Long-Term Efficacy and Safety of Low-dose Fenfluramine Treatment in Dravet Syndrome: Follow-up of the Original Patient Cohort

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INTRODUCTION

- Dravet syndrome (DS) is a rare, severe, and treatment-resistant epileptic encephalopathy that usually presents in the first year of life[1]
- About 85% of patients have a mutation in *SCN1A*, the gene coding for the neuronal voltage-gated sodium channel alpha subunit[2]
- Fenfluramine (FFA), which was original marketed as an anorectic drug and used to treat adult obesity, was identified as having antiseizure activity in several case reports in the 1980s[3-5]
- Based on these and other reports, FFA was allowed to be prescribed for pediatric refractory epilepsy in Belgium under a Royal Decree
- In 2012, Ceulemans and colleagues originally reported on a cohort of 12 DS patients who had been treated with add-on low-dose FFA for up to 19 years[6]
  - 7 of 12 patients had been seizure-free for at least 1 year at the time of the report from this cohort (2010, mean seizure-free interval: 6 years, 7 months[6])
  - Similar efficacy was sustained through the end of 2014 in the 10 patients who were still being treated[7]
- Here we update the results of FFA treatment in this cohort through the end of 2015

METHODS

- All patients from the original cohort who continued to receive low-dose FFA at the end of 2010 were included and prospectively followed through the end of 2015
- Seizure frequency was derived from a seizure diary maintained by each patient's caregiver
- Adverse events (AEs) were recorded at each study visit
- Detailed echocardiographic examinations to assess cardiac valve structure and function were conducted at least annually
- At the most recent study visit, sleep quality and quality of life were assessed for patients and their parents/caregivers using 11-point visual analog scales (0=very poor, 10=very good)

RESULTS

- 10 patients (5 males, 5 females) from the original cohort continued to receive FFA from 2010 until the end of 2015 (**Table 1**)
  - The mean age at the most recent study visit was 25.1 years (range: 9-41 years)
  - The mean current dose of FFA was 16 mg/day (0.26 mg/kg/day; range: 0.12-0.42 mg/kg/day)
  - The mean treatment duration was 17.2 years (range: 7-28 years)

Table 1: Patient Demographics, Safety, and Cardiovascular Findings

Patient number*	Gender (M/F)	Current age	Mutation type *SCN1A*	Age at start FFA	Total duration of FFA treatment	FFA dose at last FU	AED(s) combined with FFA (at last consultation)	Side effects at last FU	Number of ECHOs	Echocardiographic findings	
										Previous findings	Most recent echocardiographic examination (year)
1	F	30y	Nonsense c.2584C>T	2y2m	28y	2x5 mg = 0.12 mg/kg/d	VPA + TPM	No	6	2012: slight thickened AML without dysfunction. 2014: normal	Normal (2016)
2	F	41y	Missense c.2644A>T	16y	25y	1x20 mg = 0.26 mg/kg/d	VPA	No	9	2015: trace of mitral regurgitation. No valvulopathy	Mild diastolic LV dysfunction (grade 1); normal valves (2016)
3	M	32y	Missense (2x) c.4351C>G and c.4467G>L	7y	24y	1x20 mg = 0.27 mg/kg/d	VPA	No	4	Since 2010: stable slight thickened aortic and tricuspid valve without dysfunction	Stable thickened aortic and tricuspid valve without dysfunction (2016)
4	M	26y	Deletion (frameshift mutation) c.2322-2324delCAC	4y	22y	1x20 mg = 0.33 mg/kg/d	VPA + CLB + LEV	No	7	Since 2013: stable slight thickened AML with tricuspid leaves without dysfunction	Stable slight thickened AML with tricuspid leaves without dysfunction (2016)
5	M	23y	Missense c.680T>G	1y4m	22y	5 mg - 10 mg = 0.27 mg/kg/d	VPA + TPM + Ethyl loflazepate	No	11	March 2014: slight thickened AML + tricuspid leaves without dysfunction	Normal (2016)
6	F	28y	–	13y	15y	2x10 mg = 0.20 mg/kg/d	VPA + LTG	Fatigue	7	Normal at all examinations	Trace of mitral regurgitation; no valvulopathy (2016)
9	F	19y	Missense c.5534A>C	7y	12y	2x10 mg = 0.29 mg/kg/d	STP + CLB + VPA	No	7	Normal at all examinations	Trace of mitral regurgitation; no valvulopathy (2016)
10	M	22y	Missense c.2792G>A	11y	10y	3x5 mg = 0.24 mg/kg/d	VPA + TPM + Ethyl loflazepate	Anorexia, behavioral changes	7	2013: Slight thickened AML without dysfunction. 2014 and 2015: normal	Trace of mitral regurgitation, no valvulopathy (2016)
11	M	21y	Splice acceptor mutation c.4853-1 G>C	13y	7y	2x5 mg = 0.19 mg/kg/d	VPA + TPM	Anorexia	6	2010 and 2013: slight thickened AML + tricuspid leaves without dysfunction 2014: normal	Trace of mitral regurgitation; no valvulopathy (2015)
12	F	9y	Nonsense c.1738C>T	1y10m	7y	2x5 mg = 0.42 mg/kg/d	VPA + TPM	Aggressive behavior	9	Normal at all examinations	Normal (2016)

*The same patient numbers are used as in the original article (Ceulemans et al. *Epilepsia*, 2012). Patient 7 and patient 8 stopped fenfluramine treatment respectively in 1999 and 2003 and are not included in the prospective follow-up study.
FU: follow-up; VPA: valproate; TPM: topiramate; LTG: lamotrigine; FFA: fenfluramine; AED, antiepileptic drug; ECHO, echocardiographs; CLB: clobazam; LEV: levetiracetam; STP: stiripentol; CZP: clonazepam; AML: anterior mitral leaflet; LV: left ventricle.

- Annual seizure frequency during the 6-year follow-up is shown in **Figure 1**
- 7 patients (70%) experienced prolonged periods of seizure freedom
  - 3 patients were seizure-free for the entire 6 years
  - 4 patients experienced seizure-free intervals of at least 2 years during the study period
  - At the most recent visit both caregivers and patients were reported to have good quality of sleep and good quality of life (**Table 2**)

Table 2: Quality of Sleep and Quality of Life Assessments in Patients and Their Parents

	Quality of Sleep (0-10)		Quality of Life (0-10)	
	Patient	Parent	Patient	Parent
Mean value at last consultation	8.7	7.2	7.9	7.9

For both quality of sleep and quality of life, 0 indicates extremely bad, and 10 indicates very good.

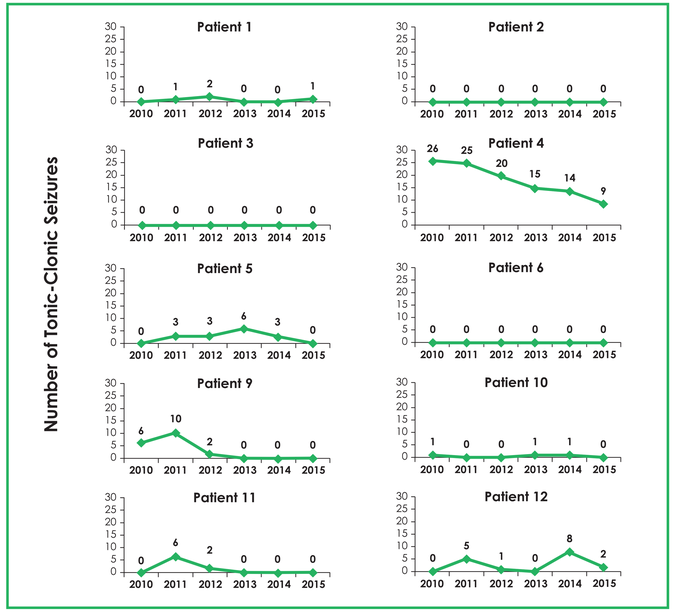
Safety

- 2 patients had mild and stable cardiac valve thickening on the most recent cardiac echocardiogram that was deemed to be clinically unimportant
- 1 patient had mild impaired diastolic function of the left ventricle
- No symptoms or echocardiographic signs of pulmonary hypertension were found
- 4 patients had trace or minimal mitral valve regurgitation (MR)
  - These findings were not clinically significant

Tolerability

- No patient withdrew from the study
- All parents indicated a much (n=5) to very much (n=5) improved global impression

Figure 1. Longitudinal Convulsive Seizure Frequency from 2010 to 2015



CONCLUSIONS

- Low-dose FFA continues to provide long-term, durable control of convulsive seizures while being well-tolerated in this cohort of DS patients
- Patients/caregivers reported high degrees of sleep quality and quality of life
- After up to 28 years of treatment, no patient has developed any clinically meaningful signs or symptoms of cardiac valvulopathy or pulmonary hypertension
- Controlled Phase 3 trials are ongoing to confirm the significant effectiveness and safety observed in this cohort

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