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Low-dose Fenfluramine Significantly Reduces Seizure Frequency in Dravet Syndrome: A Prospective Study of a New Cohort of Belgian Patients

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INTRODUCTION

- Dravet syndrome (DS) is a severe, therapy-resistant epilepsy syndrome that typically presents in the first year of life[1]
  - Between ages 1 to 5 years, seizure frequency and severity increase
  - Results in developmental delay and cognitive and behavioral problems
  - About 85% of DS patients have a mutation in *SCN1A*, coding for neuron-specific, voltage-gated sodium channel
- Fenfluramine (FFA) has been reported to have antiseizure activity[2]
  - In 1996 the report of Boel et al. showed that add-on FFA provided seizure freedom in 8 of 11 patients with self-induced seizures[3]
  - In a retrospective chart review of 12 DS patients treated with FFA 7 of 10 patients who were still receiving FFA had been seizure-free for periods of 1 to 19 years (original cohort[4])
- Here we describe the initial results from a new cohort of 7 DS patients who began add-on treatment with low-dose FFA starting in 2010 using a standardized protocol of assessments

METHODS

- Key inclusion criteria included: patients between 6 months and 50 years of age with a diagnosis of DS and therapy-resistant epilepsy
- Key exclusion criteria included: cardiovascular disease including cardiac valvulopathy, hypertension, and glaucoma
- At baseline, seizure frequency and type were recorded in a diary during a 3-month run-in observation period
- After the run-in period, FFA was added to the current antiepilepsy treatment regimen
- FFA dose could be adjusted at the discretion of the treating physician up to a maximum of 20 mg/day
- Efficacy (seizure frequency) and adverse events were monitored at scheduled and unscheduled office visits

RESULTS

- All 7 patients had confirmed mutation in *SCN1A*
- Baseline patient characteristics are shown in **Table 1**
- All patients were receiving other antiepilepsy drugs upon enrollment
  - Valproate (n=7)
  - Topiramate (n=6)
  - Clobazam (n=3)
  - Stiripentol (n=2)
  - Ethyl loflazepate (n=2)
  - Bromide (n=1)
  - Levetiracetam (n=1)

Table 1. Baseline Patient Characteristics

Patient #	Gender	Body weight (kg)	Age at start of FFA (years)	Tonic-clonic seizures during run-in period (before initiation of FFA) (#/mo)
1	M	37	11.9	15
2	M	10	1.2	3
3	F	17	5.9	0.4
4	M	40	11.9	39.7
5	F	50	13.5	2
6	M	43	19.8	2.3
7	M	59	20.3	17.7

- Details of FFA dosing are presented in **Table 2**
  - The median starting dose of FFA was 10 mg/day (0.25 mg/kg)
  - The median duration of dosing with FFA was 0.9 years

Table 2. Fenfluramine Dosing

Patient #	FFA starting dose (mg/day)	FFA starting dose (mg/kg/day)	FFA current dose (mg/day)	FFA current dose (mg/kg/day)	Duration of FFA treatment (years)
1	10	0.27	10	0.27	3.9
2	5	0.50	12.5	0.69	3.6
3	5	0.29	7.5	0.47	0.2
4	10	0.25	15	0.36	0.9
5	5	0.10	10	0.19	0.8
6	10	0.23	10	0.23	1.0
7	10	0.17	10	0.17	0.5
Median	10	0.26	10	0.27	0.9

- The effect of FFA on the TC seizure frequency is shown in **Figure 1**
  - During the 90-day run-in period the median frequency of tonic-clonic (TC) seizures was 3.0 per month (range 0.4 to 39.7)
  - All patients demonstrated a decrease in TC seizure frequency after starting FFA
- At the 6-month evaluation, the median frequency of TC seizures was 1.2 per month, representing a 73% decline
- Over the entire observation period (median 0.9 years; range 0.2 to 3.9 years) the median frequency of TC seizures was 0.9 per month, representing an 84% reduction compared with the 3-month run-in period (**Figure 2**)

Figure 1. Tonic-clonic Seizure Frequency Before and During Treatment with Fenfluramine

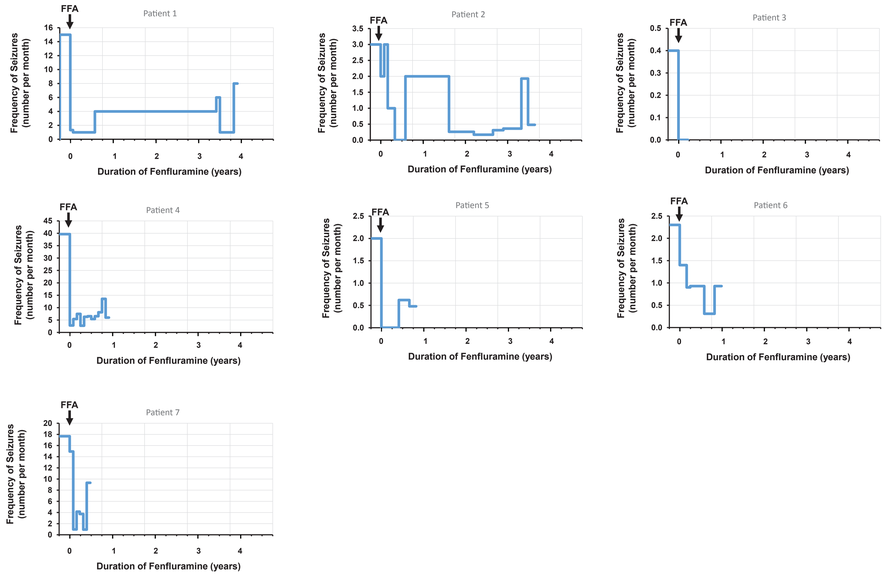
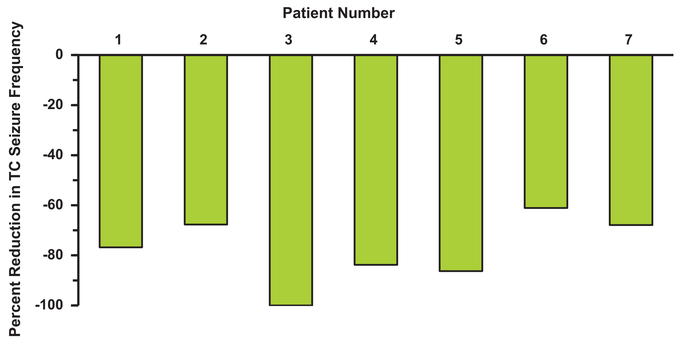


Figure 2. Change in Frequency of Tonic-clonic Seizures During Treatment with Fenfluramine



- The most common treatment-related adverse events were
  - Mild-to-moderate somnolence (n=6)
  - Anorexia (n=4)
- No echocardiographic or clinical signs of cardiac valvulopathy or pulmonary hypertension were observed in this cohort during the observation period
- One patient (Patient 2) who was hospitalized 11 times for seizures during the 90-day run-in period, experienced 4 separate episodes of status epilepticus with fever due to respiratory infection during the FFA treatment period

CONCLUSIONS

- The observed effectiveness and tolerability with add-on, low-dose FFA in this new cohort of DS patients extends the findings previously reported in the original cohort in 2012
- FFA provides clinically meaningful reduction in seizure frequency and is generally well tolerated
- A randomized, placebo-controlled, Phase 3 clinical trial is planned to confirm the efficacy and safety of FFA for the treatment of epilepsy in DS

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DISCLOSURES

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