Impact of fenfluramine on the expected SUDEP mortality rates in patients with Dravet syndrome

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ABSTRACT

Purpose: To assess the impact of fenfluramine (FFA) on the expected mortality incidence, including sudden unexpected death in epilepsy (SUDEP), in persons with Dravet syndrome (DS).
Methods: In this pooled analysis, total time of exposure for persons with DS who were treated with FFA in phase 3 clinical trials, in United States and European Early Access Programs, and in two long-term open-label observational studies in Belgium was calculated. Literature was searched for reports of SUDEP mortality in DS, which were utilized as a comparison. Mortality rates were expressed per 1000 person-years.
Results: A total of 732 persons with DS were treated with FFA, representing a total of 1185.3 person-years of exposure. Three deaths occurred, all in the phase 3 program: one during placebo treatment (probable SUDEP) and two during treatment with FFA (one probable SUDEP and one definite SUDEP). The all-cause and SUDEP mortality rates during treatment with FFA was 1.7 per 1000 person-years (95% CI, 0.4 to 6.7), a value lower than the all-cause estimate of 15.8 per 1000 person-years (95% CI, 9.9 to 25.4) and SUDEP estimate of 9.3 (95% CI, 5.0 to 17.3) reported by Cooper et al. (*Epilepsy Res* 2016;128:43−7) for persons with DS receiving standard-of-care.
Conclusion: All-cause and SUDEP mortality rates in DS patients treated with FFA were substantially lower than in literature reports. Further studies are warranted to confirm that FFA reduces SUDEP risk in DS patients and to better understand the potential mechanism(s) by which FFA lowers SUDEP risk.
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1. Introduction

Dravet syndrome is a rare, severe, treatment-resistant developmental epileptic encephalopathy with onset in the first year of life in otherwise normal infants. The syndrome is characterized initially by heat- or fever-triggered hemi-clonic and generalized convulsive seizures, often prolonged, during the first year of life, with subsequent development of other seizure types [1, 2]. In addition to high seizure burden, children with Dravet syndrome often develop comorbidities, including motor and speech impairment, learning disabilities, and behavioral problems, including autism, and have a decreased quality of life [2, 3]. Pathogenic variants of *SCN1A*, which encodes the alpha-1 subunit of the

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voltage-gated sodium channel Nav1.1 in the brain and heart, are found in 75% to 85% of Dravet syndrome cases [4], and additional cases can result from *SCN1A* mosaicism or undetected mutations, as well as from several other gene mutations (eg, *GABRG2, SCN1B, SCN2A*) [5].

A leading fear of parents and caregivers of persons with Dravet syndrome is premature mortality, including sudden unexpected death in epilepsy (SUDEP) [3, 6, 7]. SUDEP is a diagnosis of exclusion and is defined as the sudden death of a person with epilepsy not explained by status epilepticus, trauma, or other known causes [8]. Although SUDEP represents a large fraction of all epilepsy-related deaths, its incidence is likely underestimated because definitive postmortem signs or bio-markers of SUDEP do not exist [9, 10]. Both all-cause mortality and SUDEP rates are elevated in children with Dravet syndrome compared with children with pediatric epilepsy [7, 11]. Two major risk factors for SUDEP are frequency of generalized tonic-clonic seizure (GTCS) and failure to adequately control treatment-resistant seizures [12, 13], both of which are hallmarks of Dravet syndrome and likely contribute to the higher incidence of SUDEP in the disease [8, 14].

Three phase 3, double-blind, placebo-controlled trials of fenflur-amine (FFA) added to patients' anti-epilepsy drug (AED) regimens re-ported dramatic and sustained reductions in the frequency of major convulsive seizures in patients with Dravet syndrome [15, 16, 17]. These studies also demonstrated up to 80% reduction in GTCS frequency during treatment with FFA [18]. The magnitude and durability of effects of FFA on convulsive seizures, in particular GTCS, suggest that FFA may provide benefit in reducing the incidence of SUDEP in patients with Dravet syndrome. Here we present a post hoc analysis examining all-cause and SUDEP mortality in patients with Dravet syndrome treated with FFA in phase 3 clinical trials, European (EU) and United States (US) Early Access programs (EAPs), and two cohorts of Dravet syndrome patients in Belgium who have been treated with FFA for up to 32 years and compare the findings with the expected incidence of mortality and SUDEP based on published literature.

2. Methods

The incidence of all-cause and SUDEP mortality in persons with Dravet syndrome while treated with FFA was compared to prior pub-lished studies of people with Dravet syndrome not treated with FFA. A literature search was conducted to identify published reports of mor-tality in Dravet syndrome. The search strategy was "Dravet [title] AND (mortality OR death OR SUDEP)". Titles and abstracts were inspected to identify relevant studies, and the bibliographies of those papers were reviewed for additional reports of mortality studies.

The study population for this analysis comes from four sources: pa-tients participating in the international phase 3 Dravet syndrome clin-ical trials, patients treated in US and EU EAPs, and two cohorts of patients who participated in a long-term open-label study of FFA span-ning 32 years [19–21]. The protocol for each study, including the US EAP and the open-label cohort studies, was reviewed and approved by the appropriate ethics committee. All patients or their caregivers pro-vided written informed consent prior to participation in these studies. The EU EAP was not conducted as a clinical trial; therefore, consent was not required. Screening and enrollment for Studies 1 and 3 began in January 2016. Study 1 was completed in August 2017, and Study 3 was completed in August 2020. Study 2 started enrolling patients in January 2017 and was completed in June 2018. Patients enrolled in the open-label extension (OLE) study at the completion of their double-blind treatment. They enrolled in June 2016, and the most recent interim data analysis was performed on October 14, 2019. The US EAP started enrollment in November 2019, and its final data are from August 20, 2020; the EU EAP began enrollment in December 2018, with the most recent data as of July 31, 2020. The first patient in the Belgian long-term open-label cohort study began treatment in April 1988, and the most recent data summary for this ongoing study was from August 2020.

The phase 3 double-blind studies (Study 1, Study 2, Study 3) enrolled

patients aged 2 to 18 years who had a clinical diagnosis of Dravet syn-drome, and for whom seizures had not been adequately controlled by their current AEDs or other therapies [15–17]. Each study began with a six-week observation period to establish baseline convulsive seizure frequency; patients who met seizure eligibility requirements were then randomized to treatment with placebo or FFA added to their current anti-epilepsy therapy regimen. In Studies 1 and 3, which excluded pa-tients treated with concomitant stiripentol, patients were randomized 1:1:1 to placebo, FFA 0.2 mg/kg/day, or FFA 0.7 mg/kg/day, with a maximum absolute dose of 26 mg/day. The first cohort of 18 patients in Study 2 participated in a drug-drug interaction protocol and enrolled in the OLE study without randomization. The remaining patients in Study 2, who were required to be treated concomitantly with stiripentol, were randomized 1:1 to placebo or FFA 0.4 mg/kg/day, with a maximum absolute dose of 17 mg/day. Studies 1 and 3 began with a two-week titration period followed by a 12-week maintenance period. In Study 2, titration occurred over three weeks and was followed by a 12-week maintenance period. At the end of each core study, each patient un-derwent down-titration (or dummy down-titration) to an FFA dose of 0.2 mg/kg/day before entering the OLE study. All patients entering the OLE started FFA at 0.2 mg/kg/day for the first four weeks; thereafter, doses could be titrated based on efficacy and tolerability up to the maximum doses described above. In addition, adult patients (≥18 years of age) were allowed to directly enroll into the OLE. Both the US and EU EAPs were compassionate use programs that were open to patients with Dravet syndrome who were not eligible for inclusion in any of the phase 3 clinical trials. The FFA treatment regimen was as described above for the phase 3 program OLE study. Finally, the FFA dosing strategy for patients in the Belgian cohorts was similar to the one employed in the OLE study.

2.1. Analysis

The outcomes of interest were all-cause and SUDEP mortality. In-vestigators in each of the studies included in this analysis reported all treatment-emergent adverse events to Zogenix. Deaths that were deemed by study investigators to be due to SUDEP were further classi-fied by study authors using the definitions described by Nashef et al. [22], based on the case narratives.

The primary analysis was the calculation of all-cause and SUDEP mortality rates during treatment with FFA. To do this, total person-years of observation during treatment with FFA was determined by summing FFA treatment time for all patients in the four populations included in this analysis. In addition, mortality rates were calculated for patients in the phase 3 program for periods before treatment with FFA was initi-ated. For this estimate, total patient-years of observation with no exposure to FFA was determined by summing all patients' time in baseline plus all time spent during randomized controlled trials for those who received placebo. Mortality rates were expressed as deaths per 1000 patient-years of observation, with 95% CIs calculated using con-ventional methods.

No formal statistical comparisons with historical mortality estimates were conducted. Because of the post hoc nature of this study and the small number of deaths that occurred, no statistical testing of mortality rates with and without FFA treatment was performed. However, esti-mates of all-cause mortality and SUDEP rates prior to initiation of FFA treatment were used as a "check" to determine if there was an inherent difference in death rates in the patient population coming into these trials, as described in previously published reports.

3. Results

The literature search yielded 84 distinct publications; of these, one was a review article and eight presented population mortality data [7, 11, 23-29]. Studies identified by this search and through inspection of bibliographies are summarized in **Table 1**. Although each study

Table 1
Literature reports of mortality in Dravet syndrome.

Author	Year	Population	N	Death, n	Age at Death	SUDEP, n	SE, n	DS Mortality Rate	SUDEP Rate	SE Rate
Cooper et al. [11]	2016	Dravet—first 100 unrelated patients recruited to Epilepsy Genetics Research Program	100	17	7 y (median)	10	4	15.84/ 1000 py	9.32/ 1000 py	
Sakauchi et al. [28]	2011	Questionnaire to 246 hospitals	438	59*	6 y 8 mo (median)	31	21	14.4%	7.1%	4.8%
Shmuely et al. [29]	2016	Review	2599	177	8.7 y (mean)	87	56	6.8%	3.3%	2.2%
Skluzacek et al. [7]	2011	Patient-support forum surveys	833	31	4.6 y (mean)	19	10	7.0% by 18 y	2.9% by 18 y[†]	3.9% by 18 y
Akiyama et al. [23]	2010	Single-center observation	37	6	5.1 to 12.6 y	1	3	16.2%	2.7%	8.1%
Genton et al. [26]	2011	Single-center observation	24	5	24.8 y (mean)	3	1	20.8%	12.5%	4.2%
Dravet et al. [25]	1992	Single-center observation	63	10	9.8 y (mean)	2	2	15.9%	3.2%	3.2%
Oguni et al. [27]	2001	Recruitment—SME+SMEB	84	12	65 mo (mean)	3	7	14.3%	3.6%	8.3%
Brunklaus et al. [24]	2012	UK 5-year birth cohort—SCN1A+	88	5	5 y (median)	3	2	5.7%	3.4%	2.3%

Abbreviations: DS, Dravet syndrome; mo, months; py, person-years; SE, status epilepticus; SME, severe myoclonic epilepsy in infants; SMEB, severe myoclonic epilepsy in infancy—borderline; SUDEP, sudden unexpected death in epilepsy; y, years.

* A total of 63 deaths were reported, but 4 patients had insufficient data regarding the death for inclusion in the analysis of SUDEP and SE.

† The study reports an annual rate of SUDEP of 0.6%, which translates to 6 per 1000 per year.

reported elevated all-cause mortality and SUDEP rates for the populations studied, comparison of raw rates without an accurate representation of the observation period is not appropriate. Two studies reported Kaplan-Meier survival analysis to estimate mortality rates [7, 11], and the study of Cooper and colleagues appeared more rigorous [11]. We have chosen to use their all-cause mortality rate of 15.8 per 1000 person-years (95% CI, 9.89 to 25.39) and their SUDEP mortality rate of 9.32 per 1000 person-years (95% CI, 5.03 to 17.27) as comparators for our analysis (the 95% CIs were calculated based on data in Cooper et al. [11]).

A description of our study population is presented in Table 2. The age distributions of patients in these studies were similar based on medians and 25% and 75% quartiles. Patients were primarily children and adolescents. A total of 10 patients from the US EAP and the Belgium cohort were <2 years old when they started treatment with FFA, and 62 patients from the US EAP, EU EAP, and Belgium cohort were ≥19 years old upon starting FFA treatment. At the time of initiation of fenfluramine, 89.9% of patients were ≤18 years old (range of the four studies, 81.2% to 99.7%), and 30.4% were ≤5 years old (range, 26.9% to 51.2%). Observation time during treatment with FFA totaled 1185.3 patient-years, with more than half of the total coming from the phase 3 development program. Observation time while patients were not treated with FFA (ie, when they were receiving standard-of-care during the baseline period and given placebo during the randomized treatment period) was much shorter, at 85.8 patient-years.

As of the cutoff date for this interim analysis, three patients had died during participation in the phase 3 development program: two patients (ages 2 and 5 years) died while treated with FFA during the OLE study in the phase 3 program, and one 8-year-old patient died while treated with placebo in one phase 3 study. Each of these deaths was deemed by the

principal investigator to be due to SUDEP (Definite SUDEP Plus, $n = 1$; probable SUDEP, $n = 2$) and not related to FFA. None of these three patients, nor any of the other participants in these studies, exhibited echocardiographic evidence of valvular heart disease or pulmonary artery hypertension. The case narratives are presented in the online supplemental materials. No deaths have occurred in the Belgian cohorts, in the US EAP, or in the EU EAP.

Based on the mortality rate estimate reported by Cooper et al. [11] and the number of person-years of observation in the present study, we would have expected 19 all-cause deaths during treatment with FFA, assuming no effect of treatment. Similarly, we would have expected 11 of those deaths to be due to SUDEP. All-cause, as well as SUDEP-specific, mortality rates during treatment with FFA were 1.7 deaths (95% CI, 0.4 to 6.7) per 1000 person-years (Fig. 1).

Nearly all the patients in the phase 3 program participated in a 6-week baseline period prior to randomization and initiation of treatment and about one-third of them were randomized to placebo. The all cause and SUDEP mortality rates during this pre-FFL period of 85.8 person-years was 11.7 deaths per 1000 person-years (95% CI, 1.7 to 81.8).

4. Discussion

The primary analysis of our study concluded that while treated with FFA at doses ≤0.7 mg/kg/day, persons with Dravet syndrome experienced both all-cause mortality and SUDEP incidence rates of 1.7 deaths per 1000 person-years. The all-cause and SUDEP mortality rates in the present analysis are substantially lower than the 15.84 and 9.32 per 1000 person-years reported by Cooper et al. for patients with Dravet syndrome receiving standard of care [11]. In addition, the all-cause

Table 2
Demographic and baseline characteristics.

Study	Treatment	N	M:F	Age, years,* median (min, 25%, 75%, max)	Years of Observation, mean	Person-years of Observation
Phase 3	FFA	366	197:169	9 (2, 5, 13, 19)	1.75	602.8
US EAP	FFA	134	68:66	8(1, 4, 14, 32)	0.68	90.9
EU EAP	FFA	191	98:93	9 (2, 5, 15, 47)	0.74	141.8
Belgium	FFA	41	21:20	5(<1, 2, 11, 29)	8.53	349.9
Total	FFA	732	384:348	8 (<1, 5, 14, 47)	1.62	1185.3

Abbreviations: EAP, early access program; FFA, fenfluramine.

* Age is age at study entry, except for the EU EAP, in which age is age at cutoff date for this analysis.
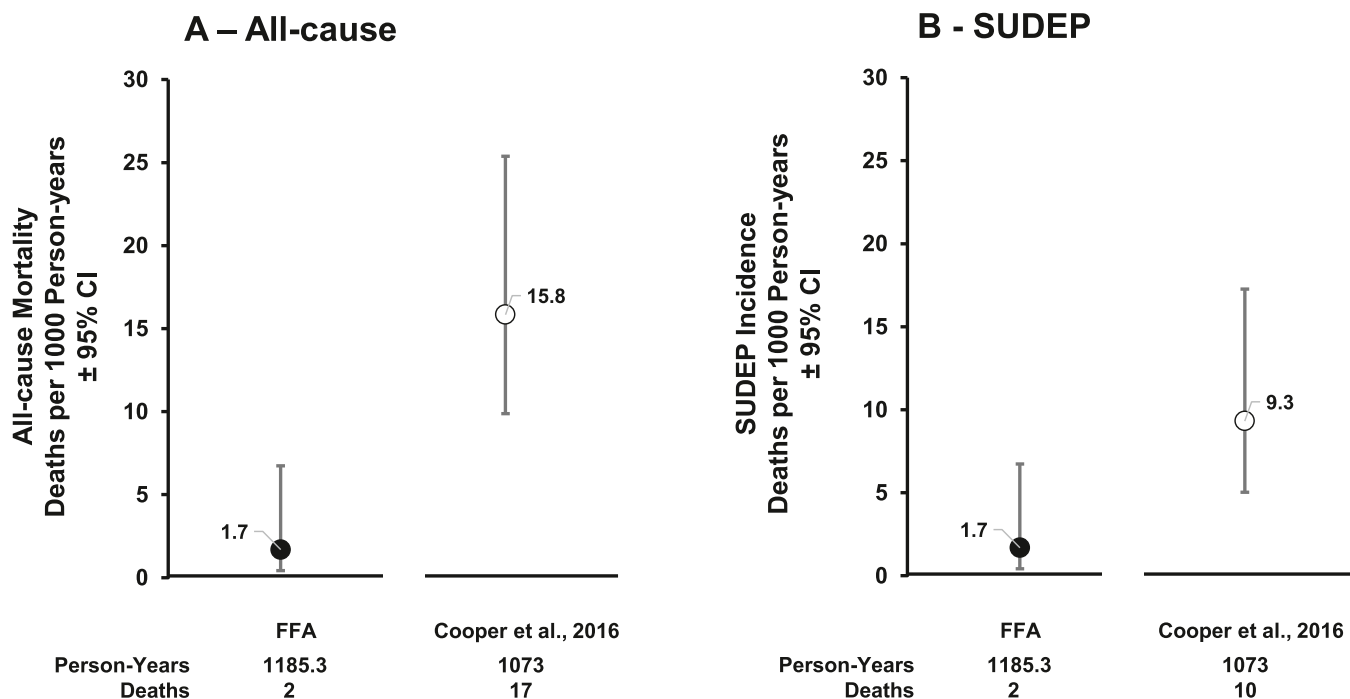
Fig. 1. Incidence of (A) All-cause and (B) SUDEP mortality in Dravet syndrome before and during treatment with fenfluramine. FFA, fenfluramine; SUDEP, sudden unexpected death in epilepsy.
The 95% CIs for the Cooper et al. rates were calculated from data presented in their report. [11].

mortality rate while treated with FFA is similar to that reported for pediatric patients with epilepsy in general (2.28 per 1000 person-years [95% CI, 1.74 to 2.82]) [30], a value about 7 times lower than observed in the DS patient population [11] . Furthermore, the SUDEP rate observed in the present study is only slightly higher than recent estimates of the incidence of SUDEP in statewide and nationwide pediatric populations with epilepsy (0.34, 1.1, and 1.17 per 1000 patient-years [31–33]). Although the number of person-years of observation prior to the addition of FFA to treatment regimens in the present study was small (85.8 patient-years), the all-cause mortality rate of 11.7 deaths per 1000 person-years is aligned with that reported by Cooper et al.

As noted above, only two of the previously published studies of death in patients with DS provided mortality rates that could be used for comparison with the present study [7, 11]. In the Skluzacek et al. report of 833 Dravet syndrome patients, 31 (3.7%) children died between the ages of 10 months and 17 years [7]: 61% due to SUDEP and 32% due to status epilepticus. These authors reported a mean annual incidence of SUDEP of 0.6%, which would correspond to 6 deaths per 1000 person-years. Although this was the largest study, patients were self-selected through survey responses, and investigators relied on parents' reports of the cause of death. In contrast, Cooper et al. studied the first 100 unrelated patients recruited to the Epilepsy Genetics Research Program who had an electroclinical phenotype consistent with Dravet syndrome [11]. Patients' physicians provided information about the circumstances of death, and postmortem records were reviewed when available. Based on these factors of the study design, we chose it for comparison with the present study.

The pathophysiology of SUDEP is not well understood, but research suggests that multiple factors may be involved. Major risk factors for SUDEP include the presence and frequency of GTCS, followed by failure to adequately control seizures [12, 34]. It appears likely that the substantial reduction in convulsive seizure frequency, including GTCS frequency, coupled with significantly prolonged periods of seizure freedom reported in the clinical trials of FFA are the major contributors to the reduction in all-cause and SUDEP mortality reported here [15-17, 35].

Severe peri-ictal respiratory dysfunction is common in Dravet

syndrome patients [36] and may also contribute to elevated SUDEP rates. Results of experiments using the DBA/1 mouse model of SUDEP offer some support for a role of FFA. The DBA/1 mice are susceptible to tonic seizures caused by several stimuli that are typically followed by respiratory arrest and death in the post-ictal period [37]. FFA, which acts in part by stimulating neuronal release of serotonin and inhibiting its reuptake, has also been shown to block seizure-induced respiratory arrest in the DBA/1 mouse model of SUDEP at doses without anticonvulsant activity [37]. In the DBA/1 mouse, drugs that enhance serotonin transmission inhibit mortality, and drugs that antagonize serotonin enhance death [37]. Further support for the role of serotonin in SUDEP comes from the observation that 5-hydroxytryptophan, a precursor for serotonin synthesis, reduced seizure-induced respiratory arrest in DBA/1 mice [38]. In the DBA/1 model, FFA prevented death via a specific serotonin receptor, 5HT4, presumably in the brainstem [39]. These results suggest that FFA may protect against SUDEP independent of its anticonvulsant activity in Dravet syndrome patients. FFA also acts as a positive modulator of the sigma 1 receptor [40], and there may be a synergistic interaction between sigma-1 and serotonin receptors, increasing serotonergic neuronal firing [41]. This interaction may contribute to the low mortality and SUDEP incidence observed in the present study.

This study is limited by its post hoc design, the short overall observation time, and the pooling of heterogeneous groups of patients from different settings (i.e., clinical trial, open-label studies, clinical practice); however, the endpoint for this analysis is mortality, which is easily identified regardless of the setting in which the patients were treated. The majority of the patients in the present analysis participated in the phase 3 development studies, and therefore, their observation time was limited by study designs. The short observation time is mitigated in part by the large number of patients included in this analysis. The small number of deaths precluded firm conclusions regarding incidence rates of deaths, including SUDEP, before and during treatment with FFA in the phase 3 development program. Although it is well established that there is a high incidence of SUDEP in Dravet syndrome, the magnitude of the increase has not been established despite multiple studies; therefore, the

selection of a single historical study for comparison may weaken our conclusions. About half of the patients were subjects in structured clinical trials that required a centrally adjudicated diagnosis of Dravet syndrome and a minimum seizure frequency for enrollment. The other patient groups may have had greater diagnostic uncertainty and variable underlying seizure rates prior to treatment; however, all investigators participating in the EAPs and in the original Belgian cohorts were expert pediatric epileptologists and were also investigators in the phase 3 studies of FFA, which may have minimized such differences. Participation in clinical trials may have influenced the level of attention that patients received, possibly altering overall risk of mortality and SUDEP.

5. Conclusion

This post hoc analysis suggests that DS patients treated with FFA experienced a substantially lower rate of all-cause and SUDEP-related mortality compared with a historical natural history cohort. Further studies are warranted to understand if this effect may be due to sustained, profound reduction in GTCS, FFA's pharmacology, or a combination of both.

Data sharing policy

Zogenix is currently in the process of developing a data sharing plan and process.

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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.

Author contributions

JHC and BSG are designated as co-first authors to reflect their important contributions to this manuscript. JHC, BSG, and ARG made substantial contributions to the conception or design of the work, drafting of manuscript content, and analysis and interpretation of data. BSG was instrumental in suggesting the analysis of SUDEP rates in patients with Dravet syndrome treated with fenfluramine and comparing the results to published values. BC, A-SS, and ML made substantial contributions to acquisition of data. AG-N, OD, BC, LL, A-SS, ED, EW, SK, AA, ML, and ARG contributed to drafting of the manuscript for content and to analysis or interpretation of data.

Declaration of Competing Interest

Dr. Cross has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo, and Marinus. She has been a speaker and has served on advisory boards for GW Pharma, Zogenix, and Nutricia; all remuneration has been paid to her department. She holds an endowed chair at UCL Great Ormond Street Institute of Child Health, as well as grants from NIHR, EPSRC, GOSH Charity, ERUK, and the Waterloo Foundation. Her research is supported by the National Institute of Health Research (NIHR) Biomedical Research centre at Great Ormond Street Hospital.

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Dr. Ceulemans has received research funding from Brabant and Zogenix and has served as consultant for Brabant and Zogenix. Dr. Ceulemans has a patent for ZX008. Dr. Ceulemans and the KU Leuven University/Antwerp University Hospital may benefit financially from a royalty arrangement that is related to this research if Zogenix is successful in marketing its product, fenfluramine. The terms of this arrangement have been reviewed and approved by the KU Leuven University/Antwerp University Hospital.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2021.10.024.

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