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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 drug-resistant epilepsy syndrome
  - Typically presents in the first year of life with initial seizures being clonic, generalized, or unilateral
  - The incidence is estimated to be 1 in 15,700 to 1 in 40,000 live births[1,2]
  - Mutations in the *SCN1A* gene, which encodes the alpha subunit of the type 1 voltage-gated sodium channel, have been found in about 80% of DS patients[3]
- Low-dose fenfluramine has been reported to reduce seizure frequency in a group of 10 DS patients who have been treated for 7 to 28 years[4,5]
  - Here we present an update on the results of an ongoing study of a new cohort of DS patients being treated with add-on low-dose fenfluramine[6]

METHODS

- Patients with diagnosis of DS between the ages of 6 months and 50 years were included
  - Patients with cardiovascular disease, including cardiac valvulopathy and drug-treated hypertension, were excluded
- Following a 3-month run-in period, fenfluramine was added to each patient's current antiepilepsy drug regimen at a dose of 0.1 to 1.0 mg/kg/day (maximum dose, 20 mg/day)
- The incidence of major motor seizures (tonic, tonic-clonic, atonic, and myoclonic seizures lasting >30 sec) in both the run-in and treatment periods was recorded in a seizure diary
- To assess cardiovascular safety, echocardiographic examinations were performed at baseline, every 3 months during the first year of fenfluramine treatment, every 6 months during the second year of fenfluramine treatment, and annually thereafter

RESULTS

Demographics

- 11 patients (mean age at start of fenfluramine, 12.5 years; range, 1.2-29.8 years) enrolled in the study and were treated with fenfluramine for a median duration of 3.0 years (range, 0.8-6.6 years) (**Tables 1 and 2**)
- All patients had a typical core DS phenotype and a confirmed de novo mutation in *SCN1A*
- All patients were treated with at least 2 other antiepileptic drugs at study entry, and 4 patients had vagal nerve stimulation with stable settings (**Table 1**)

Seizure Frequency

- Mean frequency of major motor seizures was 11.8/month during the run-in period (**Table 2**)
- All patients demonstrated a decrease in frequency of major motor seizures that was evident as early as 3 months (**Table 2**, **Figures 1 and 2**)

Table 1. Baseline Characteristics

Patient	Sex	Age at Start of FFA (yrs)	Height at Start (cm)	Weight at Start (kg)	Initial Epilepsy Treatment Regimen at Study Entry
1	M	11.9	144	35	VPA, CLB, VNS
2	F	1.2	78	10	VPA, TPM, CLB
3	M	5.9	107	17	VPA, TPM
4	M	11.9	149	40	VPA, TPM, Bromide
5	F	13.5	164	50	VPA, TPM, Ethyl loflazepate, STP
6	M	19.8	168	48	VPA, TPM, Ethyl loflazepate, STP
7	M	20.3	165	60	VPA, TPM, LEV, CLB, VNS
8	M	7.2	124	24	VPA, TPM, Ethyl loflazepate
9	F	29.8	165	64	VPA, TPM, Ethyl loflazepate, VNS
10	M	13.2	145.5	28.5	VPA, TPM, LEV, VNS
11	F	2.6	88	11.7	VPA, TPM

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

Table 2. Summary of Fenfluramine Dosing and Effect on Major Motor Seizures

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 (yrs)	Major Motor Seizures/month[a] 3-month Baseline Period	FFA Treatment[b]	Percent Reduction[c]
1	10	0.29	20	0.45	6.64	15.0[d]	4.85[d]	-67.7
2	5	0.50	12.5	0.67	6.55	2.5[d]	0.35[d]	-85.7
3	5	0.29	10	0.56	2.49	0.4[d]	0.07[d]	-83.1
4	10	0.25	15	0.33	3.42	39.7[d]	9.01[d]	-77.3
5	5	0.10	15	0.23	3.02	2.0[d]	0.49[d]	-75.6
6	10	0.21	15	0.27	3.11	2.3[d]	2.01[d]	-13.9
7	10	0.17	20	0.36	3.05	18.3	5.94	-67.5
8	5	0.21	10	0.35	1.95	20.4	0.90	-95.6
9	10	0.16	15	0.24	1.55	23.8	2.65	-88.9
10	5	0.18	7.5	0.23	0.8	4.24[d]	0.10[d]	-97.5
11	5	0.43	5	0.36	0.8	1.33[d]	0.00[d]	-100
Mean	**7.27**	**0.25**	**13.18**	**0.37**	**3.0**	**11.8**	**2.4**	**-77.5**
Median	**5**	**0.21**	**15**	**0.35**	**3.0**	**4.2**	**0.9**	**-83.1**

CLB, clobazam; LEV, levetiracetam; STP, stiripentol; TPM, topiramate; VNS, vagal nerve stimulation; VPA, valproic acid.

[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. Individual patient change in major motor seizure frequency during treatment with fenfluramine.

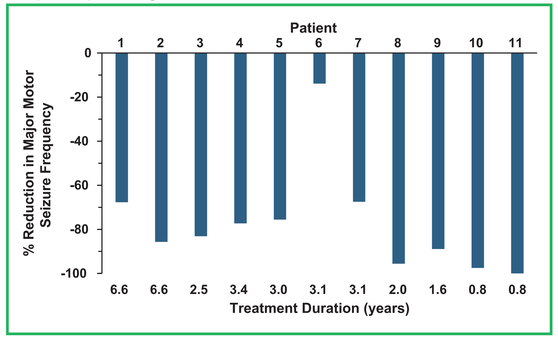
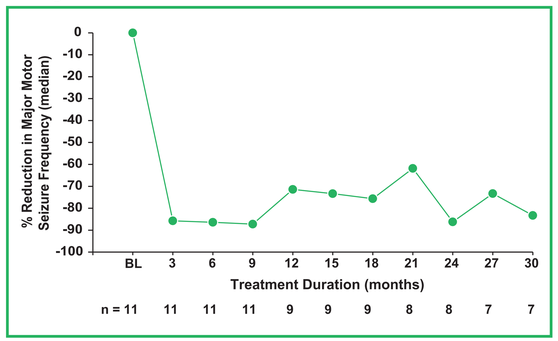


Figure 2. Percent reduction in major motor seizure frequency during treatment with fenfluramine.

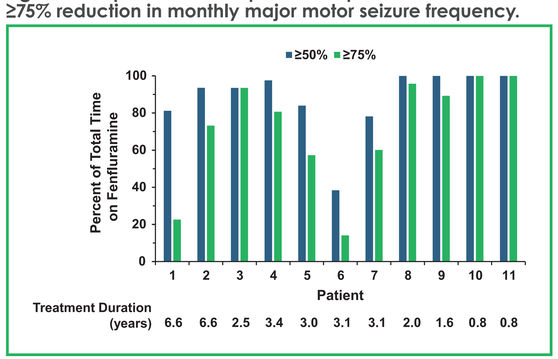


The change in the number of patients reflects the fact that entry into the study was staggered and not because patients have dropped out.

Responder Analysis

- 10 of 11 patients (91%) had a ≥50% reduction in monthly major motor seizures
- 8 out of 11 patients (73%) had a ≥75% reduction in monthly major motor seizures

Figure 3. Proportion of time patients experienced a ≥50% or ≥75% reduction in monthly major motor seizure frequency.



Safety

- The most common adverse events were somnolence (n=9) and anorexia (n=8)
- No evidence of cardiac valvulopathy or pulmonary hypertension was observed in any patient on any echocardiogram (**Table 3**)

Table 3. Echocardiographic Findings

Patient	Treatment Duration (yrs)	Baseline Findings	Number of Echocardiographies Performed During Treatment	Findings of the Last Echocardiography
1	6.64	Normal	11	Stable subnormal systolic LV function (FS 25%), stable over 1 yr[a]
2	6.55	Normal	10	Normal
3	2.49	Normal	6	Normal
4	3.42	Normal	7	Normal
5	3.02	Normal	7	Normal
6	3.11	Normal	7	Normal
7	3.05	Normal	6	Normal
8	1.95	Normal	6	Normal
9	1.55	Normal	5	Normal
10	0.8	Normal	3	Normal
11	0.8	Normal	3	Normal

[a]These findings were first seen in April 2016 and have remained stable throughout the most recent examination in August 2017 without any clinical significance. Reviewing cardiologists rated this finding as unlikely related to fenfluramine use.

CONCLUSIONS

- Low-dose fenfluramine has provided clinically meaningful reductions in major motor seizure frequency with sustained benefit noted for up to 6.6 years
- 91% of patients had a clinically meaningful reduction (≥50%) and 73% had substantial reductions (≥75%) in major motor seizure frequency
- Fenfluramine was generally well tolerated with no clinical and/or echocardiographic signs of cardiac valvulopathy or pulmonary hypertension

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DISCLOSURE

AS: Consultant/advisor, Brabant, Zogenix.
AG, BSG: Employee, Zogenix; Stock ownership, Zogenix.
LL: Consultant/advisor and Speaker: LivaNova, Novartis, Ovid, Shire, UCB, Zogenix.
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LL, **BC**, and the KU Leuven University/Antwerp University Hospital may benefit financially from a royalty arrangement that is related to this research if Zogenix is successful in marketing its product, fenfluramine. The terms of this arrangement have been reviewed and approved by the KU Leuven University/Antwerp University Hospital.

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