and carers themselves and between visits.
- Forward selection of covariates was conducted using patient and carer HRQoL data measured at all time points to determine the fixed effects in the final model. Statistically significant factors (p-value <0.05), cofounders or clinically relevant variables were retained in the final model.

Panel Linear fixed effects model

- Only covariates that varied over time were evaluated as a panel model as variables that change little or not at all over time should not be included in a fixed-effects model to avoid collinearity with the fixed effects. Thus, in both the patient and carer models, only the "frequency of SFDs per 28-day" (i.e. days without a seizure within a 28 day period) was tested as a covariate in the analysis as no other variables in the data varied over time.

Predicting utility scores

- With the quantified and adjusted relationship between HRQoL outcome data and clinically relevant covariates calculated through the regression analysis, patient and carer utility scores were predicted for each SFD.

Patient data results

- EQ-5D-Y values were highly variable between patients and across visits. Therefore, subject ID and visit ID (visit 3, 8, 12) formed the two random effect components of the final mixed effect model.
- When adjusting for age and underlying comorbidities within the mixed-effects model, the frequency of SFDs per 28-days was a significant predictor of HRQoL (gain in EQ-5D-Y utility of 0.005 per additional SFD, p<0.001).
- For the panel linear fixed-effects model, frequency of SFDs per 28-days was a significant predictor of patient EQ-5D-Y during the trial period (p <0.05).
- Comparing the final mixed-effects model to the final panel linear model, the Hausman test p-value was >0.1, suggesting that the mixed-effects model was more appropriate.
- Thus, the mixed-effects model was taken as the final model for the patient data. Coefficients and final p-values are presented in **Table 1.**

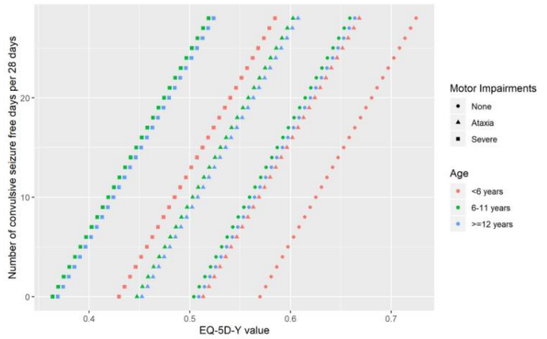
Table 1. Final Results for the Mixed Effects Model for 128 Patients for the Data EQ-5D-Y

Covariate	Coefficient†	Standard Error	p-value	Outcome Variable
28-day frequency of seizure-free days	0.005534	0.09745	<0.001	EQ-5D-Y (Patient)
Treatment group 1	0.010860	1.84241	>0.10	
Age 6-11 years	-0.065876	2.18912	>0.05	
Age >12 years	-0.060850	2.36243	>0.10	
Motor impairments: Ataxia	-0.056545	1.86204	<0.05	
Motor impairments: Severe	-0.140190	4.71504	>0.05	

†Coefficients refer to a 0-100 scale. All utility values predicted using these coefficients were divided by 100 before the predicted relationship was estimated (shown in **Figure 1**)

- **Figure 1** illustrates the predicted relationship between patient EQ-5D-Y and SFDs. As an example of how the results can be used, if we assume a typical patient aged <6 years with severe comorbidities and 10 SFDs per 28 days, they would have an EQ-5D utility of 0.48.

Figure 1. EQ-5D-Y Marginal Means for Patients Not Taking Concomitant Stiripentol



Carer data results

- As with the patient data, the carer HRQoL data indicated heterogeneity and differences in carer EQ-5D-3L scores between visits and patients.
- Thus, subject ID and visit number (visit 3, 12) formed the two random effect components of the final mixed-effects model. Both 28-day frequency of SFDs and ataxia motor impairments were statistically significant in the final mixed-effects model.
- As with the patient model the carer linear panel model also showed the frequency of SFDs per 28-days as a significant predictor of HRQoL (gain in EQ-5D-3L utility of 0.013 per additional SFD, p<0.001).
- Comparing the final mixed-effects model to the panel linear fixed effects model the panel model was statistically supported by the Hausman test (p <0.05); and was thus taken as the final model for the carer EQ-5D-3L data **(Table 2).**

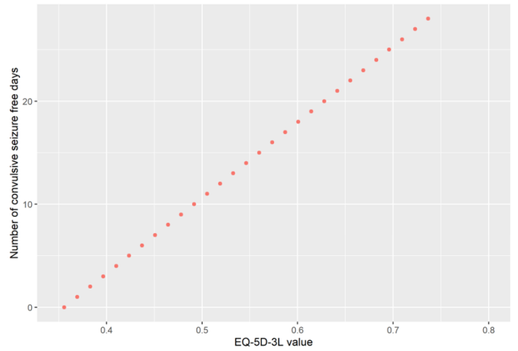
Table 2. Final Model Results for 176 Carers EQ-5D-3L Data for the Linear Panel Model

Covariate	Coefficient†	Standard Error	p-value
28-day frequency of seizure-free days	0.01361	0.3862	<0.001

†Coefficients refer to a 0-100 scale. All utility values predicted using these coefficients were divided by 100 before the predicted relationship was estimated (shown in **Figure 2**)

- The predicted relationship between carer EQ-5D-3L and the number of SFDs a patient has is illustrated in **Figure 2**. The results can be interpreted as follows: if the patient a carer was supporting had 5/28 days seizure-free per month the expected EQ-5D-3L score for that carer would be 0.42.
- For example, a typical patient aged <6 years with two comorbidities and 10 SFDs per 28-days would have an EQ-5D utility of 0.48. If on FFA, SFDs increased to 20 or 28 ("seizure-free") per 28 days, the patient utility would rise 11.4% and 20.5%, and their carer's utility by 27.7% and 49.8%, respectively.
- **Figure 2** illustrates the predicted relationship between carer EQ-5D-3L and the number of SFDs a patient has.

Figure 2. EQ-5D-3L Marginal Means for Carers



DISCUSSION

- The regression framework developed in this study provides a useful framework to identify key variables that may impact QoL for patients with DS and their carers.
- The results showed that both seizure frequency and SFDs have a significant impact on QoL for both patients and carers; this suggests that treatment options that increase SFD can substantially impact both DS patients' and carers' QoL.
- This quantitative evidence supports previous research on seizure frequency and QoL in patients and carers (9,13) and indicates that age and comorbidities also impact patients' QoL.
- Given the focus of new interventions on improving QoL for people with chronic disease, using individual-level patient and carer data within the regression framework presented could be useful to quantify the impact of interventions on QoL for patients and their carers.
- These data highlight that effective antiseizure treatments that durably increase SFDs, also improve patients' and carers' QoL in a directly quantifiable manner. It is therefore important to consider that the quality of life of both patients and carers should be assessed and taken into consideration when evaluating treatment options.

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