Real-World Use of Fenfluramine for Dravet Syndrome: A Retrospective Cohort Study Using a National Pharmacy Database

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Introduction

- In the United States (US), fenfluramine (FFA) is currently approved for management of seizures in patients ≥2 years old with Dravet syndrome (DS)[1] after demonstrating reductions in convulsive seizure frequency in 3 randomized controlled trials and an open-label extension study in patients with DS[2-5]
- FFA is distributed via a single specialty pharmacy
  - As part of FFA's Risk Evaluation and Mitigation Strategy (REMS), all patients receiving FFA obtained authorization by contacting REMS
- A high premature mortality risk has been observed in patients with DS
  - In patients with *SCN1A* pathogenic variants, the previous all-cause mortality rate per 1000 person-years was reported as 8.6 (95% CI, 5.4-13.0)[6]
- Sudden unexpected death in epilepsy (SUDEP) is a main cause of mortality in DS; SUDEP-related mortality rate in DS has been reported as 4.4 per 1000 patient-years[6]
  - Generalized tonic-clonic (GTC) seizures are associated with increased risk of SUDEP[7]
  - American Academy of Neurology and American Epilepsy Society guidelines recommend treatment with antiseizure medication in patients with GTC seizures to reduce seizure burden and risk of SUDEP[7]
- A 2023 Italian registry study of 281 patients with DS[8] and a 2021 post-hoc analysis[9] of FFA clinical trials, early access programs, and open-label studies reported a lower all-cause mortality rate in treated patients with DS compared to the expected mortality rates reported previously in the literature

Objective

- While valuable, clinical trial experiences may not reflect real-world outcomes, thus in this study we describe mortality rates and real-world use of FFA in US patients with DS who were new FFA users from commercial availability starting July 1, 2020, to March 15, 2024

Methods

- This retrospective cohort study evaluated US patients with DS who were new users of FFA obtained from the single specialty pharmacy
  - The analysis period began when FFA became commercially available (July 1, 2020)
  - Patients were required to have a DS diagnosis, and must have received their first shipment of FFA (defined as index date) ≥6 months prior to data cut; however, eligibility criteria did not impose a minimum time on treatment
  - Patients were excluded if they had received prior treatment with FFA
- Outcomes reported include demographics, initial and maintenance FFA doses, FFA persistence (by index year), duration of FFA, mortality rate, and time to death
  - For each time-based outcome, exact dates of FFA shipment were not available but were imputed to the 15th day of the reported month
  - Persistence was defined as continuous FFA shipments until last shipment plus day supply, or date of death, or discontinuation date after which there weren't any subsequent FFA shipments
  - Treatment persistence and time to death from first FFA prescription date (index) was measured using a Kaplan-Meier chart including median survival and corresponding 95% confidence intervals
    - Patients were censored at discontinuation or end of follow-up
- Standardized mortality ratios (SMRs), that compared crude mortality rates to the US general population (similar age range observed in this study of patients with DS), and 95% confidence intervals (CIs) for 2021-2023 were also reported
  - Descriptive statistics were used to summarize data

Results

- From commercial launch (July 1, 2020), through the most recent data cut (March 15, 2024), data were available for 1043 new users of FFA for DS
- Demographic data are shown in **Table 1**
  - 49.2% of patients were 6-17 years old at time of prescribing, 56.6% were prescribed FFA by a pediatric epileptologist
  - Prior to FFA treatment, 56.1% and 16.3% of patients discontinued due to failure, were contraindicated to, or intolerant of cannabidiol or stiripentol, respectively
- Median initial and maintenance FFA doses were 0.3 mg/kg/day (range: 0.1-1.1 mg/kg/day) and 0.5 mg/kg/day (range: 0.02-1.4 mg/kg/day), respectively

Overview

QUESTION

- What are the real-world patient characteristics, including treatment information, treatment persistence, and mortality, in patients with Dravet syndrome (DS) who have recently been prescribed fenfluramine (FFA) in the United States (US)?

INVESTIGATION

- We used real-world data from a specialty pharmacy to describe patient characteristics, treatment information, and treatment persistence, and to calculate crude mortality rates and standardized mortality ratios (SMRs) for US patients who have been newly prescribed FFA since commercial launch

RESULTS

- From July 1, 2020, to March 15, 2024, we identified 1043 new FFA users with DS; 49.2% of patients were 6-17 years old at first prescription
  - Prior to FFA treatment, 56.1% and 16.3% of patients discontinued due to failure, were contraindicated to, or intolerant of cannabidiol or stiripentol, respectively
  - Median maintenance FFA dose was 0.5 mg/kg/day (range: 0.02-1.4 mg/kg/day)
- FFA 12-month treatment persistence was ≥74.8%
- The estimated mortality rate was 8.02 (95% CI, 3.96-12.08) per 1000 person-years (PY)
- Overall SMR from 2021-2023 was 1.88 (95% CI, 1.05-3.14)

74.8-78.5%
of patients were persistent with FFA treatment at 1 year from 2020-2022

8.02/1000 PY
estimated mortality rate over the study period

1.88
overall SMR compared to the general population over the study period

CONCLUSIONS

- In this analysis that included all US patients treated with FFA after it became commercially available, patients with DS who were newly prescribed FFA showed good treatment persistence at 1 year
- Mortality rates agreed with those previously reported; SMRs for patients who were newly prescribed FFA were generally low

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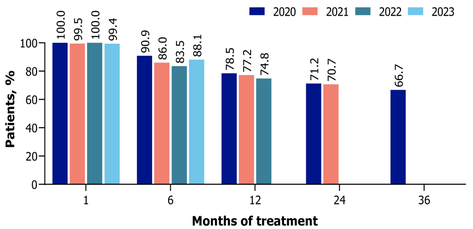
Table 1. Demographics of Real-World Patients With DS Who Are FFA Naïve

	N=1043
Age at index (years), n (%)	
<2	62 (5.9)
2-5	284 (27.2)
6-17	513 (49.2)
18-35	169 (16.2)
>35	15 (1.4)
Sex, n (%)	
Female	496 (47.6)
Male	547 (52.4)
Weight at index, kg	
Mean ± SD	35.9 ± 22.4
Median (range)	30.1 (6.4-129.3)
Prescribing provider, n (%)[a]	
Pediatric epileptologist	590 (56.6)
Pediatric neurologist	289 (27.7)
Adult neurologist	91 (8.7)
Epileptologist	53 (5.1)
Neurologist	20 (1.9)
Pediatrician	1 (0.1)
Previous ASMs, n (%)[b]	
Valproate[c]	915 (87.7)
Clobazam	660 (63.3)
Cannabidiol	585 (56.1)
Topiramate	431 (41.3)
Stiripentol	170 (16.3)
Levetiracetam	149 (14.3)
Zonisamide	52 (5.0)
Lamotrigine	48 (4.6)
Phenobarbital	26 (2.5)
Rufinamide	25 (2.4)
Ethosuximide	19 (1.8)
Felbamate	16 (1.5)

[a]A patient could have more than one prescribing physician.
[b]These include any ASM discontinued due to failure, were contraindicated to, or intolerant of.
[c]All valproate derivatives included.
ASMs, anti-seizure medications; DS, Dravet syndrome; FFA, fenfluramine; SD, standard deviation.

- 724 (69.4%) patients were still receiving FFA at data cut
- Persistence by index year at 6 months and 12 months in 2020 was 90.9% and 78.5%, respectively, and in 2021 was 86.0% and 77.2%, respectively (**Figure 1**)
  - Median treatment duration at 6- and 12-month data cut-off was 21.3 months and 24.4 months

Figure 1. FFA Treatment Persistence by Months of Treatment From 2020-2023



Persistence data are shown for yearly cohorts if a patient beginning FFA treatment by December 31 of the cohort year could have received FFA for the specified amount of time by the data cut date of March 15, 2024. Persistence data have been updated as one patient was removed from the analysis; the initial FFA shipment date and date of death were the same.
FFA, fenfluramine.

- During the analysis period, there were 15 deaths per 1869.54 patient-years of follow-up
  - One patient was removed from mortality analysis after discovering the FFA shipment date and date of death were the same
- Of these 15 patients, 80.0% were 2-17 years old and 60.0% were male (**Table 2**)
  - Patients discontinued due to failure, were contraindicated to, or intolerant of the following ASMs: valproic acid (n=15, 100%), cannabidiol (n=10, 66.7%), clobazam (n=10, 66.7%), and topiramate (n=8, 53.3%)
- The median time from first FFA shipment to death was 10.2 months (range: 1.0-28.4 months)
- In patients with a mortality event, median initial and final FFA doses were 0.3 mg/kg/day (range: 0.1-0.6 mg/kg/day) and 0.6 mg/kg/day (range: 0.3-0.8 mg/kg/day), respectively
- The estimated mortality rate was 8.02 per 1000 person-years (95% CI, 3.96-12.08)
- Overall SMR from 2021-2023 was 1.88 (95% CI, 1.05-3.14)

Table 2. Baseline Demographics and Patient Characteristics of FFA Naïve Patients With a Mortality Event

	Patients With a Mortality Event[a] n=15
Age at index (years), n (%)	
<2-5	5 (33.3)
6-17	7 (46.7)
≥18	3 (20.0)
Sex, n (%)	
Female	6 (40.0)
Male	9 (60.0)
Previous ASM use, n (%)	
Valproic acid	15 (100)
Cannabidiol	10 (66.7)
Clobazam	10 (66.7)
Topiramate	8 (53.3)
Stiripentol	2 (13.3)
Levetiracetam	2 (13.3)
Time from first shipment to death, months	
Mean (SD)	11.0 (7.41)
Median	10.2
Range	1.03-28.40

[a]A single patient with the same FFA shipment date and date of death was removed from the mortality analysis.
ASM, antiseizure medication; FFA, fenfluramine; SD, standard deviation.

Conclusions

- Because of the single specialty pharmacy model, this real-world analysis included all US patients with DS treated with FFA after it became commercially available
  - Data regarding underlying clinical characteristics or disease severity are limited
- FFA demonstrated good 1-year treatment persistence in patients with at least 1 year of data, which is reflective of good efficacy and safety at a median FFA dose of 0.5 mg/kg/day
- We report a similar all-cause mortality rate as reported by Donnan et al. (8.6 per 1000 patient-years)[6]
- Future studies will evaluate patient characteristics and causes of death, including SUDEP, and real-world use of FFA in other indications

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