

RESEARCH ARTICLE

Fenfluramine treatment for Dravet syndrome: Long term real-world analysis demonstrates safety and reduced health care burden

Alessandra Boncristiano¹ | Simona Balestrini^{1,2} | Viola Doccini¹ | Nicola Specchio^{3,4}  | Nicola Pietrafusa³ | Marina Trivisano³ | Francesca Darra^{5,6}  | Alberto Cossu⁶ | Domenica Battaglia⁷ | Michela Quintiliani⁷  | M. Luigia Gambardella⁷ | Eliana Parente⁸ | Rita Monni⁹ | Sara Matricardi^{10,11} | Carla Marini¹¹  | Francesca Ragona¹² | Tiziana Granata¹²  | Pasquale Striano^{13,14}  | Antonella Riva^{13,14}  | Renzo Guerrini^{1,2}

¹Department of Neuroscience and Medical Genetics, Children's Hospital Meyer IRCCS, Florence, Italy

²Neurofarba Department, University of Florence, Florence, Italy

³Neurology, Epilepsy and Movement Disorders Unit, Bambino Gesù Children's Hospital IRCCS, Full Member of European Reference Network EpiCARE, Rome, Italy

⁴University Hospitals KU Leuven, Leuven, Belgium

⁵Department of Engineering for Innovation Medicine, University of Verona, Verona, Italy

⁶Child Neuropsychiatry Unit, Department of Children and Maternal Health, AOUI Verona, Full Member of European Reference Network EpiCARE, Verona, Italy

⁷Pediatric 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

⁸Pediatric Neurology Unit and Epilepsy Center, Fatebenefratelli Hospital, ASST Fatebenefratelli Sacco, Milan, Italy

⁹Neuropsychiatry Department, ASST Mantova, Mantova, Italy

¹⁰Department of Pediatrics, University of Chieti, Chieti, Italy

¹¹Child Neurology and Psychiatry Unit, "G. Salesi" Children's Hospital, Azienda Ospedaliero Universitaria Delle Marche, Ancona, Italy

¹²Department of Paediatric Neuroscience, European Reference Network EpiCARE, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

¹³IRCCS Istituto Giannina Gaslini, Full Member of European Reference Network EpiCARE, Genoa, Italy

¹⁴Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genoa, Italy

Correspondence

Renzo Guerrini, Department of Neuroscience and Medical Genetics, Meyer Children's Hospital IRCCS, Viale Pieraccini 24, Florence 50139, Italy.
Email: renzo.guerrini@unifi.it

Funding information

Italian Ministry of Health, Grant/Award Number: PNRR-MR1-2022-12376642; Italian Ministry of

Abstract

Objective: Fenfluramine (FFA), stiripentol (STP), and cannabidiol (CBD) are approved add-on therapies for seizures in Dravet syndrome (DS). We report on the long-term safety and health care resource utilization (HCRU) of patients with DS treated with FFA under an expanded access program (EAP).

Methods: A cohort of 124 patients received FFA for a median of 2.8 years (34.4 months). We compared data on safety and HCRU during FFA treatment with those from a same pre-treatment period. Echocardiography was

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 The Author(s). *Epilepsia* published by Wiley Periodicals LLC on behalf of International League Against Epilepsy.

University and Research, Grant/Award
Number: PE0000006

conducted every 6 months. Information collected included gender, age, and auxological parameters (height, weight, and body mass index [BMI]) at the start (T0) and follow-up (T1); FFA treatment details (start, withdrawal, dosage); adverse events (AEs); and HCRU data including hospital admissions, status epilepticus (SE) episodes, and rescue medication use. We grouped patients by weight: ≤ 37.4 kg ($n = 68$, 54.8%) and ≥ 37.5 kg ($n = 56$; 45.1%), with FFA dosing adjusted accordingly. Statistical analyses included paired *t* test, Wilcoxon signed-rank test, Kaplan–Meier analysis, and Bonferroni correction to adjust for multiple testing.

Results: Mean age was 47 months at clinical diagnosis and 81 months at T0. The last follow-up average FFA dose was .5 mg/kg/day, with a median of .4 mg/kg/day. FFA led to a 9.5% reduction in prior treatment load. At last follow-up, 118 of 124 (91.5%) remained on FFA. Rescue medication use decreased significantly from 4.5 to 1, hospitalizations from 1 to 0, and SE episodes from 0–240 to 0–180 ($p < .001$ for all). Seizure freedom was achieved in 9 of 118 patients (7.6%). AEs occurred in 39 of 124 patients (31.5%), with no cardiac issues or deaths. There was an overall mean reduction in BMI, with no statistical significance, and never requiring FFA withdrawal.

Significance: FFA is well tolerated, without cardiac toxicity, and reduces treatment load and HCRU, suggesting improved patient management. BMI reduction in young children highlights the need for growth and nutritional monitoring.

KEYWORDS

antiseizure, encephalopathy, epilepsy, medication, pharmacoeconomics, *SCN1A*

1 | INTRODUCTION

Dravet syndrome (DS), the most frequent and studied genetic developmental and epileptic encephalopathy (DEE), is characterized by severe, drug-resistant epilepsy, cognitive and motor impairment, behavioral problems, and increased risk of premature mortality.^{1,2} Its prevalence ranges from 1.5 per 100,000 to 6.5 per 100,000 individuals.³ The complex clinical presentation of DS requires a multidisciplinary health care approach, involving expensive interventions and treatments, and imposes a significant burden on caregivers.^{3–5}

Most patients with DS carry loss-of-function pathogenic variants in the gene encoding the alpha-1 subunit of a sodium channel (*SCN1A*).² The functional consequences of this genetic defect imply that sodium-channel blockers, such as carbamazepine (CBZ) and derivatives, phenytoin (PHT), and lamotrigine (LTG) should not be used, as they may worsen the clinical picture.⁶

Among traditional antiseizure medications (ASMs), valproate (VPA) and clobazam (CLB) are indicated as first-line treatments, although no clinical trials have confirmed their efficacy for DS.⁷ Stiripentol (STP), cannabidiol (CBD), and

Key points

- Fenfluramine (FFA) reduced seizure frequency, use of rescue medications, and hospitalizations, thereby improving management of Dravet syndrome (DS) and relieving caregiver burden.
- We found a high retention rate (91.5%) and no serious adverse events after a median follow-up of 2.8 years.
- FFA reduced the polytherapy load, potentially enhancing quality of life with fewer sedative side effects.
- Decrease in body mass index (BMI) in young children suggests a need for growth monitoring and nutritional support during FFA treatment.

fenfluramine (FFA) are approved drugs in the European Union (EU) as add-on therapies based on evidence from phase III randomized-controlled trials (RCTs).^{8–12}

FFA is thought to enhance serotonin (5-HT) release and serotonergic signaling via different 5-HT receptors (1D, 2A,

2C) and acts as a positive modulator of sigma-1 opioid receptors.¹³ FFA was approved by both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2020, for the treatment of seizures associated with DS, based on regulatory trials and their open-label extension (OLE).^{10,14} A third randomized, double-blind, placebo-controlled, parallel-group trial established a dose–response relationship, showing that patients treated with .7 mg/kg/day experienced a greater reduction in convulsive seizures than those receiving .2 mg/kg/day.¹⁰

Beyond clinical trials, patients can have access to investigational but promising drugs in expanded access programs (EAPs), authorized by FDA and EMA, better known as “compassionate use.”^{4,7,15–17} Efficacy and safety of FFA investigated in a “real-world” context demonstrated a durable and consistent reduction in convulsive seizures frequency in most patients, with even better results than in initial trials (>70% reduction) and a possible reduction of ASM load in up to 50% of patients. A good tolerability was testified by high retention rates and paralleled by improvement in behavior, autonomy, communication, and motor skills, as suggested by the Clinical Global Impression (CGI) assessment.^{4,7,17}

This study builds on a previous Italian expanded-access report evaluating the efficacy of FFA in 54 patients.⁷ Here, we report on 124 patients followed for a median of 2.8 years, (34.4 months), with a focus on long-term safety and changes in health care resource utilization (HCRU).

2 | PATIENTS AND METHODS

This retrospective, observational study was conducted across nine Italian epilepsy centers. We collected data from 124 patients with a confirmed clinical and genetic diagnosis of DS, who received FFA as an add-on treatment. Patients were enrolled through various avenues: an OLE of a phase III clinical trial (26 patients), an EAP (92 patients), the Italian Medicines Agency (AIFA) fund for Orphan Drugs (5 patients), and regional funds for rare diseases (1 patient). Inclusion and exclusion criteria and informed consent were protocol specific for patients involved in the clinical trial. For the remaining patients, a specific written informed consent was obtained by parents who accepted the FFA treatment proposal. Data collection and analysis were approved by local ethics committees of each participating institution; data were anonymized for analysis and merged into a single data set.

We collected data under analysis from the first FFA administration for all patients under EAP and AIFA authorized use, or from the beginning of the OLE for patients involved in clinical trials (T0), until the last follow-up (T1, until September 2022). For each individual patient, we compared these data with those from a pre-treatment period of

the same duration as FFA treatment. These historical data were extracted from clinical notes, diaries, and the Residras registry, a national registry including longitudinal data of DS patients, <https://www.residras.com/registro.html>,¹ and cross-verified from patients' records. The initial dosage of FFA was .2 mg/kg/day and the maximum allowed dosage was .7 mg/kg/day (absolute maximum recommended 26 mg/day) for patients who were non-concomitantly treated with STP, or .4 mg/kg/day (absolute maximum recommended 17 mg/day) in patients also receiving STP. Echocardiographic follow-up was conducted every 6 months. The primary collected information included gender, age, and auxological parameters (height, weight, and body mass index [BMI]) at T0 and T1; details about FFA treatment (start date and withdrawal, if any; initial, maximum and last dosage); changes in other ASMs; adverse events (AEs); number of rescue medication administrations, number of episodes of status epilepticus (SE), and hospital admissions during the equivalent duration periods of preceding and following T0. We analyzed efficacy data in two subgroups of patients based on their body weight: those weighing ≤37.4 kg ($n=68$, 54.8%) and those weighing ≥37.5 kg ($n=56$; 45.1%). The first subgroup received a daily dose of FFA based on body weight, whereas the second subgroup received a weight-independent dose.

2.1 | Data analysis

Continuous data are presented as mean, standard deviation (SD), median (P50), and interquartile range (IQR), and categorical variables as frequencies, proportions, and percentages. Comparisons between continuous variables were conducted using the paired t test (for means) or, if the variables were not normally distributed, the Wilcoxon signed-rank test (for medians, P50). A p -value ≤.05 was considered statistically significant. Bonferroni correction was used to adjust for multiple testing. Pharmacological treatment suspension was analyzed using Kaplan–Meier analysis, a time-based survival analysis. Statistical analysis was performed using Stata/BE 17.0 for Windows (StataCorp, USA).

3 | RESULTS

We studied 124 patients (61 female, 63 male) with a clinical diagnosis of DS, associated in 118 with a demonstrated pathogenic *SCN1A* gene variant. Mean age at clinical diagnosis was 47 months (P50 20 months). Mean age at T0 was 81 months (P50 67 months).

The initial dosage of FFA ranged from .1 to .7 mg/kg/day, with a mean of .27 (SD: .12) and a P50 of .2 mg/kg/day (IQR .2–.7). Dosage of FFA at last follow-up ranged

from .2 to .7 mg/kg/day, with a mean value of .5 (SD .18) and a P50 of .4 mg/kg/day (IQR .4–.7).

At T0, 109 patients (88%) were taking VPA, 94 (76%) CLB, 59 (47.5%) STP, 30 (24%) topiramate (TPM), 14 (11%) clonazepam (CZP), 9 (7%) levetiracetam (LEV), 6 (5%) ethosuximide (ESM), 5 (4%) phenobarbital (PB), 4 (3%) zonisamide (ZNS), 4 (3%) bromide (Br), and 1 (.8%) each taking CBD, acetazolamide (ACZ), perampanel (PER), nitrazepam (NZP), felbamate (FBM), and ketogenic diet (KD).

At T1, 109 patients (88%) were still taking VPA, 85 (68%) CLB, 37 (30%) STP, 24 (19%) TPM, 14 (11%) CZP, 8 (6%) ZNS, 6 (5%) LEV, 4 (3%) ESM, 3 (2%) CBD, 2 (1.6%) PB, Br and hydrocortisone (HC), and one each on NZP, FBM, and lorazepam (LOR). In brief, 41 of 340 (12%) of pre-FFA drug regimens were discontinued during FFA treatment, whereas only a limited number were added, including ZNS (four patients), CBD (two patients), HC (two patients), and LOR (one patient). FFA addition led, therefore, to a 9.5% reduction in the pre-existing drug load (Table 1).

The mean dosage of FFA at last follow-up was .55 mg/kg/day (SD .17) for patients <37.4 kg and .43 mg/kg/day (SD .19) for patients >37.5 kg. Add-on STP was included in the treatment schedule of 17 patients (25%) of the <37.4 kg subgroup and in 20 patients (35.7%) of the >37.5 kg subgroup.

A total of 118 of 124 patients (91.5%) were still taking FFA at last follow-up (minimum follow-up: 32 days; maximum 67 months; mean 35.5 months).

3.1 | Efficacy and health care resource utilization (HCRU)

The median number of episodes treated with rescue medications in the observation period before FFA was 4.5 (IQR 0–18, range 0–432), compared to 1 (IQR 0–3, range 0–288) during the treatment period ($p < .001$). The median number of hospital admission during the observation period preceding FFA treatment was 1 (IQR 0–3, range 0–20), which decreased to 0 (IQR 0–2, range 0–16) after its introduction ($p < .001$). The range of episodes of SE also significantly reduced in the T0–T1 interval from 0–240 to 0–180 ($p < .001$).

In patients weighing <37.4 kg, the median number of seizures treated with rescue medication was 6.5 at T0, which decreased to 1 at T1 ($p < .001$); hospital admissions decreased from 2 at T0 to 1 at T1 ($p < .001$), whereas the range of episodes of SE decreased from 0–240 at T0 to 0–180 at T1 ($p < .001$).

In patients weighing >37.5 kg, the median number of seizures treated with rescue medication before FFA was 2, dropping to 0 after its introduction ($p < .001$); hospital admissions reduced from 1 at T0 to 0 at T1 ($p = .007$,

TABLE 1 Concomitant antiseizure medications (ASMs) at T0 and T1.

ASM	T0	T1
VPA	109	109
CLB	94	85
STP	59	37
TPM	30	24
CZP	14	14
LEV	9	6
ESM	6	4
PB	5	2
Br	4	2
ZNS	4	8
ACZ	1	0
PER	1	0
NZP	1	1
FBM	1	1
CBD	1	3
KD	1	0
HC	0	2
LOR	0	1
TOTAL	340	299

Abbreviations: ACZ, acetazolamide, Br, bromide, CBD, cannabidiol, CLB, clobazam, CZP, clonazepam, ESM, ethosuximide, FBM, felbamate, HC, hydrocortisone, KD, ketogenic diet, LEV, levetiracetam, LOR, lorazepam, NZP, nitrazepam, PB, phenobarbital, PER, perampanel, STP, stiripentol, TPM, topiramate, VPA, valproate, ZNS, zonisamide.

not significant after applying the Bonferroni correction), whereas the range episodes of SE dropped from 0–30 at T0 to 0–10 after FFA was started ($p < .001$).

At last follow-up, 9 of 118 patients (7.6%) still receiving treatment were seizure-free throughout the maintenance dose period.

The retention time, assessed using Kaplan–Meier survival curve, is shown in Figure 1 and Table 2.

3.2 | Safety

AEs are summarized in Table 3. They occurred in 39 of 124 patients (31.5%) treated with FFA, and included poor appetite ($n = 20$, 16.1%), followed by behavioral problems ($n = 6$, 4.8%), weight loss ($n = 5$, 4%), irritability ($n = 3$, 2.4%), diarrhea ($n = 2$, 1.6%), mild hypotonia ($n = 2$, 1.6%), seizure worsening ($n = 1$, .8%), and arterial hypertension ($n = 1$, .8%). No deaths were reported.

Echocardiographic follow-up revealed no signs of cardiac valvulopathy or pulmonary hypertension.

Because FFA is an anorectic drug and decreased appetite is the most frequently reported AE, bodyweight

and BMI were monitored during the treatment period. Weight monitoring revealed a mean increase of 3.5 kg, with no statistical significance ($p = .22$). However, as our population included mainly children who were expected to grow and gain weight, we evaluated growth variation as Z-scores, determined by the Boston Children's Hospital algorithm using height, weight, age, and gender (<http://zscore.chboston.org>). These measures are summarized in Table 4. There was a mildly significant reduction in the median Z-score from T0 to T1 for weight ($p < .001$), but not for height ($p = .034$, not significant after applying the Bonferroni correction). BMI monitoring revealed a medium decrease of 1.52, with no statistical significance ($p = .23$). We also measured BMI variation across different age groups (Table 5) and found an overall mean reduction in BMI, with no statistical significance. For children ages 2–6 years, the variation was 2.09 ($p = .01$, not significant

after applying the Bonferroni correction); for those ages 7–11 years 3.76 ($p = .2$), for the 12–18 year group variation was .52 ($p = .41$), and .09 for patients older than 18 years ($p = .98$). In none of the patients was treatment suspended due to body weight changes.

4 | DISCUSSION

The management of patients with DS often requires complex ASM polytherapies, multiple and prolonged hospitalizations, and substantial caregiver support.⁶ FFA proved to be effective and well tolerated in treating convulsive seizures, both in RCTs and real-world studies.^{16,18–24} We previously reported real-world data on 52 DS patients treated with FFA over a median follow-up of 9.0 months (IQR = 3.2–9.5) as part of the Zogenix Early Access Program at four Italian pediatric epilepsy

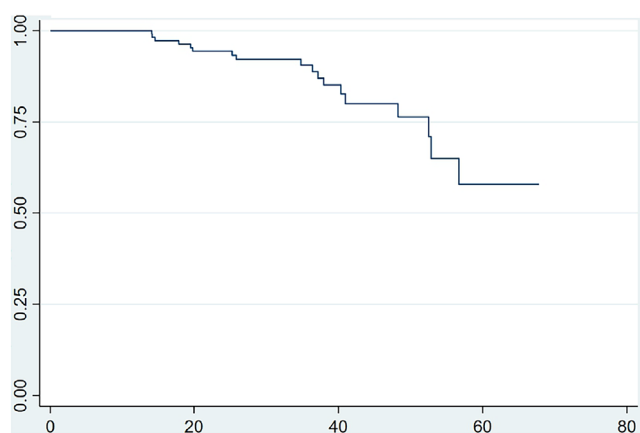


FIGURE 1 Retention of fenfluramine over time (Kaplan–Meier analysis). Horizontal axis, follow-up time in months; vertical axis, proportion of patients receiving fenfluramine treatment.

TABLE 3 Summary of adverse events reported after fenfluramine introduction.

Adverse events	Number of patients	Percentage
None	85	68.5%
Poor appetite	20	16.1%
Behavioral problems	6	4.8%
Weight loss	5	4%
Irritability	3	2.4%
Diarrhea	2	1.6%
Mild hypotonia	2	1.6%
Seizure worsening	1	.8%
Arterial hypertension	1	.8%

Time (months)	Number of patients treated	Number of patients who failed treatment	Survival function
0	0	0	1
6	116	0	1
12	114	0	1
18	105	4	.96
24	90	2	.94
30	79	2	.92
36	57	1	.90
42	30	5	.80
48	23	0	.80
54	11	3	.65
60	7	1	.57
66	2	0	.57
72	1	0	

TABLE 2 Number of patients who failed treatment with fenfluramine over time (Kaplan–Meier analysis).

TABLE 4 Variations in Z-scores for weight and height from T0 and T1 (<http://zscore.chboston.org>).

	Z-score	Median	IQR	Range	Mean	p-value (Wilcoxon signed-rank)
Weight	T0	.4	−.57 to 1.04	−4.45 to 4.82	.17	<.001
	T1	−.45	−1.45 to .58	−6.06 to 3.38	−.57	
Height	T0	0	−1.07 to 1.28	−4.63 to 4.83	.03	.034
	T1	−.36	−1.11 to 1	−3.29 to 4.44	−.23	

TABLE 5 Variations in BMI across different age groups.

Age group	Mean	p-value
2–6 year	−2.09	.01
7–11 years	−3.76	.2
12–18 years	−.52	.41
>18 years	−.09	.98

centers, and observed a clinically meaningful reduction in convulsive seizure frequency in 71% of patients, along with a low incidence of side effects and no cardiac toxicity. Here we expand on these real-world observations with a larger cohort, a longer follow-up, and the inclusion of HCRU as an indirect efficacy measurement.⁷

Although trials comparing approved drugs for DS are not available, published network meta-analysis of RCTs suggest FFA and STP to be more effective than CBD.²⁵ FFA and STP have also been used in association,⁹ but it is unclear whether their combination provides further benefit with respect to their separated use. Because the focus of our study was on safety and indirect aspects of management, we did not explore this aspect.

We explored potential indirect elements of FFA efficacy, not usually measured in clinical trials, such as reduced need for rescue medication administrations, episodes of SE, and number of hospital admissions. These factors, although not usually considered as study endpoints, contribute greatly to the burden on the management of the syndrome and are important indirect indicators of treatment efficacy. In the analysis we provided here, FFA proved effective in reducing the need for rescue medication, hospitalizations, and occurrence of SE. These reductions are important not only from a clinical standpoint but also in terms of reducing the economic and emotional burden on families and health care systems. Although the primary endpoint in most clinical trials focuses on seizure frequency, our study highlights the value of examining secondary outcomes such as HCRU and SE episodes in the long term. These measures provide a more comprehensive picture of FFA's effectiveness in real-world clinical settings. We acknowledge the potential overlap between the outcomes of decreased SE, reduced use of rescue medications, and fewer hospitalizations. These outcomes are

interconnected, as a reduction in SE episodes may lead to less need for rescue medications and fewer hospital admissions. We considered SE as the primary endpoint, given that the use of rescue medications can vary between caregivers, and hospitalization may not occur for all SE episodes, as some families may be able to manage SE at home and avoid hospital admission. Our findings are consistent with previous studies that also used HCRU endpoints. A significant reduction of SE episodes after FFA initiation in DS was reported in a multicenter German cohort, with a retention rate of 92% in adults and 83% in children.¹⁷ A 52% mean reduction (range 11%–94%) in epilepsy-related hospital contacts from baseline to the end of the treatment period was reported in 75% of patients in a retrospective study of 30 DS patients treated with FFA at a Danish center over a mean period of 29 months.¹⁶ Efficacy and safety of FFA were further confirmed by the high retention rate (Figure 1).

We observed a significant reduction in concomitant ASMs. Simplification of the medication load means fewer sedative side effects and is consistent with a less severe clinical context. Although we did not directly assess cognitive outcomes, reducing the medication burden is an important step toward optimizing the long-term management of DS. Future studies should explore the correlation between reduced polytherapy and improvements in cognitive function, quality of life, and developmental outcomes.

Our study confirms FFA to be well tolerated, without evidence of AE in 85 of 124 patients (68.5%), including no evidence of cardiac toxicity. Because the most common AEs of FFA are decreased appetite and weight loss, we monitored bodyweight and BMI. We only observed a trend for BMI reduction across all ages, not reaching statistical significance. None of the patients discontinued FFA due to weight loss or appetite decrease; therefore clinical significance of this AE appears to be limited. There is no literature investigating BMI, but our findings still suggest careful weight monitoring with a possibility of an enriching diet regimen to prevent BMI decrease. Since in childhood and adolescence BMI exhibits considerable variability, mainly related to gender and age, it is advisable to use percentile tables as a reference rather than absolute values as normally done in adults. Long-term evaluation of the potential impact of FFA on growth is ongoing.

The main limitations of this study include its retrospective design, the absence of a control group, and the lack of systematic data on actual seizure frequency. Data heterogeneity, resulting from patients being treated across nine centers, may have introduced variability in treatment practices, potentially affecting the consistency of results. We did not directly assess cognitive or behavioral improvements, which are important aspects of DS management. The historical data were obtained from Residras, the national DS registry,¹ which includes longitudinal follow-up data on SE events, the use of rescue medications, and hospitalizations. Although this source may still underestimate some variables, such as the use of rescue medication, the close follow-up of patients with DS and cross-verification from patients' records help mitigate this risk. On the other hand, this study provides valuable evidence of FFA efficacy and safety in a relatively large cohort of patients over an extended follow-up period, compared to previous studies. It reflects real-world clinical practice and includes diverse treatment scenarios (EAP, clinical trial OLE, and national/regional funding programs), thereby enhancing the generalizability of the findings. The incorporation of HCRU metrics adds meaningful clinical endpoints, highlighting the impact on patients' and caregivers' quality of life.

In conclusion, this study adds to the growing body of evidence supporting FFA as an effective and well-tolerated treatment option for patients with DS. The observed reductions in ASM load and HCRU suggest that FFA not only controls convulsive seizures but also contributes to an overall improvement in patients' management and quality of life. Although the observed reduction in BMI did not reach statistical significance, these findings highlight the importance of regular growth monitoring and nutritional support, especially in pediatric populations. Long-term, real-world data, like those provided in this study, are essential for understanding the full impact of FFA on the health and development of patients with DS, beyond the outcomes typically measured in controlled clinical trials.

AUTHOR CONTRIBUTIONS

Study concept and design: Renzo Guerrini. *Acquisition, analysis, and interpretation of data:* Alessandra Boncristiano, Simona Balestrini, Viola Doccini, Nicola Specchio, Nicola Pietrafusa, Marina Trivisano, Francesca Darra, Alberto Cossu, Domenica Battaglia, Michela Quintiliani, M. Luigia Gambardella, Eliana Parente, Rita Monni, Sara Matricardi, Carla Marini, Francesca Ragona, Tiziana Granata, Pasquale Striano, Antonella Riva, and Renzo Guerrini. *Critically review of the manuscript and approval of the final version for publication:* All authors.

ACKNOWLEDGMENTS

Children's Hospital Meyer IRCCS, Bambino Gesù Children's Hospital IRCCS, AOUI Verona, Fondazione IRCCS Istituto Neurologico Carlo Besta, IRCCS Istituto Giannina Gaslini, are full members of the ERN for rare and complex epilepsies (EpiCARE). The clinical information included in the study were partly derived from the national registry of Dravet syndrome, Residras. Open access publishing facilitated by Università degli Studi di Firenze, as part of the Wiley & Hyphen; CRUI & Hyphen; CARE agreement.

FUNDING INFORMATION

The open-label extension study was included in the ZX008-1503 study, which was sponsored by Zogenix. The work was also partly supported by funding of the Italian Ministry of Health: "Precision medicine in Dravet syndrome: from a national registry to neuronal modelling based on individual genome data" (National Recovery and Resilience Plan, NRRP-MR1-2022-12376642) to R.G. and S.B., and "Current Research 2023" assigned to R.G., S.B., N.S., N.P., M.T., and P.S.; and by funding of the Italian Ministry of University and Research (MUR): #NEXTGENERATIONEU (NGEU) NRRP, project 'A Multiscale integrated approach to the study of the nervous system in health and disease' (MNESYS, PE0000006), assigned to R.G., S.B., N.S., N.P., M.T., and P.S.

CONFLICT OF INTEREST STATEMENT

Alessandra Boncristiano has received speaker honoraria from UCB. Simona Balestrini has served on scientific advisory boards for Biocodex and Longboard Pharmaceuticals; and has received speaker honoraria from Angelini, Biocodex, Eisai, Lusofarmaco, and Jazz Pharma. Viola Doccini has served as an investigator for Biocodex. Nicola Specchio has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus, and Takeda; has received speaker honoraria from Eisai, Biomarin, Livanova, Sanofi, Jazz Pharmaceutical, UCB, and Takeda; and has served as an investigator for Zogenix, Marinus, Biomarin, UCB, and Roche. Nicola Pietrafusa has received speaker honoraria from Angelini, Zogenix, and UCB. Marina Trivisano has served on scientific advisory boards for Biomarin and Biocodex; she has received speaker honoraria from Biomarin and Orion Pharma. Francesca Darra has served on scientific advisory boards for Zogenix, Biocodex, Angelini, UCB, and Ethypharm; and has received speaker honoraria from Biocodex, GW-Jazz, and UCB. Alberto Cossu has received speaker honoraria from UCB. Domenica Immacolata Battaglia has served on scientific advisory boards for Biocodex, UCB, and Ethypharm. Eliana Parente has received speaker honoraria from UCB. Rita Monni has served on scientific advisory boards for UCB Pharmaceuticals and has received speaker

honoraria from UCB. Sara Matricardi has served on scientific advisory boards for Zogenix, UCB, and Ethypharm; and has received speaker honoraria from Biocodex, Jazz Pharmaceuticals, Eisai, and UCB. Carla Marini has served on scientific advisory boards for UCB and Ethypharm; and has received speaker honoraria from Jazz Pharmaceuticals, Eisai, and UCB. Francesca Ragona has served on scientific advisory boards for Biocodex, Zogenix, and GW-Jazz; and has received speaker honoraria from UCB and GW-Jazz. Tiziana Granata has served on scientific advisory boards for Ethypharm. Pasquale Striano has served on scientific advisory boards for Zogenix, Biocodex, GW-Jazz, Angelini, Takeda, UCB, and Ethypharm; has received speaker honoraria and funding for travel from Zogenix, Biocodex, GW-Jazz, Angelini, Takeda, and UCB; and has served as an investigator for Zogenix, Biocodex, and UCB. Antonella Riva has served on scientific advisory boards for Biocodex, UCB, Jazz Pharmaceutical, and PTC therapeutics; and has received travel grants from Jazz Pharmaceuticals. Renzo Guerrini has served on scientific advisory boards for Zogenix, Biocodex, GW-Jazz, Angelini, Takeda, Rapport Therapeutics, SK Life Science Inc., Stoke Therapeutics, UCB, and Ethypharm; has received speaker honoraria and funding for travel from Zogenix, Biocodex, GW-Jazz, Angelini, Takeda, Rapport Therapeutics, Novartis, SK Life Science Inc., Stoke Therapeutics, UCB, Marinus, and GRIN Therapeutics; and has served as an investigator for Zogenix, Biocodex, UCB, GRIN Therapeutics, SK Life Science Inc., TEVA, Marinus, Lundbeck, and The Loulou Foundation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

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

ORCID

Nicola Specchio  <https://orcid.org/0000-0002-8120-0287>

Francesca Darra  <https://orcid.org/0000-0002-1062-8438>

Michela Quintiliani  <https://orcid.org/0000-0002-8278-6953>

Carla Marini  <https://orcid.org/0000-0002-9212-2691>

Tiziana Granata  <https://orcid.org/0000-0002-0170-6836>

Pasquale Striano  <https://orcid.org/0000-0002-6065-1476>

Antonella Riva  <https://orcid.org/0000-0001-9152-5571>

REFERENCES

- Balestrini S, Doccini V, Giometto S, Lucenteforte E, De Masi S, Giarola E, et al. A registry for Dravet syndrome: the Italian experience. *Epilepsia Open*. 2023;8(2):517–34.
- Guerrini R, Conti V, Mantegazza M, Balestrini S, Galanopoulou AS, Benfenati F. Developmental and epileptic encephalopathies: from genetic heterogeneity to phenotypic continuum. *Physiol Rev*. 2023;103(1):433–513.
- Strzelczyk A, Lagae L, Wilmshurst JM, Brunklaus A, Striano P, Rosenow F, et al. Dravet syndrome: a systematic literature review of the illness burden. *Epilepsia Open*. 2023;8(4):1256–70.
- Guerrini R, Specchio N, Aledo-Serrano Á, Pringsheim M, Darra F, Mayer T, et al. An examination of the efficacy and safety of fenfluramine in adults, children, and adolescents with Dravet syndrome in a real-world practice setting: a report from the Fenfluramine European early access program. *Epilepsia Open*. 2022;7(4):578–87.
- Shmueli S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: a review. *Epilepsy Behav*. 2016;64:69–74.
- Guerrini R. Dravet syndrome: the main issues. *Eur J Paediatr Neurol*. 2012;16:S1–S4.
- Specchio N, Pietrafusa N, Doccini V, Trivisano M, Darra F, Ragona F, et al. Efficacy and safety of Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a real-world study. *Epilepsia*. 2020;61(11):2405–14.
- 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(10216):2243–54.
- 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*. 2020;77(3):300–8.
- Sullivan J, Lagae L, Cross JH, Devinsky O, Guerrini R, Knupp KG, et al. Fenfluramine in the treatment of Dravet syndrome: results of a third randomized, placebo-controlled clinical trial. *Epilepsia*. 2023;64(10):2653–66.
- 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(21):2011–20.
- Chiron C, Marchand M, 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(9242):1638–42.
- Sourbron J, Lagae L. Fenfluramine: a plethora of mechanisms? *Front Pharmacol*. 2023;14:1192022.
- Sullivan J, Scheffer IE, Lagae L, Nabbout R, Pringsheim M, Talwar D, et al. Fenfluramine HCl (Fintepla®) provides long-term clinically meaningful reduction in seizure frequency: analysis of an ongoing open-label extension study. *Epilepsia*. 2020;61(11):2396–404.
- Valls Carbó A, Beltrán Á, Sánchez-Miranda Román I, Cabal B, Gómez-Porro P, Aledo-Serrano Á, et al. What have we learned from the real-world efficacy of FFA in DS and LGS? A post-marketing study in clinical practice. *Epilepsy Behav*. 2024;151:109620.
- Gjerulfson CE, Nikanorova M, Olofsson K, Johannessen Landmark C, Rubboli G, Möller RS. Fenfluramine treatment in

pediatric patients with Dravet syndrome reduces seizure burden and overall healthcare costs: a retrospective and observational real-world study. *Epilepsia Open*. 2024;9(5):1891–900.

17. Strzelczyk A, Pringsheim M, Mayer T, Polster T, Klotz KA, Muhle H, et al. Efficacy, tolerability, and retention of fenfluramine for the treatment of seizures in patients with Dravet syndrome: compassionate use program in Germany. *Epilepsia*. 2021;62(10):2518–27.
18. Strzelczyk A, Schubert-Bast S. A practical guide to the treatment of Dravet syndrome with anti-seizure medication. *CNS Drugs*. 2022;36(3):217–37.
19. Patel S, Grinspoon R, Fleming B, Skirvin LA, Wade C, Wolper E, et al. The long-term efficacy of cannabidiol in the treatment of refractory epilepsy. *Epilepsia*. 2021;62(7):1594–603.
20. 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.
21. Devinsky O, Nabbout R, Miller I, Laux L, Zolnowska M, Wright S, et al. Long-term cannabidiol treatment in patients with Dravet syndrome: an open-label extension trial. *Epilepsia*. 2019;60(2):294–302.
22. Park YD, Linder DF, Pope J, Flamini JR, Moretz K, Diamond MP, et al. Long-term efficacy and safety of cannabidiol (CBD) in children with treatment-resistant epilepsy: results from a state-based expanded access program. *Epilepsy Behav*. 2020;112:107474.
23. Iannone LF, Arena G, Battaglia D, Bisulli F, Bonanni P, Boni A, et al. Results from an Italian expanded access program on Cannabidiol treatment in highly refractory Dravet syndrome and Lennox–Gastaut syndrome. *Front Neurol*. 2021;12:673135.
24. Scheffer IE, Halford JJ, Miller I, Nabbout R, Sanchez-Carpintero R, Shiloh-Malawsky Y, et al. Add-on cannabidiol in patients with Dravet syndrome: results of a long-term open-label extension trial. *Epilepsia*. 2021;62(10):2505–17.
25. Guerrini R, Chiron C, Vandame D, Linley W, Toward T. Comparative efficacy and safety of stiripentol, cannabidiol and fenfluramine as first-line add-on therapies for seizures in Dravet syndrome: a network meta-analysis. *Epilepsia Open*. 2024;9(2):689–703.

How to cite this article: Boncristiano A, Balestrini S, Doccini V, Specchio N, Pietrafusa N, Trivisano M, et al. Fenfluramine treatment for Dravet syndrome: Long term real-world analysis demonstrates safety and reduced health care burden. *Epilepsia*. 2025;66:1110–1118. <https://doi.org/10.1111/epi.18241>