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Low-dose Fenfluramine Provides Significant and Long-term Seizure Reduction in Dravet Syndrome: Update and Follow-up of the Prospective Study

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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 a developmental 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 continuing observations 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

- Fifteen patients (ages 1.2 to 29.8 years) enrolled in the study (**Table 1**) and were treated with fenfluramine for a median duration of 3.0 years (range, 0.1 to 7.2 years) (**Table 2**)
- Median frequency of major motor seizures was 2.4 per month in the run-in period

Table 1. Individual Patient Demographics

Patient	Sex	Age at Start of FFA (years)	Current Age (years)	Initial Epilepsy Treatment Regimen at Study Entry
1	M	11.9	19.0	VPA, CLB, VNS
2	F	1.2	8.4	VPA, TPM, CLB
3	M	5.9	9.0	VPA, TPM
4	M	11.9	15.9	Bromide, VPA, TPM
5	F	13.5	17.6	STP, TPM, VPA, ethyl loflazepate
6	M	19.8	23.9	VPA, TPM, ethyl loflazepate, STP
7	M	20.3	23.8	VPA, LEV, CLB, TPM, VNS
8	M	7.1	10.1	VPA, TPM, ethyl loflazepate
9	F	29.8	32.4	VPA, TPM, ethyl loflazepate, VNS
10	M	13.2	14.7	VPA, TPM, LEV, VNS
11	F	2.6	4.0	VPA, TPM
12	M	2.8	3.5	VPA, TPM, CLB
13	M	5.3	6.1	VPA, CLB, STP
14	M	4.1	4.3	VPA, TPM, clonazepam
15	M	8.3	8.4	VPA, TPM, clonazepam

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 87% with a range of 5% to 100% (**Table 2** and **Figure 1**)
- 13/15 (87%) patients experienced a ≥50% reduction and 10/15 (67%) experienced a ≥75% reduction in major motor seizures

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 Run-in Period	Major Motor Seizures/Month[a] FFA Treatment[b]	Major Motor Seizures/Month[a] Percent Reduction[c]
1	10	0.29	20	0.43	7.1	15.0[d]	4.8	-68%
2	5	0.50	12.5	0.63	7.2	2.5[d]	0.3	-87%
3	5	0.29	10	0.53	3.1	0.4[d]	0.05	-87%
4	10	0.25	17.5	0.35	4.0	39.7[d]	7.8	-89%
5	5	0.10	15	0.22	4.1	2.0[d]	0.4	-80%
6	10	0.21	15	0.26	4.1	2.3[d]	2.2	-5%
7	10	0.17	20	0.34	3.5	18.3	5.2	-71%
8	5	0.21	15	0.48	3.0	20.4	0.7	-96%
9	10	0.16	15	0.23	2.5	23.8	1.8	-92%
10	5	0.18	7.5	0.20	1.5	4.2[d]	0.3	-94%
11	5	0.43	5	0.34	1.4	1.3[d]	0.1	-91%
12	2.5	0.14	5	0.33	0.8	2.4	0.7	-70%
13	2.5	0.13	5	0.26	0.8	1.4	0.1	-92%
14	2.5	0.14	5	0.29	0.2	0.6	0.3	-48%
15	2.5	0.12	5	0.24	0.1	1.7	0	-100%
Mean	**6.0**	**0.22**	**11.5**	**0.34**	**2.9**	**9.1**	**1.7**	**-78%**
Median	**5.0**	**0.18**	**12.5**	**0.33**	**3.0**	**2.4**	**0.4**	**-87%**

FFA, fenfluramine.

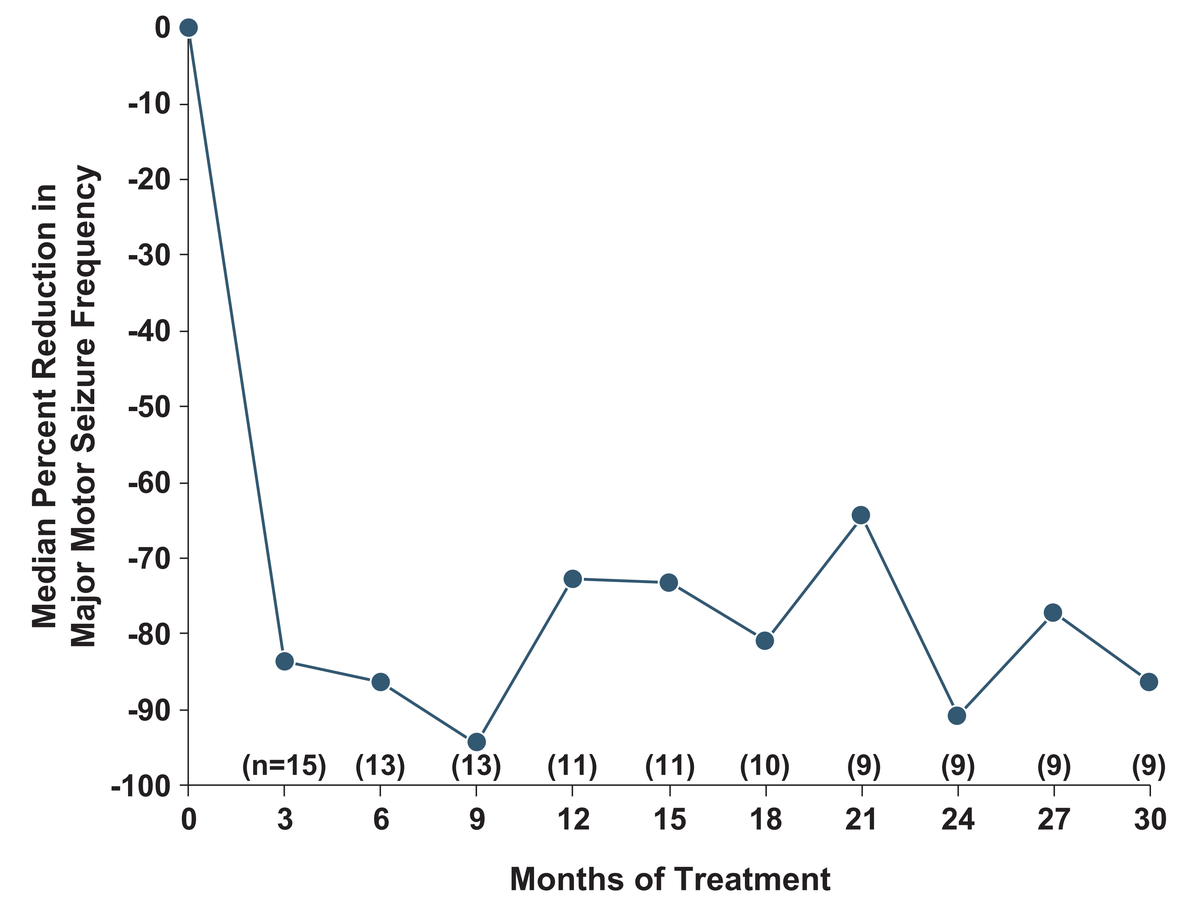
[a]Major motor seizures were defined as tonic-clonic, tonic, clonic, atonic, and myoclonic seizures lasting >30 sec.

[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 run-in 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



- The most common adverse events were anorexia (n=11), sleepiness (n=9), fatigue (n=8), mood changes (n=8), sleep problems (n=3), headache (n=2), and thrombocytopenia (n=1)
- No patient had echocardiographic or clinical evidence of cardiac valvulopathy or pulmonary hypertension
  - Patient 1 had minor thickening of the aortic valve and mild hypokinesis at the most recent examination, which were deemed to be without clinical significance

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
- The efficacy and safety of fenfluramine in this DS cohort were recently replicated in 2 randomized controlled trials demonstrating a superior reduction in convulsive seizure frequency vs placebo

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

AS: Consultant/advisor: Brabant, Zogenix.
FM: Investigator: Brabant, Zogenix.
AG, **BSG**: Employee: Zogenix; Stock ownership: Zogenix.
LL: Consultant/advisor and Speaker: LivaNova, Novartis, Ovid, Shire, UCB, Zogenix.
BC: Consultant/advisor and Investigator: Brabant, Novartis, UCB, Zogenix.

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