Antiseizure Medication Regimen Adjustment After Fenfluramine Initiation: Lessons Learned From European Early Access Program in Pediatric and Adult Patients With Dravet Syndrome

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Background

- Dravet syndrome (DS) is a rare developmental and epileptic encephalopathy characterized by seizure onset within the first year of life, high seizure frequency, and developmental, motor and behavioral delays[1]
- Fenfluramine (FFA) is approved in the United States, European Union, United Kingdom, Israel, and Japan for the treatment of seizures associated with DS in patients ≥2 years old[2-6]
- Because DS persists into adulthood, long-term FFA treatment data are needed
- Real-world data examining FFA dosing and concomitant antiseizure medication (ASM) dosing in pediatric and adult patients receiving FFA are lacking

Objective

- Here, we report FFA dosage and concomitant ASM dose adjustments in pediatric and adult patients who participated in the European Early Access Program (EAP) supported by Zogenix/UCB

Methods

- The EAP was opened in 2018 to provide patients with an unmet medical need with access to a medicine not yet available by prescription
  - Germany, Italy, Spain, Ireland, and the United Kingdom participated in the EAP until European Medicines Agency (EMA) approval in 2020
  - Patients continued receiving FFA under the EAP program until FFA was commercially available in their respective country
- Prior to EMA approval, the EAP was available at specialized and approved centers with epileptologists on site
  - Patients were eligible through their physician if they had a confirmed DS diagnosis, no alternative treatment, and were not eligible to enroll in a clinical trial
  - Physicians completed an initial product request form on behalf of suitable participants
  - Subsequent, non-initial request forms were completed by physicians to renew FFA supply
- Key contraindications for participation included hypersensitivity to FFA or any of its excipients, valvular heart disease, pulmonary arterial hypertension, or treatment with a monoamine oxidase inhibitor within 14 days prior
- The maximum FFA dose allowed in the EAP without concomitant stiripentol (STP) was 0.7 mg/kg/d (maximum daily dose, 26 mg/d) and 0.4 mg/kg/d (maximum daily dose, 17 mg/d) with concomitant STP

Results

DEMOGRAPHICS

- At the last request, of 269 total patients, 192 (71.4%) were pediatric patients and 77 (28.6%) were adults (≥18 years old); 48.3% of patients were female (**Table 1**)
  - Patients came from Germany (43.9%), Italy (39.0%), Spain (10.8%), United Kingdom (4.5%), and Ireland (1.9%)
- Concomitant STP use at initial request was reported in 54.7% and 44.2% of pediatric and adult patients, respectively
- In pediatric patients, mean (SD) weight was 26.0 (12.6) kg at initial request and 27.8 (13.5) kg at non-initial requests
- In adult patients, mean (SD) weight was 68.5 (22.2) kg at initial request and 66.8 (17.2) kg at non-initial requests
- For participants with ≥2 requests, the median time from initial request to final request was 603.8 days (range, 39.1–1505.0 days)
- Of 41 (15.2%) participants who withdrew from the EAP, 7 withdrew due to seizure worsening, 8 due to other adverse events, 13 due to lack of effectiveness, and 13 for reason unknown

Overview

QUESTION

What was the early clinical experience with fenfluramine (FFA) in terms of dosage, and its effect on concomitant antiseizure medication dose adjustments, in pediatric and adult patients with Dravet syndrome (DS) in Europe?

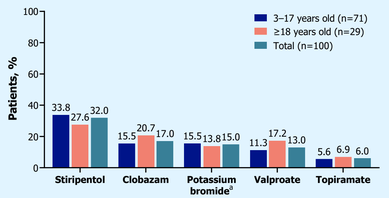
INVESTIGATION

Using real-world clinical practice experience from the European early access program (EAP), we report FFA dosage and concomitant antiseizure medication (ASM) adjustments in pediatric and adult patients

RESULTS

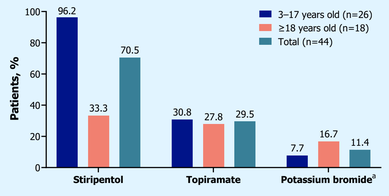
- Of 269 total patients, 192 (71.4%) were pediatric patients (3–17 years old) and 77 (28.6%) were adults (≥18 years old) at their last FFA request
- In the total population, mean (SD) weight was 38.1 (30.0) kg at initial request and 37.3 (22.2) kg at non-initial requests
- Concomitant STP use at initial request was reported in 54.7% and 44.2% of pediatric and adult patients, respectively
- Concomitant ASM dose increases were observed in 25.6% of the total population; of ASMs with dose increases, valproate was most common (34.1%)
- Concomitant ASM dose reductions were observed in 54.1% of the total population; of ASMs that were dose reduced, STP was most common (32.0%; **Figure 1**)
- Concomitant ASM withdrawals were observed in 25.6% of the total population; of ASMs withdrawn, STP was most common (70.5%; **Figure 2**)

Figure 1. Concomitant ASMs With Dose Reductions During EAP



[a]Mostly prescribed in Germany.
ASM, antiseizure medication; EAP, Early Access Program.

Figure 2. Concomitant ASMs Withdrawn During EAP



[a]Mostly prescribed in Germany.
ASM, antiseizure medication; EAP, Early Access Program.

CONCLUSIONS

- Patients with DS who enrolled in the EAP received FFA doses within the recommended maximum dose ranges for pediatric and adult patients
- Concomitant ASM dose adjustments were observed in the vast majority of patients upon FFA initiation
- Meaningful concomitant ASM dose reductions and withdrawals in both pediatric and adult patients reflect the effectiveness of FFA in each population

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Table 1. Patient Characteristics at Initial Request and Non-initial Requests

Variable	Total N=269[a]	3–17 Years[b] n=192[a]	≥18 Years[b] n=77[a]
Age at initial request, years			
Mean (SD)	12.0 (9.5)	7.1 (3.8)	24.4 (8.2)
Median	8.9	6.2	22.0
Range	1.0–46.1	1.0–15.4	13.6–46.1
Age at last request[b], years			
Mean (SD)	15.1 (9.6)	10.1 (3.9)	27.6 (8.2)
Median	12.0	9.0	25.5
Range	3–50	3–17	18–50
Female, n (%)	130 (48.3)	94 (49.0)	36 (46.8)
Concomitant STP use at initial request, n (%)	139 (51.7)	105 (54.7)	34 (44.2)
Weight at initial request, kg			
Mean (SD)	38.1 (30.0)	26.0 (12.6)	68.5 (22.2)
Median	30.0	22.0	64.0
Range	9.6–133	9.6–65.0	25.0–133.0
Weight at non-initial requests, kg	N=1587[c]	n=1199[c]	n=388[c]
Mean (SD)	37.3 (22.2)	27.8 (13.5)	66.8 (17.2)
Median	29	23.0	64.0
Range	10–132	10.0–77.0	27.0–132.0

[a]N and n represent number of patients with an initial FFA request for each age group.
[b]Age groups were defined based on the age at last request.
[c]N and n represent the number of multiple non-initial requests for each age group (i.e., a single patient will require multiple follow-up, non-initial requests to continue receiving FFA).
SD, standard deviation; STP, stiripentol.

FFA ADMINISTRATION

- In pediatric patients, median (range) FFA dosages at initial and non-initial requests were 7.77 (2.10–25.91) mg/d and 11.7 (1.80–25.91) mg/d, respectively (**Table 2**)
- In adult patients, median (range) FFA dosages at initial and non-initial requests were 17.28 (7.10–25.91) mg/d and 17.28 (4.32–25.91) mg/d, respectively

Table 2. Overall, Daily, and Weight-Adjusted FFA Dosage With or Without Concomitant STP

	Total		3–17 Years		≥18 Years	
Variable, mg/d	Initial Request n=269	Non-Initial Requests n=1587	Initial Request n=192	Non-Initial Requests n=1199	Initial Request n=77	Non-Initial Requests n=388
Dosage						
Mean±SD	11.89±7.02	13.93±5.90	9.63±6.07	12.33±5.19	17.52±5.99	18.89±5.15
Median	10.43	13.6	7.77	11.7	17.28	17.28
Range	1.20–25.91	1.80–25.91	2.10–25.91	1.80–25.91	7.10–25.91	4.32–25.91
Dosage (w/ STP)	n=139	n=640	n=105	n=501	n=34	n=139
Mean±SD	10.42±5.34	11.97±4.51	8.89±4.95	10.80±4.32	15.16±3.36	16.20±1.84
Median	9.1	11.7	7.77	9.9	17.28	17.28
Range	1.73–17.28	2.20–17.28	1.73–17.28	2.20–17.28	7.77–17.28	7.77–17.28
Dosage (w/o STP)	n=130	n=947	n=87	n=698	n=43	n=249
Mean±SD	13.46±8.19	15.26±6.35	10.52±7.12	13.43±5.48	19.39±6.93	20.39±5.76
Median	11.7	13.82	8.2	12.4	21.8	21.8
Range	1.20–25.91	1.80–25.91	1.20–25.91	1.80–25.91	7.10–25.91	4.32–25.91
Variable, mg/kg/d						
Dosage						
Mean±SD	0.35±0.18	0.43±0.16	0.38±0.19	0.47±0.15	0.27±0.11	0.30±0.10
Median	0.35	0.43	0.43	0.43	0.24	0.3
Range	0.09–0.69	0.09–0.69	0.09–0.70	0.09–0.69	0.17–0.61	0.09–0.69
Dosage (w/ STP)	n=139	n=640	n=105	n=501	n=34	n=139
Mean±SD	0.32±0.12	0.35±0.09	0.33±0.12	0.37±0.07	0.26±0.10	0.27±0.07
Median	0.35	0.35	0.42	0.4	0.2	0.26
Range	0.17–0.43	0.09–0.69[a]	0.17–0.43	0.09–0.69	0.17–0.43	0.16–0.43
Dosage (w/o STP)	n=130	n=947	n=87	n=698	n=43	n=249
Mean±SD	0.39±0.22	0.48±0.17	0.44±0.23	0.54±0.15	0.29±0.12	0.31±0.11
Median	0.35	0.52	0.43	0.52	0.26	0.33
Range	0.09–0.70	0.09–0.69	0.09–0.70	0.09–0.69	0.17–0.61	0.09–0.69

[a]Patients exceeding maximum dose with STP may have discontinued STP.
n=number of requests.
d, day; SD, standard deviation; STP, stiripentol; w/, with; w/o, without.

Table 3. Change in Concomitant ASM Use Upon FFA Initiation

Variable, n (%)	Total	3–17 Years	≥18 Years
Concomitant ASM dose adjustment[a]	n=185	n=138	n=47
Yes	172 (93.0)	125 (90.6)	47 (100.0)
No	6 (3.2)	6 (43.5)	0
Missing[b]	7 (3.8)	7 (50.7)	0
Confirmed concomitant ASM adjustment[a]	n=172	n=125	n=47
Dose increase	44 (25.6)	36 (28.8)	7 (14.9)
Dose reduction	93 (54.1)	71 (56.8)	29 (61.7)
Withdrawn	44 (25.6)	26 (20.8)	18 (38.3)
Reported ASM dose increase[a]	n=44	n=37	n=7
Valproate	15 (34.1)	10 (27.0)	5 (71.4)
Clobazam	9 (20.5)	9 (24.3)	0
Stiripentol	4 (1.0)	4 (10.8)	0
Reported ASM dose reduction[a]	n=100	n=71	n=29
Stiripentol	32 (32.0)	24 (33.8)	8 (27.6)
Clobazam	17 (17.0)	11 (15.5)	6 (20.7)
Potassium bromide	15 (15.0)	11 (15.5)	4 (13.8)
Valproate	13 (13.0)	8 (11.3)	5 (17.2)
Topiramate	6 (6.0)	4 (5.6)	2 (6.9)
Reported ASM withdrawn[a]	n=44	n=26	n=18
Stiripentol	31 (70.5)	25 (96.2)	6 (33.3)
Topiramate	13 (29.5)	8 (30.8)	5 (27.8)
Potassium bromide	5 (11.4)	2 (7.7)	3 (16.7)

[a]ASM adjustments were not mutually exclusive; a participant could experience multiple adjustments or adjustments to multiple drugs.
[b]Missing=no YES/NO was added, but adjustment was done based on the free text.
n=number of participants. Only data with a confirmed ASM name was included.
ASM, antiseizure medication; FFA, fenfluramine.

CONCOMITANT ASM DOSE ADJUSTMENTS

- 93% of patients had concomitant ASM dose adjustments after FFA initiation (**Table 3**)
- Concomitant ASM dose reductions were observed in 56.8% of pediatric patients; of ASMs with dose reductions, STP was most common (33.8%)
- Concomitant ASM dose reductions were observed in 61.7% of adult patients; of ASMs with dose reductions, STP was most common (27.6%)
- Concomitant ASM dose increases were observed in 28.8% of pediatric patients; of ASMs with dose increases, valproate was most common (27.0%)
- Concomitant ASM dose increases were observed in 14.9% of adult patients; of ASMs with dose increases, valproate was most common (71.4%)
- Concomitant ASM withdrawals were observed in 20.8% of pediatric patients; of ASMs withdrawn, STP was most common (96.2%)
- Concomitant ASM withdrawals were observed in 38.3% of adult patients; of ASMs withdrawn, STP was most common (33.3%)

Conclusions

- Here, we report baseline characteristics, FFA dosage, and ASM dose adjustments in 269 patients, 77 of whom were adults, in the first real-world experience described with FFA in DS
- Patients with DS who enrolled in the EAP received FFA doses within the recommended maximum dose ranges for pediatric and adult patients
- Concomitant ASM dose adjustments were observed in the vast majority of patients upon FFA initiation
  - All adult patients and 77.6% of pediatric patients withdrew or reduced the dose of a concomitant ASM
- Meaningful concomitant ASM dose reductions and withdrawals in both pediatric and adult patients reflect the effectiveness of FFA in each population
- Safety data were not evaluated in this real-world study
- Future studies will evaluate the impact of FFA on other healthcare resource utilization, including emergency room visits and hospitalizations, in patients with DS

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