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

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INTRODUCTION

- Dravet syndrome (DS) is a rare, severe, and often drug-resistant epilepsy syndrome
  - Incidence is 1 in 20,900 to 1 in 40,000 live births
  - Typically presents as epileptic encephalopathy in infancy
  - *SCN1A* mutation found in approximately 85% of DS patients
- Fenfluramine has been reported to have long-term beneficial activity in a cohort of DS patients in Belgium[1]
- Here we describe the results from a prospective, open-label study of low-dose fenfluramine in a new cohort of DS patients with initiation of a standardized protocol of assessments

METHODS

- Patients from 6 months to 50 years of age with a diagnosis of DS were eligible to enroll
- Patients with cardiovascular disease, including drug-treated hypertension and cardiac valvulopathy, were excluded
- Following a 3-month run-in period, fenfluramine was added to each patient's current anti-epileptic drug regimen at a dose of 0.1 to 0.5 mg/kg/day (maximum 20 mg/day)
- The incidence of major motor seizures (tonic, clonic, tonic-clonic, atonic, and myoclonic seizures lasting >30 sec) in both the run-in and treatment periods was assessed via a seizure diary
- Periodic echocardiographic examinations during the treatment period were used to assess cardiovascular safety

RESULTS

- Nine patients (ages 1.2 to 29.8 years) enrolled in the study and were treated with fenfluramine for a median duration of 1.5 years (range, 0.11 to 4.77 years) (**Table 1**)
- Median frequency of major motor seizures was 15.0 per month in the run-in period

Table 1. Individual Patient Demographics

Patient	Sex	Age at Start of FFA (years)	Height at Start (cm)	Weight at Start (kg)	Mutation in *SCN1A*	Initial Epilepsy Treatment Regimen at Study Entry
1	M	11.9	144	35	De novo nonsense mutation (c.4497delT)	VPA, CLB, VNS
2	F	1.2	78	10	De novo missense mutation (c.296T>A)	VPA, TPM, CLB
3	M	5.9	107	17	De novo nonsense mutation (c.969T>G)	VPA, TPM
4	M	11.9	149	40	De novo duplication (c.3427-4002+?dup)	Bromide, VPA, TPM
5	F	13.5	164	50	De novo nonsense mutation (c.58C>T)	STP, TPM, VPA, ethyl loflazepate
6	M	19.8	168	48	De novo splice site mutation (IVS22+1 G>A)	VPA, TPM, ethyl loflazepate, STP
7	M	20.3	165	60	De novo splice site mutation (c.2589+3A>T)	VPA, LEV, CLB, TPM, VNS
8	M	7.2	124	24	De novo frameshift mutation (c.657-658delAG)	VPA, TPM, ethyl loflazepate
9	F	29.8	165	64	De novo missense mutation (c.2875T>C)	VPA, TPM, ethyl loflazepate, VNS

CLB, clobazam; F, female; FFA, fenfluramine; LEV, levetiracetam; M, male; STP, stiripentol; TPM, topiramate; VNS, vagal nerve stimulation; VPA, valproic acid.

- All patients demonstrated a reduction in seizure frequency during the treatment period with a median reduction of 75% with a range of 28% to 100% (**Table 2** and **Figure 1**)

Table 2. Individual Patient Clinical Information

Patient	Initial FFA Dose mg/day	Initial FFA Dose mg/kg/day	Most Recent FFA Dose mg/day	Most Recent FFA Dose mg/kg/day	Treatment Duration (years)	Major Motor Seizures/Month[a] 3-month Baseline Period	Major Motor Seizures/Month[a] FFA Treatment[b]	Major Motor Seizures/Month[a] Percent Reduction[c]
1	10	0.29	20	0.44	5.06	15.0[d]	4.5[d]	-70%
2	5	0.50	12.5	0.69	4.70	2.5[d]	0.4[d]	-84%
3	5	0.29	10	0.62	0.78	0.4[d]	0[d]	-100%
4	10	0.25	15	0.36	1.50	39.7[d]	7.3[d]	-82%
5	5	0.10	15	0.25	1.64	2.0[d]	0.7[d]	-68%
6	10	0.21	10	0.19	1.57	2.3[d]	1.5[d]	-37%
7	10	0.17	15	0.27	1.02	18.3	13.2	-28%
8	5	0.21	5	0.17	0.63	20.4	0.8	-96%
9	10	0.16	10	0.16	0.30	23.8	6.0	-75%
Mean	7.8	0.24	12.5	0.35	1.9	13.8	3.8	-71%
Median	10	0.23	12.5	0.29	1.5	15.0	1.5	-75%

FFA, fenfluramine.

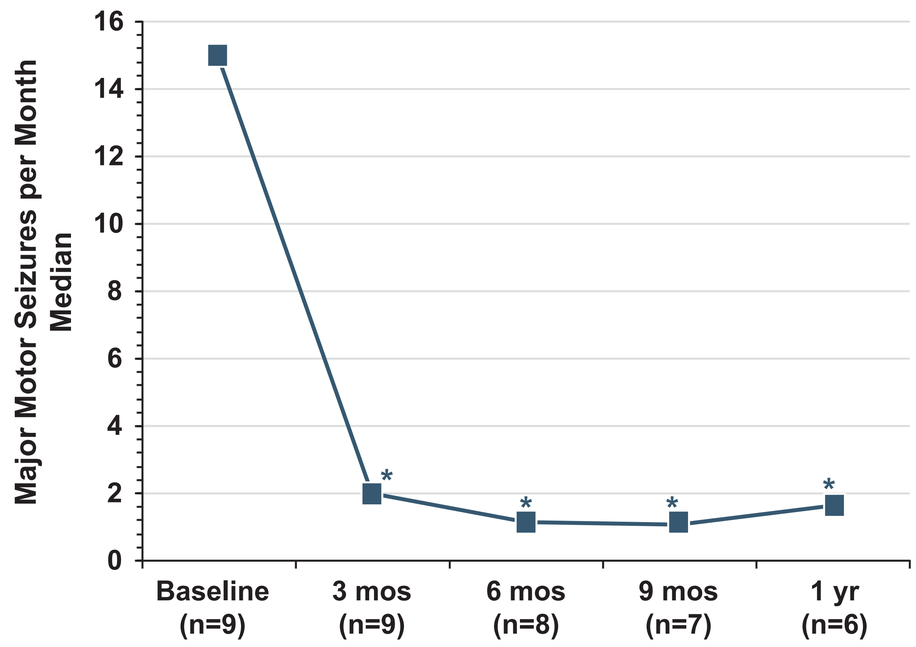
[a]Major motor seizures were defined as tonic-clonic, tonic, clonic, atonic, and myoclonic seizures lasting >30 sec.

[b]Monthly seizure frequency was calculated as the total number of seizures during the treatment period divided by the total number of treatment days multiplied by 30 days/month.

[c]Percent reduction refers to the entire treatment period compared with the seizure frequency per month in the baseline period.

[d]Tonic-clonic seizures were the only major motor seizures observed in these patients both before and during treatment with fenfluramine.

Figure 1. Effect of Add-on Fenfluramine on the Frequency of Major Motor Seizures in DS Patients



*Significant differences in Wilcoxon non-parametric test ($p<0.05$) compared with baseline period.

- Seven of 9 patients (78%) experienced a ≥50% reduction in major motor seizure frequency
- Sleep quality and quality of life assessments at the most recent study visit are presented in **Table 3**

Table 3. Overall Sleep Quality and Quality of Life in DS Patients and Their Parents

	Patients	Parents
Sleep quality	8.1	7.9
Quality of life	7.4	7.6

- The most common adverse events were somnolence (n=5 patients) and anorexia (n=4)
- Fatigue (n=3), sleep difficulties (n=2), and non-convulsive status epilepticus (n=3) occurred in 2 or more patients during treatment
- Except for episodes of non-convulsive status epilepticus, all treatment-emergent adverse events were deemed to be of mild-to-moderate severity
- No evidence of cardiac valvulopathy or pulmonary hypertension was observed

CONCLUSIONS

- The effectiveness of low-dose fenfluramine as an add-on therapy for DS in this new cohort supports previous findings[1,2]
- Fenfluramine exhibited a favorable tolerability profile in this patient population with no echocardiographic or clinical evidence of cardiac valvulopathy or pulmonary hypertension
- Further studies are warranted and prospective controlled clinical studies are underway to more fully define the benefit-risk ratio of this novel treatment in DS

REFERENCES

1. Ceulemans B, et al. *Epilepsia*. 2012; 53(7):1131-9.
2. Ceulemans B, et al. *Epilepsia*. 2016; 57(7):e129-34.

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DISCLOSURES

AG is an employee of Zogenix, Inc.

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