168

Long-term Efficacy and Safety of Low-dose Fenfluramine Treatment in Dravet Syndrome

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INTRODUCTION

- Dravet syndrome (DS) is a severe therapy-resistant epilepsy syndrome that is caused by an *SCN1A* mutation in about 70%-80% of cases[1,2]
- Fenfluramine (FFA) has been reported to have antiepileptic activity,[3] although its anticonvulsant mechanism of action has yet to be fully elucidated
- FFA had been previously used in high doses (≥60 mg/day) often in combination with phentermine for weight loss but was withdrawn from the US and European markets in 1997 when its association with cardiac valvulopathy and pulmonary hypertension became known
- Exploratory use of FFA for refractory pediatric epilepsy in the 1990s in Belgium led to an investigator-initiated study approved by the ethics committee
- A retrospective analysis of 12 patients with Dravet syndrome who were treated with low doses of FFA (0.12 to 0.90 mg/kg/day) for periods of 1 to 19 years reported that 7 of 10 patients who were still receiving FFA at the last examination in 2010 had been seizure-free for at least 1 year.[4] Two patients had stopped treatment; 1 due to lack of effect and a second due to a shortage of drug supply during which the patient remained seizure-free while off FFA
- Here we report on the effectiveness and safety of continued long-term use of low-dose FFA as add-on treatment in 10 Dravet syndrome patients from the original cohort who are still being treated with FFA

METHODS

Patients

- All patients of the original cohort who were still receiving low-dose FFA for Dravet syndrome were eligible to be included in this analysis

Fenfluramine

- Dose could be adjusted up to a maximum of 1 mg/kg/day (and not exceeding a daily dose of 20 mg)

Assessments

- Seizure diary maintained by parents or caregivers
- Electroencephalography (EEG) performed at least annually
- Cardiovascular examination performed at least annually
  - Electrocardiogram (ECG)
  - Echocardiography was assessed by cardiologists qualified to assess cardiac valve structure and function
- Adverse events were surveyed by a questionnaire at least annually

RESULTS

Patient Disposition

- 10 patients in the original cohort were still being treated with FFA as of May 26, 2015 and were included in this analysis (**Tables 1** and **2**)

Table 1. Patient Characteristics

Parameter	Value
Gender	5 Male – 5 Female
Current age[a]	23.5 ± 8.83 years
Current weight[a]	63.7 ± 20.56 kg
Age when starting FFA[a]	6.2 ± 5.35 years
Duration of FFA treatment[a]	16.6 ± 7.74 years
Starting dose of FFA[a]	12.0 ± 5.87 mg/day (0.62 ± 0.28 mg/kg/day)
Current dose of FFA[a]	16.0 ± 4.59 mg/day (0.27 ± 0.27 mg/kg/day)

[a]Mean ± SD.

Table 2. Individual Patient Characteristics

Patient #	Gender	Current Age (years)	Current Weight (kg)	Age at Start of FFA (years)	Starting Dose of FFA mg/day (mg/kg/day)	Current Dose of FFA mg/day (mg/kg/day)	Duration of FFA Treatment (months)[a]
1	M	30	75	6	20 (0.87)	20 (0.27)	293
2	M	20	61	2	5 (0.38)	15 (0.25)	161
3	F	7	21.9	1	10 (1.00)	10 (0.46)	63
4	F	26	99	13	20 (0.56)	20 (0.20)	164
5	M	22	51.6	1	10 (0.91)	15 (0.29)	244
6	F	17	64	7	20 (0.83)	20 (0.31)	124
7	F	29	80	2	10 (0.67)	10 (0.13)	317
8	M	25	58	3	5 (0.42)	20 (0.34)	264
9	M	19	52.5	12	10 (0.29)	10 (0.19)	80
10	F	40	74	15	10 (0.23)	20 (0.27)	287

[a]Includes duration of treatment prior to the present observation period.

Antiepileptic Effectiveness

- Average treatment duration was 16.6 years (**Table 1**)
- At the most recent follow-up consultation, 6 patients (60%) had been seizure-free for at least 2 years (range 2 to 15 years) (**Figure 1**)
- 1 additional patient demonstrated a 2-year seizure-free period during 2011 and 2012
- This cohort of patients continued to experience clinically meaningful seizure control
  - 90% demonstrated an average of fewer than 1 seizure per month during the observation period
  - 50% demonstrated an average of fewer than 0.5 seizures per month during the observation period

Figure 1. Longitudinal Convulsive Seizure Frequency: 2010 to 2014

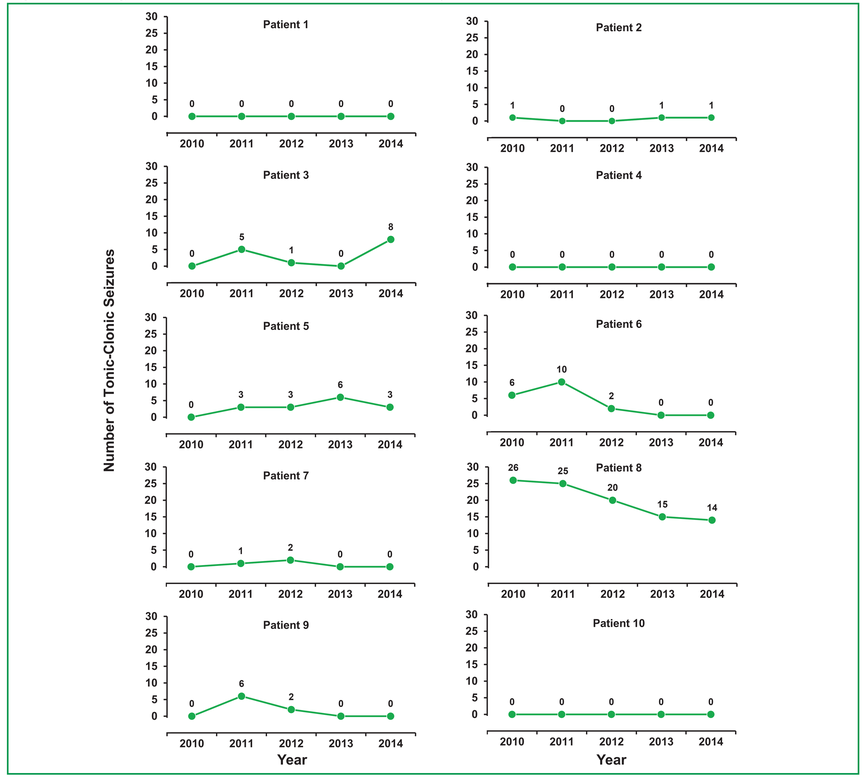

Table 3. Effectiveness of Fenfluramine in Treatment of Dravet Syndrome

Patient #	Current AEDs in Combination with FFA	Number of Tonic-Clonic Seizures in Year Before Last Consultation[a]	EEG at Last Consultation	Current Duration of Seizure Freedom[b]
1	VPA	0	Normal	13 years
2	VPA, TPM, ethyl loflazepate	1	Slowing background activity, no epileptic activity	
3	VPA, TPM	9	Normal	
4	VPA, LTG	0	Normal	9.5 years
5	VPA, LEV, ethyl loflazepate	3	Multifocal epileptic activity	
6	VPA, STP, CLB	0	Normal	2 years
7	VPA, TPM	0	Normal	2 years
8	VPA, LEV, ethyl loflazepate	12	No epileptic activity, no background activity	
9	VPA, TPM	0	Normal	2 years
10	VPA	0	Normal	15 years

[a]These values may differ from those presented in Figure 1 because they represent seizure activity for the 12 months prior to the visit which may occur at any time during the year whereas the numbers in Figure 1 represent seizure activity for the specified calendar year.
[b]May include treatment duration prior to 2010.
VPA, valproate; TPM, topiramate; LTG, lamotrigine; STP, stiripentol; LEV, levetiracetam; CLB, clobazam.

Table 4. Cardiovascular Echocardiographic Findings

Patient #	Number of Echocardiographies Performed	Previous Echocardiographic Findings (year)	Most Recent Echocardiographic Findings (year)	Cardiac Clinical Signs
1	3	Slightly thickened aortic leaflets, stable (2010-2012)	Yes, aortic and tricuspid valve (2014)	None
2	4	Transient slightly thickened AML (2013)	Normal (2014)	None
3	8	Normal (2010-2014)	Normal (2015)	None
4	5	Normal (2010-2014)	Normal (2014)	None
5	10	Transient slightly thickened AML and tricuspid valve (2014)	Normal (2015)	None
6	5	Normal (2010-2013)	Normal (2014)	None
7	4	Transient slightly thickened AML (2012)	Normal (2014)	None
8	6	Slightly thickened AML, stable (2013-2014)	Yes, mitral and tricuspid valve (2015)	None
9	5	Transient slightly thickened mitral/ tricuspid leaves (2010-2013)	Normal (2014)	None
10	7	Normal (2013)	Normal (2014)	None

AML, anterior mitral leaflet.

Safety

- Adverse events included anorexia (n=2), aggressive behavior (n=1), and fatigue (n=1). All were mild without the need of dose adjustment or interruption of FFA therapy

CONCLUSIONS

- Low-dose FFA continues to provide long-term, clinically meaningful seizure control in the patients from the original cohort published in 2012
  - 7 of 10 patients (70%) in this group have experienced long intervals of seizure freedom (≥2 years)
  - 9 of 10 patients (90%) have had an average of <1 seizure per month during the observation period
- Long-term longitudinal echocardiographic assessments continue to demonstrate no clinically meaningful signs of valvulopathy or pulmonary hypertension
  - Transient cardiac valve morphologic changes in 4 patients
  - Minor persistent valve morphologic changes in 2 patients
  - No clinical signs or symptoms of cardiac valvulopathy or pulmonary hypertension were reported in any patient
- Low-dose FFA was generally well tolerated

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