NEW virtual campus and online learning environment

ILAE ACADEMY

Improve your skills and knowledge in epileptology

- Work on your competencies
- Explore the course portfolio
- Track your progress
- Earn a certificate

The International League Against Epilepsy (ILAE) introduces highly interactive, practice-oriented online courses for healthcare professionals worldwide who diagnose and treat epilepsy.

The ILAE Academy offers:

- Competency-based e-learning for different levels of expertise[1]
- Content developed by ILAE experts
- Realistic cases covering most common epilepsies

EXPLORE AND REGISTER
www.ilae-academy.org

1. Blümcke, Ingmar, et al. "Roadmap for a competency-based educational curriculum in epileptology: report of the Epilepsy Education Task Force of the International League Against Epilepsy." *Epileptic Disorders* 21.2 (2019): 129-140.

ILAE/5/2020/PRINT

Received: 4 May 2020 | Revised: 18 August 2020 | Accepted: 19 August 2020

DOI: 10.1111/epi.16690

Epilepsia®

FULL LENGTH ORIGINAL RESEARCH

Efficacy and safety of Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: A real-world study

Nicola Specchio[1] | Nicola Pietrafusa[1] | Viola Doccini[2] | Marina Trivisano[1] | Francesca Darra[3] | Francesca Ragona[4] | Alberto Cossu[3] | Silvia Spolverato[3] | Domenica Battaglia[5] | Michela Quintiliani[5] | Maria Luigia Gambardella[5] | Anna Rosati[2] | Davide Mei[2] | Tiziana Granata[4] | Bernardo Dalla Bernardina[3] | Federico Vigevano[6] | Renzo Guerrini[3]

[1]Rare and Complex Epilepsy Unit, Department of Neuroscience, Bambino Gesù Children's Hospital IRCCS, Full Member of European Reference Network EpiCARE, Rome, Italy

[2]Neuroscience Department, A. Meyer Children's Hospital–University of Florence, Full Member of European Reference Network EpiCARE, Florence, Italy

[3]Child Neuropsychiatry, Department of Surgical Sciences, Dentistry, Gynecology, and Pediatrics, University of Verona, Verona, Italy

[4]Department of Pediatric Neuroscience, IRCCS Foundation Carlo Besta Neurological Institute, Full Member of the European Reference Network EpiCare, Milan, Italy

[5]Pediatric Neurology, Department of Woman and Child Health and Public Health, Child Health Area, A. Gemelli University Polyclinic Foundation, IRCCS, Catholic University of the Sacred Heart, Rome, Italy

[6]Department of Neuroscience, Bambino Gesù Children's Hospital IRCCS, Full Member of European Reference Network EpiCARE, Rome, Italy

Correspondence
Nicola Specchio, Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome, P.zza S. Onofrio 4, 00165 Rome, Italy.
Email: nicola.specchio@opbg.net

Abstract

Objective: Dravet syndrome (DS) is a drug-resistant, infantile onset epilepsy syndrome with multiple seizure types and developmental delay. In recently published randomized controlled trials, fenfluramine (FFA) proved to be safe and effective in DS.

Methods: DS patients were treated with FFA in the Zogenix Early Access Program at four Italian pediatric epilepsy centers. FFA was administered as add-on, twice daily at an initial dose of 0.2 mg/kg/d up to 0.7 mg/kg/d. Seizures were recorded in a diary. Adverse events and cardiac safety (with Doppler echocardiography) were investigated every 3 to 6 months.

Results: Fifty-two patients were enrolled, with a median age of 8.6 years (interquartile range [IQR] = 4.1-13.9). Forty-five (86.5%) patients completed the efficacy analysis. The median follow-up was 9.0 months (IQR = 3.2-9.5). At last follow-up visit, there was a 77.4% median reduction in convulsive seizures. Thirty-two patients (71.1%) had a ≥50% reduction of convulsive seizures, 24 (53.3%) had a ≥75% reduction, and five (11.1%) were seizure-free. The most common adverse event was decreased appetite (n = 7, 13.4%). No echocardiographic signs of cardiac valvulopathy or pulmonary hypertension were observed. There was no correlation between type of genetic variants and response to FFA.

Significance: In this real-world study, FFA provided a clinically meaningful reduction in convulsive seizure frequency in the majority of patients with DS and was well tolerated.

KEYWORDS

childhood epilepsy, convulsive seizures, Dravet syndrome, fenfluramine, SCN1A

Nicola Specchio and Nicola Pietrafusa contributed equally to this paper.

1 | INTRODUCTION

Dravet syndrome (DS) is a rare, drug-resistant, developmental, and epileptic encephalopathy with onset in infancy,[1] characterized by multiple types of epileptic seizures, developmental delay, cognitive impairment, and crouch gait.[2]

It is estimated that DS incidence ranges from 1 in 15 700 to 1 in 40 000. In >80% of patients, a sodium voltage-gated channel alpha subunit 1 gene (*SCN1A*) genetic variant can be demonstrated, although diagnosis is based on clinical criteria.[25]

Patients with DS have an increased risk of sudden unexpected death in epilepsy, with a mortality rate of 7%-18% under the age of 18 years.[6] A high frequency of generalized tonic-clonic seizures is a major risk factor for this outcome.[7]

Valproate, clobazam, and stiripentol are considered as first-line treatment in DS. Ketogenic diet, topiramate, and cannabidiol (CBD) represent second-line treatment choices. Levetiracetam, bromides, zonisamide, and vagal nerve stimulation can be taken in account as third line.[810]

The drugs most recently approved or nearing US Food and Drug Administration (FDA) and European Medicine Agency (EMA) approval are stiripentol, CBD, and fenfluramine (FFA). Stiripentol waas approved in the USA in 2018, whereas in Europe, Canada, and Japan it has been available since 2007 and 2012.[11,12] In 2018 and 2019, the FDA and EMA, respectively, approved the use of CBD (EMA as add-on with clobazam) for treating seizures in DS, based on a randomized controlled trial (RCT).[13,14] In June 2020, the FDA approved FFA for the treatment of seizures in patients with DS.

FFA was effective for the treatment of convulsive seizures in DS in open-label studies[1517] and in two placebo RCTs.[18,19] It was also reported to be effective for the treatment of nonconvulsive status epilepticus (NCSE).[20]

Although RCTs are required for FDA and EMA approval of an investigational drug, both regulatory agencies can authorize expanded access programs (EAPs), also referred as compassionate use. In the 2019, Zogenix supported an EAP of FFA in patients with a clinical diagnosis of DS, without echocardiographic signs of cardiac valve disfunction and pulmonary arterial hypertension. Here, we evaluate efficacy and safety of add-on FFA in a series of patients with DS consecutively enrolled within the EAPs at four Italian pediatric centers, in a real-world clinical practice context.

Key Points

- DS is a drug-resistant, infantile onset epilepsy syndrome with multiple seizure types and developmental delay
- We administered FFA to 52 DS patients in the context of a recently approved early access program
- The median follow-up was 9.0 months; at last follow-up visit, there was a 77.4% median reduction in convulsive seizures
- Fifty-three percent of patients had a ≥75% reduction, and 11.1% were seizure-free
- The most common adverse event was decreased appetite (13.4%); no signs of cardiac valvulopathy or pulmonary hypertension were observed

2 | MATERIALS AND METHODS

2.1 | Study design and patient population

This is a prospective independent, open-label study conducted at four Italian epilepsy centers prescribing FFA in the context of an EAP granted by Zogenix. All patients with a clinical diagnosis of DS, consecutively seen, whose parents accepted FFA treatment proposal were enrolled if they had no echocardiographic signs of cardiac valve disfunction and pulmonary arterial hypertension and had been on stable doses of antiseizure medications (ASMs) for ≥4 weeks. An institutional review board at each site approved the treatment and study protocols, and parents/caregivers provided written informed consent before any study-related assessments. The study was conducted in accordance with the Good Clinical Practice guidelines and local standard operating procedures.

2.2 | Procedures and study design

Demographic and clinical data, including the *SCN1A* genetic variants, were collected. Genetic variants were stratified into three groups: loss of function, missense in the pore region (S5-S6), and missense outside the pore region.

Primary outcome was efficacy of FFA; secondary outcome was tolerability.

The study was planned with a 28-day baseline period and a titration period, followed by a maintenance period. During the baseline period, parents/caregivers completed written diaries of all countable seizure types. We collected data on convulsive seizures only, defined as hemiclonic, tonic, clonic, generalized tonic-clonic, and focal with clearly observable motor signs. Concomitant ASMs were recorded at baseline. After the baseline observation period, patients received FFA hydrochloride (2.5 mg/mL) in oral solution (Zogenix) at a gradually increasing dose from 0.2 to 0.7 mg/kg/d (twice daily) until tolerated or a maximum dose of 26 mg/d (17 mg/d if in coadministration with stiripentol). Duration of the titration period and maximum dose were at

the physician's discretion, based on clinical response. During the maintenance period, dose changes of FFA and other ASMs were allowed and recorded. Clinical evaluation including seizure count and evaluation of adverse events (AEs) was done every 3 months.

2.3 | Assessment of efficacy

The primary efficacy endpoint was the percentage change in the frequency of convulsive seizures from baseline per 28 days measured through last follow-up visit (titration plus maintenance period). The frequency was calculated as the number of convulsive seizures recorded after FFA initiation, divided by the number of days from titration to last follow-up visit (LFV). The result was multiplied by 28 for a monthly frequency. Both median and mean percentage change from baseline were calculated using the following formula: (seizure frequency through LFV − seizure frequency during baseline) × 100/seizure frequency during baseline.

We noted the proportion of patients who had ≥25%, ≥50%, ≥75%, or 100% reduction in convulsive seizures from baseline; those with seizure reduction ≥ 50% were defined as responders. The proportion of patients with an increase or no change (≥0% and <25%) in seizure frequency was also recorded. These data were calculated as detailed above. The proportions of seizure-free patients and of those with no more than one convulsive seizure for 6 months were also recorded. Finally, to facilitate comparability of findings between this study and previous RCTs, we calculated the monthly median percentage reduction in convulsive seizures and the percentages of responders at 3 months of follow-up.

We evaluated the effect of FFA also on nocturnal and self-induced seizures. To evaluate a difference in efficacy by age, we also compared seizure frequency in patients aged <6 years and those >6 years of age. At last follow-up visit, we administered the Clinical Global Impression (CGI) scale to caregivers to assess the effects of FFA on behavior, autonomy, communication, and motor skills. We applied the chi-square test to determine whether significant differences had emerged in the items explored.

2.4 | Assessment of tolerability

The number and percentage of subjects with AEs were summarized in terms of severity and relationship to study drug. Serious AEs (SAEs) were summarized separately. Cardiovascular safety was assessed via Doppler echocardiogram at baseline and every 6 months (or every 3 months at the physician's discretion).

2.4.1 | Statistical analysis

All demographic, clinical, efficacy, and safety data were analyzed. Continuous data were summarized using descriptive statistics including means, standard deviations, medians, lower and upper quartiles, and ranges. Categorical variables were summarized with frequencies and percentages. A statistical hypothesis testing was planned; for categorical results, a chi-square test or the Fisher exact test was performed, as appropriate. Wilcoxon signed-rank test was used for continuous variables. A P value ≤ .05 was considered statistically significant. Statistical analysis was performed using R version 3.2.3 (R Foundation for Statistical Computing, https://www.r-project.org/).

3 | RESULTS

3.1 | Demographics and baseline characteristics

Fifty-two patients (29 males) with a median age of 8.6 years (interquartile range [IQR] = 4.1-13.9, range = 2.1-28.6), all carrying *SCN1A* genetic variants, were enrolled (Table 1; see Table S1). The median follow-up was 9.0 months (IQR = 3.6-9.5, range = 3.0-14.9). Mean patient weight was 35.0 kg (range ± standard deviation [SD] = 11.0-97.0 ± 21.5). Mean dose of FFA was 0.46 mg/kg/d (range ± SD = 0.2-0.7 ± 0.16). Patients were previously treated with a median of three ASMs (IQR = 2-3). At the beginning of FFA administration, patients were on a median of three ASMs (IQR = 2-3); the most commonly used drugs were valproate (n = 47), clobazam (n = 42), stiripentol (n = 31), topiramate (n = 5), and clonazepam (n = 5). Three patients had previously been treated with an artisanal formulation of CBD. Valproic acid blood levels, measured before starting FFA and at last follow-up, did not differ significantly (77.4 μg/mL vs 71.1 μg/mL, P = .2).

3.2 | Efficacy

Data on seizure frequency were available for 45 patients (86.5%). The remaining seven patients were excluded from the analysis of efficacy because data collection was incomplete (Table 2).

Monthly median convulsive seizure frequency was 6.0 (IQR = 4-14.0) at baseline and 1.9 (IQR = 0.5-4.5) at last follow-up (Figure 1), with a median 77.4% (IQR = 43.6-94.4) percentage reduction in convulsive seizure frequency.

Thirty-two of 45 patients (71.1%) experienced a ≥50% reduction in convulsive seizure frequency with a mean FFA dose of 0.41 mg/kg/d (range ± SD = 0.20-0.80 ± 0.14). Twenty-four patients (53.3%) achieved ≥75% reduction, and five patients (11.1%) became seizure-free (Figure 2).

TABLE 1 Baseline demographics and clinical features (N = 52)

Characteristic	Value[a]
Patients	52
Sex	
Male	29 (54.7)
Female	24 (45.3)
Age at enrollment, y	8.6 (4.1-13.9, range = 2.1-28.6)
Children, age <18 y	46 (88.5)
Adults	6 (11.5)
Weight, kg	35.3 (11.0-97.2 ± 21.5)
Previous ASMs	2 (1-3)
Current ASMs, patients, n (%); dose, mg/kg/d	
VPA	47 (90.4); 20.7 (8.8-40 ± 7.7)
CLB	42 (80.7); 0.4 (0.14-1.0 ± 0.2)
STP	31 (59.6); 30.0 (13.5-52.3 ± 10.5)
TPM	5 (9.6); 4.7 (1.4-8 ± 1.9)
CZP	5 (9.6); 0.07 (0.02-0.1 ± 0.05)
LEV	3 (5.8); 35.5 (31.2-45.4 ± 5.8)
PB	3 (5.8); 2.0 (1.6-2.5 ± 0.4)
ETS	2 (3.8); 27.6 (20.0-35.3 ± 7.6)
ZNS	1 (1.9); 3.5
KD	2 (3.8)
VPA blood levels, μg/mL	
At enrollment	77.4 (35.0-125.0 ± 18.0)
At last follow-up	71.1 (45.0-105.0 ± 13.2)
FFA dose, mg/kg/d	0.46 (0.2-0.7 ± 0.16)
Follow-up, mo	9.0 (3.6-9.5, range = 3.0-14.9)
Convulsive seizures	
GTCS	35 (67.3)
Focal, with observable motor signs	11 (21.1)
Hemiclonic	9 (17.3)
Other type of seizures	
Focal, without clearly observable motor signs	8 (15.4)
Atypical absence	9 (17.3)
Myoclonic	5 (9.6)
Baseline convulsive seizure frequency	
Mean	15.5 (1-100 ± 20.7)
Median	6 (4.0-14.0)
Titration period, d	13.4 (7.0-21.0 ± 3.1)
FFA withdraws	
Inefficacy	1 (1.9)
Increased seizure frequency	2 (3.8)
Refractory SE	1 (1.9)

Abbreviations: ASM, antiseizure medication; CLB, clobazam; CZP, clonazepam; ETS, ethosuximide; FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; KD, ketogenic diet; LEV, levetiracetam; PB, phenobarbital; SE, status epilepticus; STP, stiripentol; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

[a]Values are given as n (%), mean (range ± standard deviation), or median (1st quartile-3rd quartile).

Five (11.1%) patients remained seizure-free for at least 6 months, and another four (8.9%) experienced no more than a single convulsive seizure during the same time interval.

Considering 3 months of follow-up, we found a median percentage reduction of convulsive seizures of 73.3 (IQR = 44.5-93.3) and a reduction in convulsive seizures of ≥50% in 68.9% of patients (Table 2).

Monthly median percentage reduction in convulsive seizures in patients with clearly observable focal seizures with motor signs or hemiclonic seizures was 87.1% compared to 74.5% in those with generalized tonic-clonic seizures, with no statistically significant differences ($P = .375$; see also Table 2).

When considering the age at the time of the study, we could not find a significant difference in the monthly median percentage reduction of convulsive seizures ($P = .08$) between patients younger than 6 years and those older than that age. We could only identify a trend suggesting greater efficacy in younger patients (84.3% vs 70.1%; Table 2).

When analyzing the effects of the coadministration of stiripentol on efficacy, we observed that cotreatment with this drug resulted in a monthly median percentage reduction of convulsive seizures of 72.7%, versus 90.6% observed in patients not taking it, and the response rate was, respectively, 65.6% and 81.2%, approaching statistical significance ($P = .085$).

Seven patients (15.6%) had not achieved a significant reduction in seizure frequency, and five of them (71.4%, or 11.1% of the total number) experienced a median percentage worsening of convulsive seizures of 44.8 (IQR = 12.0-86.6).

FFA determined a reduction in the frequency of nocturnal seizures in 56.0% of patients (14 of 25 presenting sleep-related seizures) and a reduction in the frequency of self-induced seizures in 60.0% of patients (three of five).

Titration varied from 7 to 21 days, with an average of 13.4 days. There were no differences in titration duration between different investigators. In patients with loss of appetite, the mean titration period was 13 days, and in the remaining patients it was 13.11 days. We could not find differences in efficacy either.

FFA treatment allowed a simplification of baseline treatment in 24 patients (46.1%) with tapering of other ASMs;

TABLE 2 Efficacy data (n = 45)

Characteristic	Value[a]
Last follow-up convulsive seizure frequency	
Mean	3.9 (0.0-4.8 ± 17.6)
Median	1.9 (IQR = 0.5-4.5)
Percentage reduction in CS frequency from baseline	
Mean	57.1 (54.4)
Median	77.4 (53.6-93.6)
0-<25 reduction in CS frequency	8 (17.8)
≥25% reduction in CS frequency	37 (82.2)
≥50% reduction in CS frequency	34 (75.6)
≥75% reduction in CS frequency	25 (55.6)
100% reduction in CS frequency	5 (11.1)
Seizure-free for 6 mo	5 (11.1)
One seizure in 6 mo	4 (8.9)
Three months of follow-up convulsive seizure frequency	
Percentage reduction in CS frequency from baseline	73.4 (44.5-93.3)
≥50% reduction in CS frequency	31/45 (68.9)
Patients with GTCS	32 (71.1)
Percentage reduction in CS frequency from baseline	74.5 (42.3-93.8)
≥50% reduction in CS frequency	22/32 (68.7)
Patients without GTCS[b]	13 (28.9)
Percentage reduction in CS frequency from baseline	87.1 (61.6-98.1)
≥50% reduction in CS frequency	11/13 (84.6)
Patients younger than 6 y	17/45 (37.8)
Percentage reduction in CS frequency from baseline	84.3 (68.9-98.1)
≥50% reduction in CS frequency	14/17 (82.3)
Patients older than 6 y	28/45 (62.2)
Percentage reduction in CS frequency from baseline	70.1 (41.6-89.4)
≥50% reduction in CS frequency	18/28 (64.3)
Patients with STP	29 (64.6)
Percentage reduction in CS frequency from baseline	72.7 (32.9-87.1)
≥50% reduction in CS frequency	19/29 (65.5)
Patients without STP	16 (35.5)
Percentage reduction in CS frequency from baseline	90.6 (62.3-98.3)
≥50% reduction in CS frequency	13/16 (81.2)

Abbreviations: CS, convulsive seizures; GTCS, generalized tonic-clonic seizures; IQR, interquartile range; STP, stiripentol.

[a]Values are given as n (%), mean (range ± standard deviation), or median (1st quartile-3rd quartile).

[b]Patients with focal (with observable motor signs) and hemiclonic seizures.

in six of 31 patients (19.3%) with concomitant stiripentol, the overall dose of the latter was reduced; moreover, in six patients (11.5%), one of the concomitant ASMs was discontinued. More specifically, in seven patients ASMs were stopped or lowered after 2 consecutive months of seizure freedom; two of them experienced seizure recurrence. In four additional patients, a simplification of concomitant ASMs was performed following 25%-75% reduction of seizure frequency. In three remaining patients who did not benefit from FFA addition, reduction of coadministered drugs, carried out to decrease the drug load, did not influence seizure frequency.

Looking at correlations between clinical/demographic features and outcome (responders vs nonresponders), we could not find a statistically significant difference. A higher number of baseline concomitant and previous ASMs correlated with nonresponders (respectively, $P = .04$ and $P = .02$; see Table S2). Correlation between genetic variant subgroups and response to FFA failed to uncover any association ($P = .2$).

The CGI scale, administered to 49 patients/parents at last follow-up, indicated improvements in different items, including behavior in 21 patients (42.8%, $P = .32$), autonomy in 20 (40.2%, $P = .12$), communication in 28 (57.1%, $P = .003$), and motor skills in 21 (42.8%, $P = .02$). Details are presented in Table S4.

3.3 | Safety

Data on safety were available for all patients. The most common AE was decreased appetite (n = 7, 13.4%; Table 3). This AE was apparent at a mean FFA dose of 0.43 mg/kg/d; it was mild in most patients (n = 6) and led to dose reduction in three. Three of seven patients who reported decreased appetite experienced a clinically irrelevant loss of weight, in none of them resulting in FFA discontinuation. One patient subsequently withdrew topiramate, recovering a normal appetite.

Other AEs were observed in six patients (11.5%). One patient had interstitial pneumonia (SAE), which required hospitalization. One patient manifested temporary periungual cyanosis (mild AE). During FFA administration, one patient experienced myoclonic seizures, which had never been observed before (moderate AE); one patient manifested an increase of seizure frequency, and one manifested refractory status epilepticus (SE; SAE with hospitalization); in the latter two patients, FFA was withdrawn.

In two patients, worsening of fever-related seizures was observed; one of them had a prolonged seizure during fever (SAE with hospitalization), and another experienced recurrent febrile seizures that did not respond to endorectal diazepam.

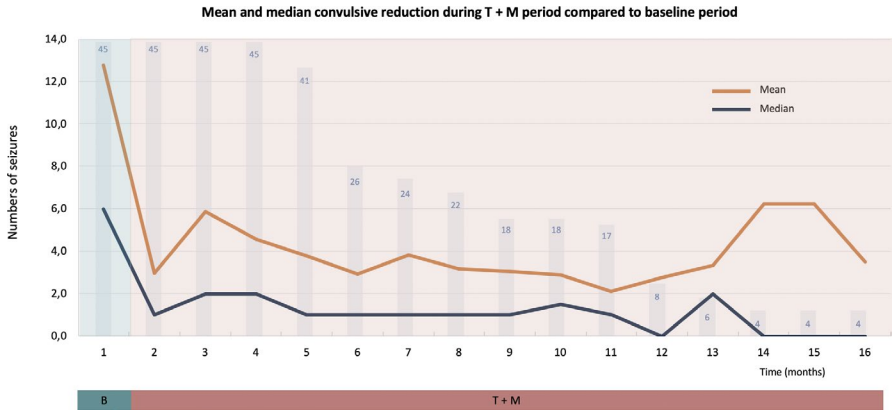

FIGURE 1 The graph shows the mean and median absolute reduction in monthly frequency of convulsive seizures during the titration (T) and maintenance (M) period, compared with the baseline observation period (B). The figure shows, in parallel, the number of patients in follow-up

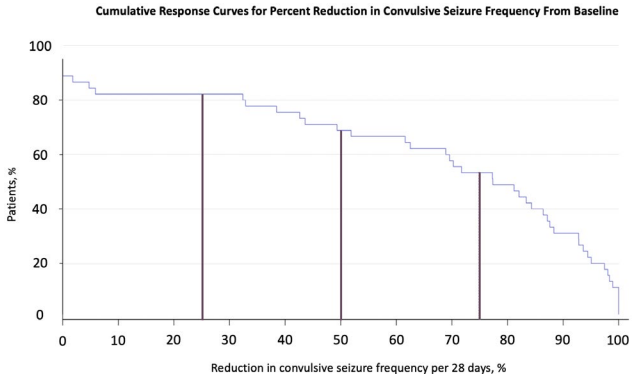

FIGURE 2 Cumulative response curves for percentage reduction in convulsive seizure frequency from baseline. Results are plotted for combined titration and maintenance periods. Vertical lines represent 25%, 50%, and 75% reduction in convulsive seizure frequencies; percentages correspond to the proportion of patients who met or exceeded each response level

TABLE 3 Adverse events reported (N = 52)

Characteristic	Value[a]
Decreased appetite	7 (13.2)
Outcome	
Resolved	2/7 (28.6)
Not resolved/ongoing	5/7 (71.4)
Severity	
Mild	6/7 (85.7)
Moderate	1/7 (14.3)
Decreased weight	3/7 (42.8)
Action taken with FFA	
Reduction of FFA	3/7 (42.8)
None	4/7 (57.2)
Other AEs	6/52 (11.3)[b]
SAE	4/52 (7.5)
Hospitalization	2/52 (3.7)
FFA total daily dose, mg/kg/d	0.48 (0.3-0.8 ± 0.14)
Normal echocardiogram	52/52 (100)

Abbreviations: AE, adverse event; FFA, fenfluramine; SAE, serious AD.

[a]Values are given as n (%) or mean (range ± standard deviation).

[b]See text.

None of the patients experienced clinical or echocardiographic signs of cardiac valvulopathy or pulmonary hypertension.

4 | DISCUSSION

DS is characterized by a high seizure burden, associated with a series of neurological comorbidities such as developmental and motor delay, and behavioral disturbances.[2] Prolonged convulsive seizures in DS often require emergency room admission.[21] The severity and extreme resistance to medications results in an urgent need for developing new and more effective pharmacologic treatments.

In this first open-label, real-world treatment experience with FFA in DS, we documented that add-on FFA administration can provide a durable and clinically significant reduction in convulsive seizure frequency in the majority of patients. Similar results from retrospective and prospective open-label studies in the Belgian DS cohort have been reported in a small group of patients who were treated for over 28 years, based on maintained efficacy, in the absence of signs of valvulopathy.[1517]

We found a median percentage reduction of convulsive seizures of 77.4 and a reduction in convulsive seizures of ≥50% in 71.1% of patients. Even considering differences in study design, results observed in our cohort seem to be slightly better than those reported in the two prospective, double-blind, placebo-controlled trials published earlier (Figure 3).[18,19] When analyzing our data with respect to a 3-month follow-up period, we found a median percentage reduction of convulsive seizures of 73.3, with a ≥50% reduction in 68.9% of patients. These results indicate a slightly better efficacy than observed in recent RCTs.

One factor that may explain the more favorable response we recorded is the possibility of adjusting and personalizing

the dose. One hundred nineteen[18] and 87[22] DS patients were enrolled in two recently published RCTs. In the larger trial (patients without stiripentol), which featured two arms of FFA, 0.2 and 0.7 mg/kg/d, the percentages of ≥50% responders were 38% and 68%, respectively, versus only 5% in the placebo group. In the 0.7-mg/kg/d group, 8% of patients were seizure-free during the 14-week trial duration, and the median reduction in seizure frequency was 74.9%.[18] In the other study, which included patients cotreated with stiripentol, ≥50% responders at 0.4 mg/kg/d were 54% in the FFA arm compared to 5% in the placebo group; the median percentage reduction from baseline in convulsive seizures was 63.1.[19] The preliminary results of an interim analysis of a long-term open-label extension study showed that 64.4% of patients had a ≥50% reduction of convulsive seizures, and 41.2% experienced a ≥75% reduction.[23] Overall, in this extension study, efficacy remained stable over >1-year follow-up, with an average decrease of monthly convulsive seizure frequency of 66.8%.[23] The RCT evaluating the efficacy of stiripentol, added to valproic acid and clobazam in DS,[12] documented a ≥50% reduction in convulsive seizures in 71% of patients, and a significant reduction of episodes of SE.[12]

A recent first description of a patient with DS with NCSE successfully treated with 0.6-mg/kg/d oral load of FFA[20] warrants further investigations (Table 4).

CBD has recently been approved for the treatment of DS based on results of a trial showing that 43% of patients on CBD and 27% of those on placebo experienced at least 50% seizure reduction.[13]

The long-term effects of add-on CBD were reported for patients with DS and Lennox-Gastaut syndrome in an open-label study with a 50% monthly reduction of major motor seizures.[24]

Overall, stiripentol associated with clobazam, FFA, and CBD associated with clobazam are three promising options for patients with DS. Although no comparative trials have been performed, figures emerging from published studies suggest a slight superiority of FFA on convulsive seizures.[25]

In our open-label study, FFA treatment allowed a reduction in the number of associated ASMs, resulting in discontinuation of stiripentol in 13.4% of patients, and of a different drug in 26.9%. Reducing the ASM load is highly warranted in DS, as most patients are on a median of three ASMs, and 38% are still experiencing weekly seizures.[21,26]

Although we did not observe a greater efficacy of FFA in children treated sooner after seizure onset, future studies should specifically address FFA efficacy in the early stages to fully assess its potential as a first-line treatment option.

Assessment obtained by the CGI scale suggested that FFA treatment was accompanied by improved behavior, autonomy, communication, and motor skills. Although assessing behavioral issues in children with severe encephalopathies is always difficult, and providing inferences based on a scale nears oversimplification, we consider this preliminary observation of interest and worth a specific study design in future trials.

A relatively small percentage of our patients did not achieve a significant reduction in seizure frequency, and 11.1% experienced seizure worsening. Among them, one patient experienced, while on FFA, recurrence of convulsive SE that was nonresponsive to common treatments

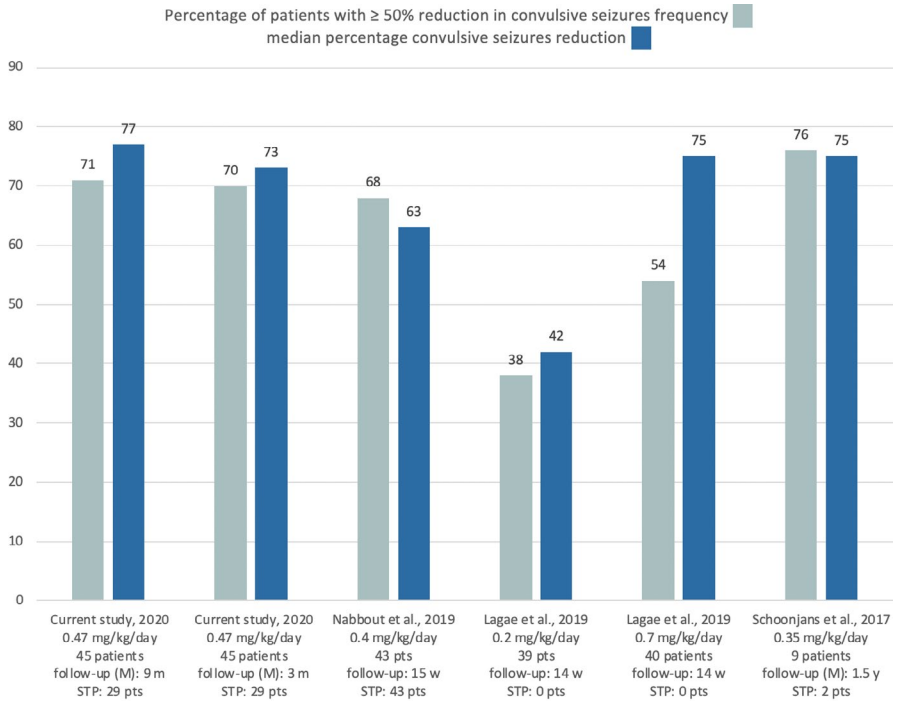

FIGURE 3 Comparison of the percentages of patients with ≥50% reduction in seizure frequency and the median percentage reduction of monthly frequency of seizures in different studies. The figure also shows the mean dose of fenfluramine (mg/kg/d), total number of patients, follow-up, and number of treated with stiripentol in the different studies. M, median; m, months; pts, patients; STP, patients with stiripentol; w, weeks

TABLE 4 Most common concomitant ASM dose adjustments (N = 52)

Characteristic	Value, n (%)
Patients with STP	31 (59.6)
STP reduction	6 (11.5)
STP discontinuation	1 (1.9)
Other ASM reduction	8 (15.4)
Other ASM discontinuation	6 (11.5)

Abbreviations: ASM, antiseizure medication; STP, stiripentol.

(benzodiazepine, phenobarbital), and required anesthesiologic intervention with deep sedation. A previous report mentioned a patient in whom FFA was discontinued due to seizure worsening.[19] Looking at clinical characteristics of patients experiencing worsening of seizures in our series, we could not single out a specific phenotypic profile, or a particular form of DS. Mutation types did not differ either, if compared with the overall sample of patients. Because fluctuations of seizure frequency are frequently seen in DS, future FFA treatment studies will focus on whether its use definitely carries a risk of seizure worsening in some patients.

The AE profile of FFA in our DS cohort appeared to be mild when compared with earlier experiences. We observed anorexic effects, usually mild, early in treatment in 13.4%. None of the patients withdrew FFA due to AEs. In the two previous RCTs, adverse effects on appetite were seen in 38%[18] and 44%[19] of patients; weight decrease was seen in a few patients, and only one experienced weight loss that led to drug discontinuation.[18]

Absence of clinical or echocardiographic signs of cardiac valvulopathy or pulmonary hypertension is consistent with previous studies, where only traces of regurgitation, which is a normal physiologic finding and cannot be considered evidence of valve dysfunction,[27] were observed during a median of 256 days.[18,22,28] Although FFA appears to be safe, further studies are necessary to assess its long-term safety on cardiac valves, even considering that 40 mg/d of FFA carries a 9.2-fold (95% confidence interval = 2.1-40.8) lower risk of severe valvulopathy than 60 mg/d when used as a treatment for adult obesity, most commonly in combination with phentermine.[29]

We found FFA coadministration not to cause significant differences in valproate plasma levels. It was previously reported that FFA does not significantly modify the pharmacokinetics of valproate, clobazam (and nor-clobazam), and stiripentol; however, the association of stiripentol, clobazam, and valproate might have effects on the pharmacokinetics of FFA and norfenfluramine, and therefore, FFA should be adjusted and reduced when added to the previously mentioned triad of drugs.[30] We found no statistical difference in treatment efficacy when comparing patients with versus those without stiripentol ($P = .085$). However, in view of the small sample size and of the pharmacokinetics of these ASMs, this aspect should be investigated further.

We found no evidence that the type *SCN1A* genetic variant may influence sensitivity to FFA; again however, studies with a considerably larger number of patients will clarify this aspect.

Based on studies on zebrafish models of DS, FFA documented its activity on the serotonin receptors and sigma-1 receptors that seem to have a role in mediating seizure activity in DS.[31,32] The selective agonism on 5-HT1D and 5-HT2C and antagonism on sigma-1 receptors might be one of the mechanisms of action of FFA, which seems to be targeted for DS patients. Repurposing of other medications that act on serotonin receptors has been recently hypothesized.[33]

4.1 | Study limitations

This study is limited by the small sample size, the relatively short median follow-up, the open-label design, and lack of a control group.

5 | CONCLUSIONS

Efficacy shown by FFA in reducing convulsive seizures in our cohort, if confirmed by future RCTs, might in the near future support an indication to use FFA as a first-line treatment for DS. We emphasize that, although we have reported that lower doses of FFA were as effective as those used in previous RCTs, based on clinical improvement we reduced the overall load of concomitant medications, and no evidence of interactions with valproate emerged; our observations are preliminary and additional studies are needed to confirm them.

In conclusion, FFA was safe and provided sustained, clinically meaningful convulsive seizure reduction in this real-world study. Other studies are needed to better establish the long-term safety and efficacy, and to clarify the response profile of DS patients to FFA.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ACKNOWLEDGMENTS

We thank the patients and their families for participation in this study; and Associazione Dravet Italia Onlus (http://dravet-italia.org/), which provided useful support through access to the RESIDRAS database (National Registry on Dravet Syndrome and other syndromes related to *SCN1A* and

PCDH19 genetic variants). This study was done also through a collaboration of Italian EpiCARE centers.

CONFLICT OF INTEREST

All authors were subinvestigators or principal investigators in the clinical trials ZX008-1502 and ZX008-1503, sponsored by Zogenix. N.S., N.P., M.T., F.V., and R.G. have received consulting fees from Zogenix. None of the other authors has any conflict of interest to disclose.

ORCID

Nicola Specchio https://orcid.org/0000-0002-8120-0287
Nicola Pietrafusa https://orcid.org/0000-0003-2446-796X
Marina Trivisano https://orcid.org/0000-0002-9841-8581
Alberto Cossu https://orcid.org/0000-0001-6945-6151
Anna Rosati https://orcid.org/0000-0002-8754-7214
Davide Mei https://orcid.org/0000-0001-6790-6251
Tiziana Granata https://orcid.org/0000-0002-0170-6836
Federico Vigevano https://orcid.org/0000-0001-7513-0051
Renzo Guerrini https://orcid.org/0000-0002-7272-7079

REFERENCES

1. Cetica V, Chiari S, Mei D, Parrini E, Grisotto L, Marini C, et al. Clinical and genetic factors predicting Dravet syndrome in infants with SCN1A mutations. Neurology. 2017;88:1037–44.
2. Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American consensus panel. Pediatr Neurol. 2017;68:18–34.
3. Dravet C, Bureau M, Bernardina BD, Guerrini R. Severe myoclonic epilepsy in infancy (Dravet syndrome) 30 years later. Epilepsia. 2011;52:1–2.
4. Depienne C, Trouillard O, Saint-Martin C, Gourfinkel-An I, Bouteiller D, Carpentier W, et al. Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients. J Med Genet. 2009;46:183–91.
5. Bayat A, Hjalgrim H, Møller 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:e36–e9.
6. Skluzacek JV, Watts KP, Parsy O, Wical B, Camfield P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. Epilepsia. 2011;52:95–101.
7. Cooper MS, Mcintosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, et al. Mortality in Dravet syndrome. Epilepsy Res. 2016;128:43–7.
8. Wirrell EC, Nabbout R. Recent advances in the drug treatment of Dravet syndrome. CNS Drugs. 2019;33:867–81.
9. Nabbout R, Copioli C, Chipaux M, Chemaly N, Desguerre I, Dulac O, et al. Ketogenic diet also benefits Dravet syndrome patients receiving stiripentol: a prospective pilot study. Epilepsia. 2011;52:e54–e7.
10. Zamponi N, Passamonti C, Cappanera S, Petrelli C. Clinical course of young patients with Dravet syndrome after vagal nerve stimulation. Eur J Paediatr Neurol. 2011;15:8–14.
11. Cross JH, Caraballo RH, Nabbout R, Vigevano F, Guerrini R, Lagae L. Dravet syndrome: treatment options and management of prolonged seizures. Epilepsia. 2019;60(S3):S39–48.
12. Chiron C, Marchand MC, Tran A, Rey E, D'Athis P, Vincent J, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. Lancet. 2000;356:1638–42.
13. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med. 2017;376:2011–20.
14. Arzimanoglou A, Brandl U, Cross JH, Gil-Nagel A, Lagae L, Landmark CJ, et al. Epilepsy and cannabidiol: a guide to treatment. Epileptic Disord. 2020;22:1–14.
15. Ceulemans B, Boel M, Leyssens K, Van Rossem C, Neels P, Jorens PG, et al. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. Epilepsia. 2012;53:1131–9.
16. Ceulemans B, Schoonjans AS, Marchau F, Paelinck BP, Lagae L. Five-year extended follow-up status of 10 patients with Dravet syndrome treated with fenfluramine. Epilepsia. 2016;57:e129–e34.
17. Schoonjans A, Paelinck BP, Marchau F, Gunning B, Gammaitoni A, Galer BS, et al. Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome: a prospective study of a new cohort of patients. Eur J Neurol. 2017;24:309–14.
18. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2019;394:2243–54.
19. Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, et al. Fenfluramine for treatment-resistant seizures in patients with Dravet syndrome receiving stiripentol-inclusive regimens: a randomized clinical trial. JAMA Neurol. 2019;77:300–8.
20. Specchio N, Pietrafusa N, Ferretti A, Trivisano M, Vigevano F. Successful use of fenfluramine in nonconvulsive status epilepticus of Dravet syndrome. Epilepsia. 2020;61:831–3.
21. Aras LM, Isla J, Mingorance-Le MA. The European patient with Dravet syndrome: results from a parent-reported survey on antiepileptic drug use in the European population with Dravet syndrome. Epilepsy Behav. 2015;44:104–9.
22. Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, et al. Fenfluramine for treatment-resistant seizures in patients with Dravet syndrome receiving stiripentol-inclusive regimens. JAMA Neurol. 2019;77:300–8.
23. Lagae L, Sullivan J, Nabbout R, Pringsheim M, Farfel G, Lock M.Fenfluramine HCL (Fintepla®) provides long-term clinically meaningful reduction in seizure frequency: results of an open-label extension study. Paper presented at: American Epilepsy Society Annual Meeting; November 30–December 4, 2018; New Orleans, LA.
24. Laux LC, Bebin EM, Checketts D, Chez M, Flamini R, Marsh ED, et al. Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: expanded access program results. Epilepsy Res. 2019;154:13–20.
25. Chiron C. Stiripentol for the treatment of seizures associated with Dravet syndrome. Expert Rev Neurother. 2019;19:301–10.
26. De Liso P, Chemaly N, Laschet J, Barnerias C, Hully M, Leunen D, et al. Patients with Dravet syndrome in the era of stiripentol: a French cohort cross-sectional study. Epilepsy Res. 2016;125:42–6.
27. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017;30:303–71.

28. Lai W, Pringsheim M, Farfel G.Long-term cardiovascular safety of Fintepla® (fenfluramine HCl oral solution) in the treatment of Dravet syndrome: interim analysis of an open-label safety extension study. Paper presented at: American Epilepsy Society Annual Meeting; November 30–December 4, 2018; New Orleans, LA.
29. Li R, Serdula MK, Williamson DF, Bowman BA, Graham DJ, Green L. Dose-effect of fenfluramine use on the severity of valvular heart disease among fen-phen patients with valvulopathy. Int J Obes. 1999;23:926–8.
30. Boyd B, Smith S, Gammaitoni A, Galer BS, Farfel GM. A phase I, randomized, open-label, single-dose, 3-period crossover study to evaluate the drug-drug interaction between ZX008 (fenfluramine HCl oral solution) and a regimen of stiripentol, clobazam, and valproate in healthy subjects. Int J Clin Pharmacol Ther. 2019;57:11–9.
31. Sourbron J, Schneider H, Kecskés A, Liu Y, Buening EM, Lagae L, et al. Serotonergic modulation as effective treatment for Dravet syndrome in a zebrafish mutant model. ACS Chem Neurosci. 2016;7:588–98.
32. Sourbron J, Smolders I, de Witte P, Lagae L. Pharmacological analysis of the anti-epileptic mechanisms of fenfluramine in scn1a mutant zebrafish. Front Pharmacol. 2017;8:1–13.
33. Sourbron J, Partoens M, Scheldeman C, Zhang Y, Lagae L, Witte P. Drug repurposing for Dravet syndrome in scn1Lab −/− mutant zebrafish. Epilepsia. 2019;60:e8–e13.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Specchio N, Pietrafusa N, Doccini V, et al. Efficacy and safety of Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: A real-world study. *Epilepsia*. 2020;00:1–10. https://doi.org/10.1111/epi.16690