Low-dose Fenfluramine Significantly Reduces Seizure Frequency in Dravet Syndrome: Update of the Prospective Study

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INTRODUCTION

- Dravet syndrome (DS) is a rare, severe, and often 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]
- We have recently reported similar findings in a new cohort of 9 DS patients treated with low-dose fenfluramine in a prospective study using a standardized protocol of assessments[6]
  - Here we present an update on the results of this study

METHODS

- Patients with diagnosis of DS (with or without *SCN1A* mutation) 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

- 9 patients (mean age, 15.0 years; range, 1.2-29.8 years) enrolled in the study and were treated with fenfluramine for a median duration of 2.1 years (range, 0.83-5.60 years) (**Table 1**)
- All patients had a typical core DS phenotype and a confirmed de novo mutation in *SCN1A* (**Table 1**)
- All patients were treated with at least 2 other antiepileptic drugs at study entry, and 3 patients had a vagal nerve stimulator with stable settings (**Table 1**)

Seizure Frequency

- Median frequency of major motor seizures was 15.0/month during the run-in period (**Table 2, Figure 1**)
- All patients demonstrated a decrease in frequency of major motor seizures that was evident as early as 3 months, with sustained benefit noted at 1 year (**Table 2, Figure 1**)
  - Median frequency of major motor seizures during the initial 3 months of fenfluramine treatment was 2.0/month (median decrease, 84%)
  - Median frequency of major motor seizures during the first 12 months of fenfluramine treatment was 1.0/month (median decrease, 79%)

Table 1: 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

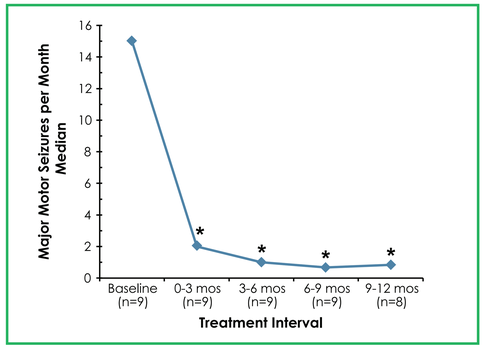
CLB, clobazam; F, female; FFA, fenfluramine; LEV, levetiracetam; M, male; STP, stiripentol; TPM, topiramate; VNS, vagal nerve stimulation; VPA, valproic acid.

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

Patient	Initial FFA Dose		Most Recent FFA Dose		Treatment Duration	Major Motor Seizures/Month[a] (% Reduction[c])			
	mg/day	mg/kg/day	mg/day	mg/kg/day	Years	3-month Baseline Period	0- to 3-month FFA Treatment[b]	0- to 12-month FFA Treatment	Total Treatment Period
1	10	0.27	20	0.41	5.60	15.0[d]	1.0[d] (-93%)	2.2[d] (-85%)	5.05[d] (-66%)
2	5	0.50	12.5	0.68	5.25	2.5[d]	2.0[d] (-20%)	0.9[d] (-63%)	0.4[d] (-82%)
3	5	0.29	10	0.61	1.49	0.4[d]	0 (-100%)	0.08[d] (-79%)	0.05[d] (-86%)
4	10	0.25	15	0.38	2.42	39.7[d]	5.6[d] (-86%)	6.7[d] (-83%)	9.3[d] (-76%)
5	5	0.10	15	0.26	1.91	2.0[d]	0 (-100%)	0.4[d] (-79%)	0.6[d] (-70%)
6	10	0.23	15	0.25	2.32	2.3[d]	1.3[d] (-44%)	0.9[d] (-61%)	1.9[d] (-20%)
7	10	0.17	15	0.27	1.58	18.3	12.4 (-32%)	13.2 (-28%)	10.9 (-40%)
8	5	0.21	7.5	0.27	0.98	20.4	3.3 (-84%)	1.0 (-95%)	1.0 (-95%)
9	10	0.16	15	0.24	0.83	23.8	6.9 (-71%)	–	3.7 (-85%)
Mean	**7.8**	**0.24**	**13.9**	**0.37**	**2.7**	**13.8**	**3.6 (-70%)**	**3.2 (-72%)**	**3.7 (-69%)**
Median	**10**	**0.23**	**15**	**0.27**	**2.1**	**15.0**	**2.0 (-84%)**	**1.0 (-79%)**	**1.9 (-76%)**

[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] % 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 (FFA).

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

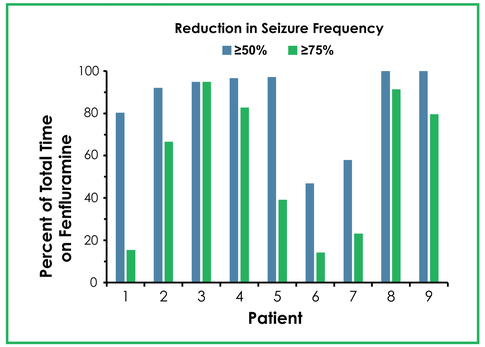


* $P<0.05$ compared with baseline period (Wilcoxon nonparametric test).

Responder Analysis (Figure 2)

- 6 of 9 patients (66%) demonstrated ≥50% reduction in frequency of major motor seizures for at least 90% of the time they were treated with fenfluramine (**Figure 2**)
- 5 of 9 patients (56%) experienced ≥75% reduction in frequency of major motor seizures for at least 60% of the time that they were treated with fenfluramine (**Figure 2**)

Figure 2. 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=5) and anorexia (n=4)
- No evidence of cardiac valvulopathy or pulmonary hypertension was observed in any patient on any echocardiogram
- One patient had a subnormal systolic function
  - Fractional shortening of 26% and ejection fraction of 53%
  - Due to mild hypokinesia of the interventricular septum
  - No clinical significance

CONCLUSIONS

- The results of this latest analysis of the new cohort suggest that low-dose fenfluramine provides significant improvement in seizure frequency while being generally well tolerated in DS patients
- When looking at month-by-month effectiveness, 7 of 9 patients experienced a ≥50% reduction in seizure frequency for at least 80% of the months they were being treated
- The effectiveness and safety of low-dose fenfluramine as add-on therapy for DS in the new prospective cohort supports previous findings

REFERENCES

1. Bayat A, Hjalgrim H, Moller RS. The incidence of *SCN1A*-related Dravet syndrome in Denmark is 1:22,000: a population-based study from 2004 to 2009. *Epilepsia*. 2015;56(4):e36-9.
2. Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in *SCN1A* mutation-positive Dravet syndrome. *Brain*. 2012;135(Pt 8):2329-36.
3. Bender AC, Morse RP, Scott RC, Holmes GL, Lenck-Santini PP. *SCN1A* mutations in Dravet syndrome: impact of interneuron dysfunction on neural networks and cognitive outcome. *Epilepsy Behav*. 2012;23(3):177-86.
4. Ceulemans B, Schoonjans A-N, Marchau F, Paelinck B, Lagae L. Five-year extended follow-up of 10 Dravet patients treated with fenfluramine. *Epilepsia*. 2016;57(7):e129-34.
5. Schoonjans A-N, Marchau F, Paelinck B, Lagae L, Ceulemans B. Long term efficacy and safety of low-dose fenfluramine treatment in Dravet syndrome: follow-up of the original patient cohort. Presented as part of the Zogenix Scientific Exhibit during the 70th Annual Meeting of the American Epilepsy Society, December 2-6, 2016, Houston, TX.
6. Schoonjans A-N, Paelinck B, Marchau F, Gammaitoni A, Gunning B, Galer B, et al. Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome. *Eur J Neurol*. 2016 Oct 28. [Epub ahead of print]

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