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CRITICAL REVIEW

Comprehensive scoping review of fenfluramine's role in managing generalized tonic–clonic seizures in developmental and epileptic encephalopathies

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Abstract

Developmental and epileptic encephalopathies (DEEs) are characterized by pharmacoresistant seizures and developmental delay. Patients with DEEs experience multiple seizure types, including tonic–clonic seizures (TCS) that can be generalized tonic–clonic (GTCS) or focal evolving to bilateral tonic–clonic (FBTCS). Fenfluramine (FFA) has demonstrated efficacy in reduction of TCS in patients with Dravet syndrome (DS), Lennox–Gastaut syndrome (LGS), and other DEEs. Using the PRISMA-ScR (Preferred Reporting Items for Systematic Review and Meta-Analyses extension for Scoping Review) guidelines, we performed a scoping review to describe changes in TCS in patients treated with FFA. A comprehensive search of five literature databases was conducted up to February 14, 2023. Studies were included if they reported change in GTCS or TCS (but not FBTCS) after treatment with FFA in patients with DEEs. Duplicate patients and studies with unclear efficacy data were excluded. Fourteen of 422 studies met the eligibility criteria. Data extracted and evaluated by expert clinicians identified 421 unique patients with DS (in nine studies), CDKL5 deficiency disorder, *SCN8A*-related disorder, LGS, *SCN1B*-related disorder, and other DEEs. The median percent reduction in GTCS or TCS from baseline was available in 10 studies ($n = 328$) and ranged from 47.2% to 100%. Following FFA treatment, 10 studies ($n = 144$) reported ≥50% reduction in GTCS or TCS from baseline in 72% of patients; in nine of those ($n = 112$), 54% and 29% of patients achieved ≥75% and 100% reduction in GTCS or TCS from baseline, respectively. Overall, this analysis highlighted improvements in GTCS or TCS frequency when patients were treated with FFA regardless of the DEE evaluated. Future studies may confirm the impact of FFA on TCS reduction and on decreased premature mortality risk (including sudden unexpected death in epilepsy), improvement in comorbidities and everyday executive function, decreased health care costs, and improvement in quality of life.

KEYWORDS
Dravet syndrome, epilepsy, Lennox–Gastaut syndrome, seizure, SUDEP

1 | INTRODUCTION

Developmental and epileptic encephalopathies (DEEs) are a group of rare disorders characterized by pharmacoresistant seizures of multiple types that present early in infancy or childhood.[1,2] Patients with DEEs often experience both focal and generalized seizures, but tonic–clonic seizures (TCS) or generalized TCS (GTCS) are a prominent feature of most DEEs.[3-5] Both the underlying etiology and epileptiform activity contribute to the cognitive and behavior impairment in these patients.[1,3,5-8]

In general, the main goals of treatment include reduction in seizure severity (frequency, type, and duration) and management of associated comorbidities to improve patient and family quality of life (QOL).[9,10] Seizure refractoriness may worsen cognitive and behavioral comorbidities, including intellectual disability and/or motor impairments.[11]

In all epilepsies, a history of TCS (including GTCS and focal to bilateral TCS [FBTCS]) and seizure refractoriness are consistently cited as major risk factors for premature death and sudden unexpected death in epilepsy (SUDEP).[12–18] SUDEP is a poorly understood—yet common—cause of death in patients with DEEs and epilepsy in general,[13] and it is also a leading fear of parents and caregivers.[4,19,20] As such, antiseizure medications (ASMs) that can reduce seizure burden, namely GTCS and TCS, may reduce the risk of death in patients with DEEs.[13,21]

Fenfluramine (FFA) has a unique mechanism of action that targets the serotonergic system and sigma-1 receptors (S1R).[22] It is approved for the treatment of seizures in Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) in patients ≥2 years old in the USA[23] and as add-on therapy for the treatment of seizures associated with DS and LGS in the EU, UK, and Japan.[24-27] FFA has been demonstrated to decrease GTCS frequency in DS and LGS.[28-31]

Here, we aim to provide a comprehensive overview of FFA efficacy in reducing GTCS or TCS in a group of DEEs inclusive of but beyond DS and LGS.

Key points

- Patients with DEEs exhibit TCS, including GTCS.
- This review describes the change in GTCS or TCS from baseline after treatment with FFA as reported in published studies of a group of DEEs.
- In patients with the DEEs analyzed, FFA was associated with clinically significant reduction of GTCS or TCS from baseline.
- Future studies may evaluate FFA impact on behavior, sleep, cognition, and reduced risk of death (including SUDEP).

2 | MATERIALS AND METHODS

This review was conducted as per the PRISMA-ScR (Preferred Reporting Items for Systematic Review and Meta-Analyses extension for Scoping Review) guidelines.

2.1 | Search strategy

A comprehensive search of BIOSIS Previews, Embase, PubMed, MEDLINE, and Northern Light Life Sciences Conference Abstracts without time or language restriction was conducted up to February 14, 2023. Clinical trials, research articles, and published congress abstracts involving the following search terms were evaluated: "fenfluramine" or "ZX008" and "seizure" or "epilepsy". No date limitations or language restrictions were applied; translations of relevant non-English language articles were obtained if needed. Relevant articles were also identified through searches of authors' personal files. This was performed to ensure relevant congress abstracts that were not published, as in the case of late-breaker abstracts, were captured.

2.2 | Eligibility criteria

Studies were included if they described patients with a DEE (according to the International League Against Epilepsy definition[3,5,32]) who reported change in GTCS or TCS after treatment with FFA. Studies were excluded if there were insufficient or unclear efficacy data reported, if duplicate patients could not be discerned (as in the case of patients described in more than one publication), or if data from published abstracts were not available as presentations at an international congress. In the case of duplicate patients, the study that provided the most comprehensive overview of the patient(s) was

evaluated and included. When necessary, authors reviewed study methodology and patient details to ensure cases were eligible.

2.3 | Definitions and use of FFA

In this review, incidence of GTCS or TCS was documented if the publication described the occurrence of "GTCS" or "TCS". GTCS refers to generalized (onset) tonic–clonic seizures; efficacy in reducing secondary generalized seizures or FBTCS was not specifically captured. Among the various studies, doses may have been reported as "fenfluramine" (base) or "fenfluramine hydrochloride". For consistency, doses were converted and are reported as FFA base equivalents in this review.

2.4 | Data collection and outcomes of interest

For each study, we collected the type of study and type of DEE evaluated. The type of convulsive seizure evaluated (GTCS, TCS, or other relevant umbrella term) was captured, as was the number of patients for whom there were evaluable data for change in those seizure types after FFA treatment. Additional variables extracted from the studies included demographics, FFA dose, duration of FFA exposure, and evaluation period. Seizure reduction outcomes reported as the median percent reduction from baseline in GTCS or TCS and/or the proportion of patients achieving GTCS or TCS reduction thresholds were included. If needed, the authors requested additional data from UCB Pharma.

2.5 | Statistical analysis

Findings are summarized descriptively. Specifically, medians, means, ranges, and standard deviations (SDs) were used for continuous variables and percentages for categorical variables.

3 | RESULTS

3.1 | Literature search findings

The literature search and review of authors' files resulted in 422 studies, including one late-breaking abstract. Additional duplicate records were identified ($n = 147$) and removed prior to screening. Two hundred seventy-five titles and abstracts were then independently screened by two expert clinicians (A.G.-N., R.N.) for eligibility. Of those, 21 full-text papers or abstracts/posters were evaluated. Two papers required further review by the lead authors. One study described patients with self-induced seizures, but due to age of seizure onset and intelligence quotient > 75, the authors decided to exclude one patient because he was unlikely to have an underlying DEE.[33] Another paper was excluded due to study methodology (specifically titration to efficacy) differing substantially from the other open-label studies reviewed.[34] One poster[30] assessed GTCS reduction in two separate randomized controlled studies.[35,36] Overall, 14 studies met the eligibility criteria (Figure 1); the data extraction process is described in Table S1.

3.2 | Overview of studies

Of the 14 studies that met the inclusion criteria, 12 were full-length publications, including one that was initially presented as a poster[37] and has since been published as a full-length article.[38] Two of the studies were presented in one poster[30] where pooled data from 2 parent studies was included.[35,36] Three were randomized controlled trials (RCTs), four were observational studies, three were open-label studies, three were case reports/series, and one was an open-label extension (OLE) study of patients who had completed a phase 3 RCT. Patients were provided with FFA through an early access program in three of the studies.[39-41] One retrospective case report described a patient who had enrolled in the DS OLE study de novo as an adult.[42]

3.3 | Patient characteristics

Among the 14 studies, 646 patients were enrolled and treated with FFA for the following DEEs: DS ($n = 378$), LGS ($n = 247$), CDKL5 deficiency disorder (CDD; $n = 6$), *SCN8A*-related disorder ($n = 3$), *SCN1B*-related disorder ($n = 1$), and other DEEs ($n = 11$). Of the 646, there were 421 (65.2%) unique patients with evaluable GTCS or TCS (Table 2). Demographics specific to the patients experiencing GTCS or TCS at baseline could be discerned for eight of the 14 studies ($n = 36$). Of those 36 patients, 52.8% were female, and the mean ± SD age was 10.4 ± 7.4 years. Those patients were on a mean of 2.7 concomitant ASMs at the start of FFA (range = 1–5).[33,39,42-47]

3.4 | FFA regimens

The typical starting dose of FFA in these studies was .2 mg/kg/day (maximum of 26 mg/day or 17 mg/

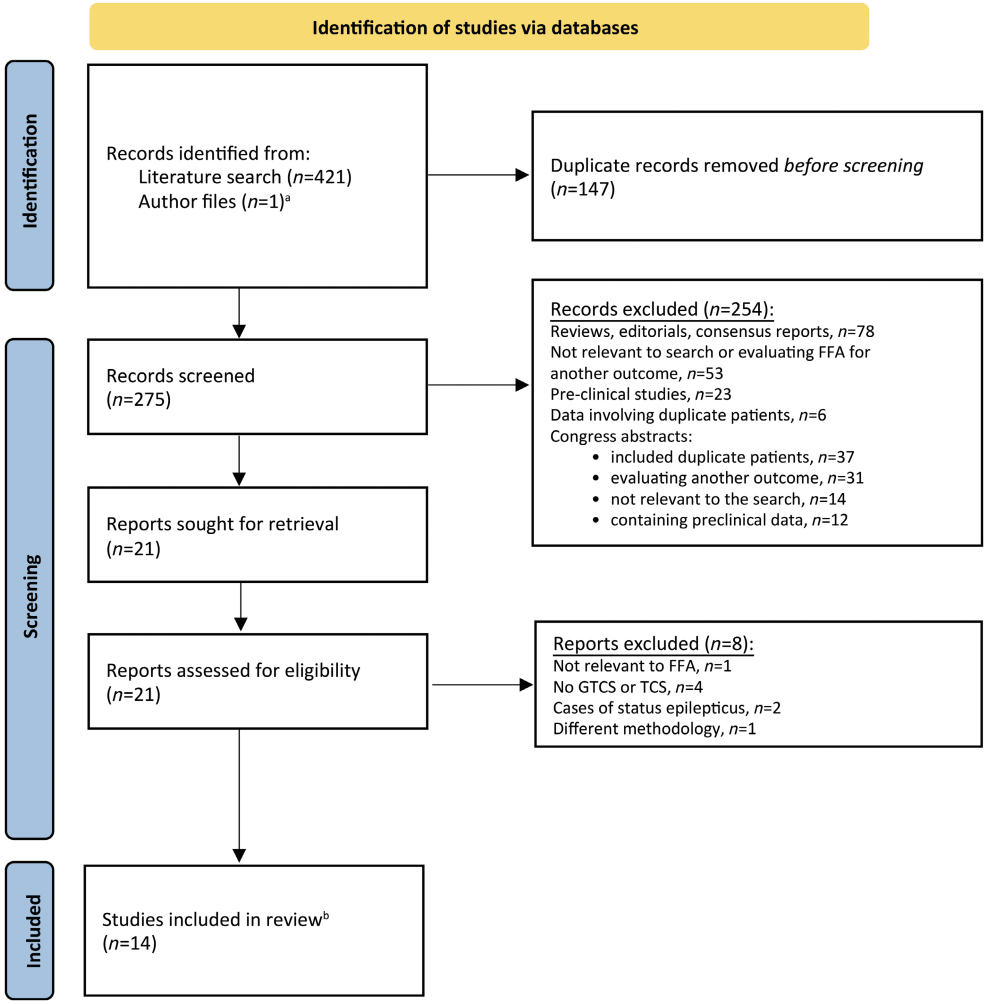

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) flow diagram. [a]One congress abstract was identified by the authors; because it was a late-breaker congress abstract, it was not published or found through the literature search. [b]One congress abstract described data from two published studies and thus will be described here as two separate studies. FFA, fenfluramine; GTCS, generalized tonic–clonic seizure; TCS, tonic–clonic seizure.

day if given with stiripentol [STP]), and the dose was titrated per protocol or by physician discretion (Table 1). Patients were treated with FFA for a duration ranging from 2 months to 27 years, but the evaluation period for GTCS or TCS reduction varied among the different studies (up to a mean of 10 years; Table 2). Disposition for the evaluable patients with GTCS or TCS was available for five of the 14 studies ($n = 17$)[39,42-44,46]; most patients (88.2%) were continuing FFA at last follow-up. Of the two patients with DS who discontinued treatment, one discontinued FFA due to lack of efficacy, and one patient was seizure-free and chose to stop FFA. The patient who became seizure-free remained seizure-free for 2 years after discontinuing FFA.[43] In the other studies, disposition was not explicitly described, or discontinuation rates could not be discerned only for those patients experiencing GTCS or TCS.

3.5 | Efficacy results

Median percent reduction in GTCS or TCS frequency from baseline was available from 10 studies, and the proportion of patients achieving seizure reduction thresholds from baseline was reported or could be calculated in 10 studies. Both types of outcomes were reported or discernable in six of the studies.[39,40,42,45-47] Studies and the endpoints reported are described in Table 2.

The median percent reduction in GTCS or TCS from baseline ranged from 47.2% to 100% in 328 patients. Two of those studies reported data for two different FFA dosages (Table 2, Figure 2). In the four non-DS publications specifically (Devinsky et al.,[47] Aledo-Serrano et al.,[39] Knupp et al.,[29] and Zhu et al.[46]), the median percent reduction in GTCS or TCS from baseline ranged from 48.8% to 100% in 115 patients. In the three DS RCTs, median percent reductions in GTCS ranged from 47.2% to 90.8%; in the other DS

TABLE 1 Overview of study designs ($N = 14$).

First author (listed by DEE alphabetically)	DEE evaluated	Study design	Adjunctive FFA dosage regimen	Seizure endpoint evaluated
Boel[33]	Intractable self-induced seizures[a]	Retrospective, observational	Titrated to response and tolerability per physician discretion	Seizures (including GTCS)
Ceulemans et al. (2012)[43]	DS	Retrospective, observational	Titrated to response and tolerability per physician discretion	Seizures (including GTCS)
Ceulemans et al. (2016)[44]	DS	Prospective, observational	Titrated to response and tolerability per physician discretion (maximum daily dose of 17 mg/day, not exceeding .86 mg/kg/day	TCS
Devinsky et al.[b] (2019)[30]	DS	Double-blind phase 3 RCT	.2 or .7 mg/kg/day (max 26 mg/day); titrated from .2 to .7 mg/kg/day over 2 weeks	GTCS
Devinsky et al.[c] (2019)[30]	DS	Double-blind phase 3 RCT	.4 mg/kg/day with stiripentol (max, 17 mg/day); titrated from .2 to .4 mg/kg/day over 3 weeks	GTCS
Schoonjans et al.[45]	DS	Prospective, open-label	.22–.86 mg/kg/day titrated to response and tolerability (max 17 mg/day)[d]	Major motor seizures (including TCS)[e]
Specchio et al.[40]	DS	Prospective, open-label	.2–.7 mg/kg/day (max, 26 mg/day or 17 mg/day if with stiripentol); titrated to response and tolerability per physician discretion	GTCS
Steinhoff et al.[42]	DS	Retrospective case report	.2 mg/kg/day titrated to response and tolerability per protocol (max, 26 mg/day or 17 mg/day if with stiripentol)	GTCS
Strzelczyk et al.[41]	DS	Retrospective, observational	Titrated to response and tolerability to .7 mg/kg/day (max, 26 mg/day) or .4 mg/kg/day with stiripentol (max, 17 mg/day)	GTCS
Sullivan et al.[37]	DS	Double-blind phase 3 RCT	.2 or .7 mg/kg/day (max, 26 mg/day); titrated from .2 to .7 mg/kg/day over 2 weeks	GTCS
Devinsky et al. (2021)[47]	CDD	Investigator-initiated open-label	Titrated to response and tolerability; maximum dose of .7 mg/kg/day (max, 26 mg/day)	GTCS
Aledo-Serrano et al.[39]	*SCN8A*	Retrospective case series	.2–.7 mg/kg/day titrated to response and tolerability per physician discretion	GTCS or overall seizures[f]
Knupp et al.[29]	LGS	OLE	.2 or .7 mg/kg/day (max, 26 mg/day); titrated from .2 to .7 mg/kg/day over 2 weeks	GTCS
Zhu et al.[46]	*SCN1B*	Retrospective case report	.2 mg/kg/day titrated gradually to .7 mg/kg/day	GTCS

Abbreviations: CDD, CDKL5 deficiency disorder; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; FFA, fenfluramine; GTCS, generalized tonic-clonic seizure(s); LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomized controlled trial; SCN1B, *SCN1B*-related disorder; SCN8A, *SCN8A*-related disorder; s, seconds; TCS, tonic-clonic seizure(s).

[a]All patients were initially reported as having self-induced seizures; five patients were later diagnosed with DS and described in Ceulemans et al.[44] and one patient was excluded after author review.

[b]Data for change in GTCS frequency were reported in Devinsky et al.[30] (Child Neurology Society meeting), but Lagae et al.[35] is the parent RCT.

[c]Data for change in GTCS frequency were reported in Devinsky et al.[30] (Child Neurology Society meeting), but Nabbout et al.[36] is the parent RCT.

[d]Doses were reported as 'fenfluramine HCl' in this study, but were converted here to FFA base equivalents for consistency.

[e]Major motor seizures defined as tonic-clonic, tonic, clonic, atonic, and myoclonic seizures lasting >30 s.

[f]Exact change in GTCS was not reported for one patient and was thus described as reduction in overall seizure frequency.

TABLE 2 Overview of FFA treatment in patients reporting GTCS or TCS in 14 studies.

First Author (listed alphabetically by author name and DEE)	DEE evaluated	Overall study population, *N* = 646	Nonduplicate patients evaluated for GTCS or TCS reduction, *n* = 421	Observation period	FFA treatment duration, mean or median (range)[a]	Median % reduction in GTCS or TCS (range)	Patients achieving		
							≥50% reduction, *n* (%)	≥75% reduction, *n* (%)	100% reduction, *n* (%)
Boel[33]	Intractable self-induced seizures	11	5[b]	Treatment period	Median 6.4 years (3–7.8)	NR	5 (100)	5 (100)	3 (60)
Ceulemans[43]	DS	12[c]	2	Treatment period	Mean 10 years (9–11)	NR	1 (50)	1 (50)	1 (50)
Ceulemans[44]	DS	10	10	5 years	Mean 16.1 years (6–27)	NR	6 (60)	6 (60)	6 (60)
Devinsky[30,31]	DS	79	FFA .2 mg/kg/day: 29	14 weeks	14 weeks	47.6 (−43.9 to 100)	NR	NR	NR
			FFA .7 mg/kg/day: 31			79.9 (−140.1 to 100)	NR	NR	NR
Devinsky[30]	DS	43	39	15 weeks	15 weeks	64.2 (−115.6 to 100)	NR	NR	NR
Schoonjans[45]	DS	9	9	Treatment period	Mean 1.9 years (.3–5.1)	75.0 (28 to 100)	7 (77.8)	5 (55.6)	1 (11.1)
Specchio[40]	DS	52	32	3 months	Median 9 months (3–14.9)[d]	74.5 (42.3 to 93.8)	22 (68.8)	NR	NR
Steinhoff[42]	DS	1	1	Treatment period	21 months	100	1 (100)	1 (100)	1 (100)
Strzelczyk[41]	DS	78	76	3 months	Median 255.5 days (31–572)[d]	NR	52 (68.4)	34 (44.7)	18 (23.7)
Sullivan[31,37]	DS	94	FFA .2 mg/kg/day: 34	14 weeks	14 weeks	47.2 (−87.6 to 100)	NR	NR	NR
			FFA .7 mg/kg/day: 38			90.8 (3.6 to 100)	NR	NR	NR
Devinsky[47]	CDD	6	5	Treatment period	Mean 5.3 months (2-9)[d]	90.0 (86 to 100)	5 (100)	5 (100)	1 (20)
Aledo-Serrano[39]	*SCN8A*	3	3	Treatment period	Median 3.7 years (.8–4.2)	100.0 (86 to 100)[e]	3 (100)	3 (100)	2 (66.7)
Knupp[29,31]	LGS	247	106	Up to 15 months	Up to 15 months	48.8 (−2625 to 100)	NR	NR	NR
Zhu[46]	*SCN1B*	1	1	Treatment period	10 months	50.0	1 (100)	0 (0)	0 (0)

Abbreviations: CDD, CDKL5 deficiency disorder; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; FFA, fenfluramine; GTCS, generalized tonic–clonic seizure(s); LGS, Lennox–Gastaut syndrome; NR, not reported; *SCN1B, SCN1B*-related disorder; *SCN8A, SCN8A*-related disorder; TCS, tonic–clonic seizure(s).

[a]Treatment duration for only the patients with evaluable GTCS or TCS (*n* = 421), unless otherwise noted.

[b]Eleven patients were described in this study, but 5 were also included in the Ceulemans et al.[43] and subsequent Ceulemans et al.[44] publications and are thus not included as part of this citation in this analysis. One patient was deemed by authors as not having a DEE and was excluded from analysis.

[c]Twelve patients were described in this study, but 10 were prospectively followed in the Ceulemans et al. 2016 publication[44] (including 5 from Boel and Casaer[33]); therefore, only 2 patients are included as part of this citation in this analysis.

[d]Treatment duration is reported for all patients in the study.

[e]Exact change in GTCS was not reported for one patient and was thus described as reduction in overall seizure frequency.

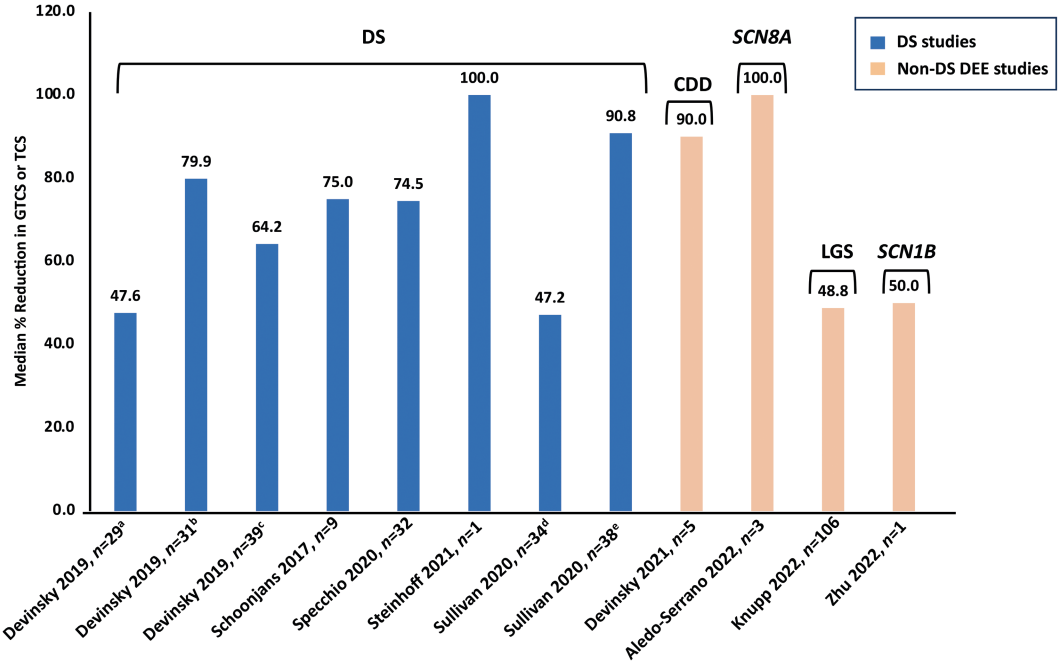

FIGURE 2 Median percent reduction in generalized tonic–clonic seizures (GTCS) or tonic–clonic seizures (TCS) from baseline in six Dravet syndrome (DS) studies and four non-DS developmental and epileptic encephalopathies (DEEs; $n = 328$). Two reports are displayed as two separate bars because two FFA dose regimens were evaluated in those studies.[30,37] [a]Parent randomized controlled trial (RCT) is Lagae et al.,[35] and this bar reflects the median percent reduction associated with fenfluramine (FFA) .2 mg/kg/day. [b]Parent RCT is Lagae et al.,[35] and this bar reflects the median percent reduction associated with FFA .7 mg/kg/day. [c]Parent RCT is Nabbout et al.[36] [d]This bar reflects the median percent reduction associated with FFA .2 mg/kg/day. [e]This bar reflects the median percent reduction associated with FFA .7 mg/kg/day. CDD, CDKL5 deficiency disorder; *SCN1B, SCN1B*-related disorder; *SCN8A, SCN8A*-related disorder.

publications (case reports or open-label studies, $n = 3$), the median reductions reported were 75.0%, 74.5%, and 100% (Table 2, Figure 2).

Another outcome evaluated was the proportion of patients to achieve seizure reduction thresholds, which was discernable in 10 studies ($n = 144$; Table 2); of those, 72% of patients achieved a ≥50% reduction in GTCS or TCS from baseline (Figure 3A). The study by Specchio et al.[40] ($n = 32$) reported only ≥50% reduction (and not ≥75% or 100%) and is thus not included in the evaluation of the other seizure reduction thresholds. Among the other nine studies ($n = 112$), 54% and 29% of patients achieved ≥75% and 100% reduction in GTCS or TCS from baseline, respectively (Figure 3A). Focusing on the non-DS studies, 100%, 93%, and 36% of patients achieved ≥50%, ≥75%, and 100% reductions in GTCS or TCS from baseline, respectively (Figure 3B).

4 | DISCUSSION

Although DEEs are heterogeneous and associated with variable phenotypes and seizure types, most patients with DEEs experience GTCS. This scoping review identified 14 studies describing patients with DEEs treated with FFA; 65% of patients in the studies selected for analysis ($n = 421$) reported GTCS or TCS. A smaller study of 36 patients with DEEs also reported that 64% of patients were experiencing GTCS.[48] One of the main goals of DEE treatment is to alleviate seizure burden by targeting the most problematic seizure type.[10] Although total cessation of seizures is not likely to be attainable for these patients, a reduction, especially of the most severe seizures, could mitigate neurodevelopmental delay, improve QOL, minimize polypharmacy, and reduce injury and premature death, namely, SUDEP. In this analysis, FFA treatment was generally associated with improvements in GTCS or TCS frequency regardless of the DEE studied.

4.1 | Benefits of seizure reduction and impact of FFA

Among the different DEEs, just as there is variability in seizure types and severity, the extent of developmental delay may also vary depending on the influence of epileptiform activity. Early and effective seizure control, especially use of an ASM that targets the epileptiform activity, may lessen the worsening of developmental, cognitive, sleep, and behavioral comorbidities.[9,49] In patients with

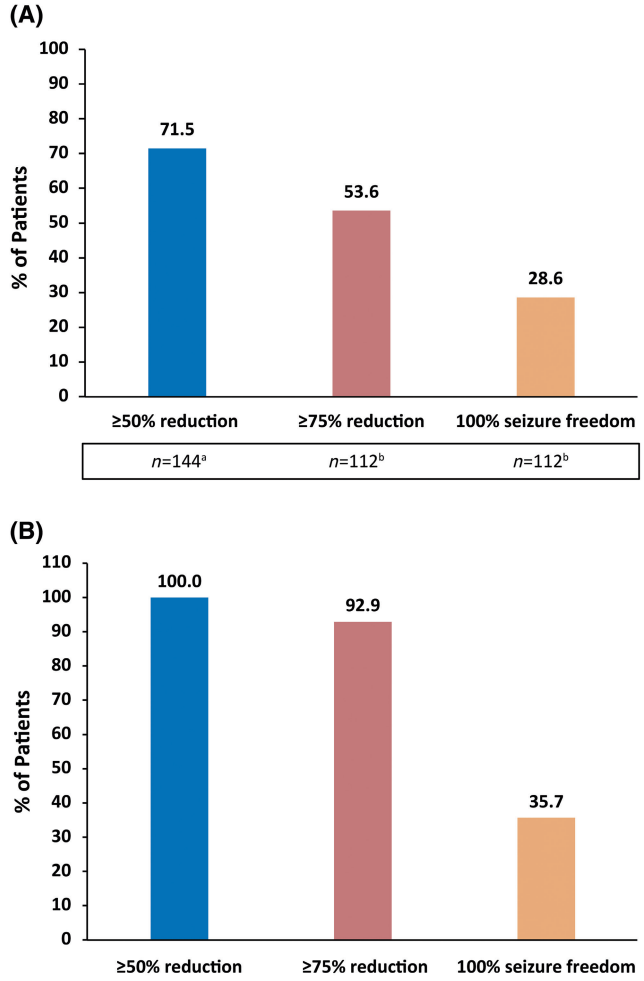

FIGURE 3 Proportion of patients to achieve generalized tonic–clonic seizure (GTCS) or tonic–clonic seizures reduction thresholds from baseline in (A) studies evaluating any developmental and epileptic encephalopathy (DEE), and (B) four studies evaluating non-Dravet syndrome (DS) DEEs ($n=14$). (A) Studies evaluating any DEE. [a]A ≥50% reduction was reported or could be calculated in 10 studies: Boel 1996 ($n=5$, other DEE),[33] Ceulemans 2012 ($n=2$, DS),[43] Ceulemans 2016 ($n=10$, DS),[44] Schoonjans 2017 ($n=9$, DS),[45] Specchio 2020 ($n=32$, DS),[40] Steinhoff 2021 ($n=1$, DS),[42] Strzelczyk 2021 ($n=76$, DS),[41] Devinsky 2021 ($n=5$, CDKL5 deficiency disorder [CDD]),[47] Aledo-Serrano ($n=3$, *SCN8A*-related disorder),[39] Zhu ($n=1$, *SCN1B*-related disorder).[46] [b]Nine studies reported data to evaluate proportion of patients to achieve ≥75% and 100% reduction in GTCS as above, excluding Specchio 2020.[40] (B) Four studies evaluating Non-DS DEEs ($n=14$): Boel 1996 ($n=5$, other DEE),[33] Devinsky 2021 ($n=5$, CDD),[47] Aledo-Serrano ($n=3$, *SCN8A*-related disorder),[39] Zhu ($n=1$, *SCN1B*-related disorder).[46]

DS, caregivers and physicians agreed with 78% and 83% consensus, respectively, that delay in use of optimal therapies was associated with poor developmental outcomes.[50] One study evaluating burden of disease in patients with drug-resistant LGS reported that developmental delay, behavioral problems, and other neurological defects were associated with higher monthly seizure count.[51] An association between seizure frequency and cognitive impairment and lower health-related QOL (HRQoL) has been reported in adult patients with DS,[52] and a 10-year prospective study identified that lower HRQoL was observed in an older patient group (≥16 years old) compared with younger patient groups.[53]

Caregivers of patients with DS treated with FFA have reported shorter postictal recovery times, as well as non-seizure benefits, including improved cognition, focus, and alertness.[54,55] These findings were corroborated by clinicians in a similar study in the EU.[55] The international consensus panel of physicians and caregivers of patients with DS also indicated that in their experience, patients on FFA demonstrated "improved alertness and/or behavior."[50] In three of the studies evaluated in this review, caregivers reported improvements in sleep quality, communication, behavior, and QOL scale scores after treatment with FFA was initiated.[30,40,45] Surveys of patients in the UK and France with DS or LGS demonstrated that fewer seizures and more seizure-free days were associated with higher QOL scores.[56] Notably, FFA's impact on everyday executive function (EF) may not be entirely related to improvement in seizure frequency. A post hoc evaluation of patients treated with FFA in two of the DS RCTs revealed that only half of the preschool children who exhibited clinically meaningful improvement on at least one BRIEF-P (Behavior Rating Inventory of Executive Function–Preschool) index or composite also experienced clinically meaningful reduction in monthly convulsive seizure frequency (MCSF). Although responses were dose-dependent, there did not appear to be a correlation with improvement in seizure control, suggesting that FFA may have direct effects on everyday EF.[57]

For caregivers themselves, benefits are also observed when patients are on effective treatment. In the studies by Jensen et al., caregivers reported improvement in their own sleep quality and less feelings of being overwhelmed, stressed, and anxious.[54,55] These benefits have also been observed in adult patients. When treated with FFA, 50% of adult patients in the DS EU early access program (EAP; $n=24$) demonstrated ≥75% reduction in MCSF, which was sustained through 12 months of treatment in 80% of patients; this likely translated to positive ratings on the Clinical Global Impression–Improvement (CGI-I) scale, which reflect both seizure and nonseizure outcomes.[58] Similarly, patients who enrolled in the DS OLE as adults ($n=44$) demonstrated clinically meaningful ratings on CGI-I, and no new safety signals were observed over a median duration of FFA exposure of 14 months.[59]

Improved seizure control may also lead to reduction in use of other ASMs, which reduces pill burden and subsequent pharmacy costs,[60] and may lessen risk

of adverse events (AEs; including neurocognitive and behavioral AEs)[8,11] as well as leading to a reduction in overall health care resource utilization. One study that surveyed caregivers of patients with CDD indicated that physical health domain scores were higher in individuals on 0–1 ASMs than in those on ≥3 ASMs.[61] Two studies described in this analysis highlighted a reduction in concomitant use of ASMs when FFA was initiated.[40,41] In the German EAP study ($n = 78$), 45% of patients with DS were able to discontinue at least one concomitant ASM, the most common of which was STP; additionally, 23% were able to reduce the dose of a concomitant ASM.[41] These data are not specific to the patients with GTCS or TCS at baseline but are relevant nonetheless and were subsequently confirmed by the later published secondary analysis.[58]

Patients with uncontrolled seizures and, specifically, TCS are also at increased risk of physical injuries.[62] In a retrospective cohort study of patients with epilepsy, 50 of 53 severe injuries were due to GTCS; seven patients reported having multiple severe injuries, and all were due to GTCS.[63] Although these data are not specific to patients with DEEs, they highlight the additional strain uncontrolled seizures can have on patients, caregivers, and the health care system.

The exact cause of SUDEP is unknown, but multiple pathophysiologic mechanisms are likely involved,[64] including serotonin dysregulation as a likely key player.[65] As mentioned previously, poor seizure control and, more specifically, the presence of GTCS are significant risk factors for SUDEP.[18,64] The MORTEMUS study evaluated 11 cases of SUDEP that occurred while patients were monitored in an epilepsy unit[16]; all 11 deaths were induced by a GTCS. The systematic review by Harden et al. reported that patients with epilepsy who experience one to two 2 GTCS per year have a fivefold greater risk of SUDEP than patients without GTCS; this increases to >15-fold in patients experiencing three or more GTCS per year.[13] The rates of SUDEP in drug-resistant epilepsies, as well as in DS, have been studied and reported, but there is an unmet need to more clearly understand the risk in patients with DEEs. A retrospective cohort study discovered that among 42 of 510 patients with DEEs who died, SUDEP accounted for 19 of 42 (45%). This results in an estimated SUDEP rate of 2.8 per 1000 person-years (95% confidence interval = 1.6–43) in patients with genetic DEEs.[7] Ultimately, a reduction in GTCS is likely to lessen the risk of SUDEP,[15] and available treatment options that can reduce those risks are needed. In DS, a post hoc analysis revealed that mortality rates due to SUDEP were substantially lower (1.7 per 1000 person-years) in patients with DS treated with FFA than in controls reported in the literature.[12]

4.2 | FFA mechanisms

FFA's mechanism involving dual-action serotonergic and S1R pharmacology is responsible for its numerous seizure and nonseizure benefits. Preclinical studies in *Scn1lab* zebrafish and an N-methyl-D-aspartate-kindled mouse model have confirmed FFA's activity at 5-$HT_{1D,2A,2C}$ along with activity at S1R, which contribute to the antiseizure activity.[66-69] The dual activity is further involved in restoring the balance between γ-aminobutyric acidergic inhibition and glutamatergic excitation.[70,71] Additionally, in models of dizocilpine-treated mice, positive modulation at S1R in vitro by FFA was associated with positive behavioral effects.[22,72] Various preclinical studies have shown that a reduction in serotonin influenced tonic convulsive thresholds and, conversely, treatment with serotonergic agents (including FFA) reduced seizures and mortality.[73,74] A recent paper evaluating the antiseizure potency of FFA, norfenfluramine, and their individual enantiomers also revealed that all compounds were active against maximal electroshock-induced seizures in rodent seizure models.[75] A mouse model of SUDEP recognized that FFA, mediated by 5-HT_4 agonism, was able to block seizure-induced respiratory arrest.[76-78] FFA has also demonstrated inhibition of cortical spreading depolarization when mice were treated with FFA, which is a primary mechanism involved in cardiorespiratory collapse and SUDEP. Lastly, FFA has been shown to reduce myelin degeneration and neuroinflammation, as well as restore dendritic arborization, which contributes to its antiseizure effects, including GTCS reduction, and may suggest disease-modifying effects.[79,80]

4.3 | FFA efficacy

The results of our review highlight the published efficacy in GTCS and TCS reduction in studies of patients with DEEs; there are also published data regarding GTCS efficacy in other rare epilepsy syndromes, for example, Sunflower syndrome.[81,82] This adds to the already established data from the FFA clinical trial program, demonstrating sustained efficacy in seizure reduction and a tolerable safety profile.

Although there may be other publications evaluating GTCS reduction in DS or other DEEs,[83] to our knowledge, there are no systematic literature reviews and/or meta-analyses providing comparisons between ASMs for GTCS or TCS efficacy.

4.4 | FFA safety and tolerability

A formal safety analysis was not performed for this review, but the AEs reported in these studies were consistent with

those observed in the DS and LGS clinical trial program, as well as those described in the prescribing information (e.g., decreased appetite, somnolence, fatigue).[23] Additionally, as reinforced in the long-term cardiovascular safety analyses of the DS and LGS clinical trial patients,[84-86] there were no cases of valvular heart disease or pulmonary arterial hypertension observed in the patients described in this review. Indirect comparisons to cannabidiol (CBD) and STP have revealed that FFA is generally well tolerated compared to CBD[87,88] and has less frequent serious treatment-emergent AEs than both CBD and STP.[87-89]

4.5 | Limitations

This analysis has several limitations, many arising from the heterogeneity of the source data. Because we were evaluating a subpopulation of patients within larger groups described in the literature, demographics or disposition data for the patients with the specific seizure types of interest (GTCS or TCS) could not be discerned for all of the studies presented; this was particularly the case for the larger studies (Lagae et al.,[35] Nabbout et al.,[36] Knupp et al.[29]). Additionally, there were three studies that evaluated total seizure reduction (which included GTCS or TCS), and therefore, the frequency of other seizure types may have impacted the results in a positive or negative manner.[33,43,45] It is also possible that additional patients who did not report GTCS or TCS at baseline may have developed GTCS or TCS during the study, but those patients would not have been part of the analysis. Studies where patients may have been duplicated or where there were insufficient or difficult to capture data available were excluded, and thus, an opportunity for a larger dataset may have been missed.[58,90-94] During screening, one paper was excluded due to differences in study methodology.[34] Although the protocols of the other open-label studies allowed titration to efficacy and tolerability, patients in the open-label study of patients with LGS by Lagae et al. were only titrated to 50% reduction in convulsive seizure frequency. Doses were kept at that "effective dose," and thus, the authors of this review felt the full potential of FFA was not achieved for the patients in that study and would limit the results of this analysis. These issues that contributed to study selection may suggest selection bias, but authors reviewed the studies thoroughly, and wherever possible, the most recent study with the most complete dataset was selected for inclusion. The variability in seizure reduction across the studies was also likely due to the wide range of sample sizes, patient age, variation in number of concomitant ASMs, and treatment durations, but this also emphasizes that FFA is effective in reducing GTCS or TCS in a variety of patient populations and DEE types.

5 | CONCLUSIONS

To our knowledge, this is the first review to summarize the efficacy of one ASM in the reduction of GTCS or TCS occurring in a group of DEEs beyond DS and LGS. In this analysis of 421 patients with up to six different types of DEEs (71% DS), FFA demonstrated a clinically meaningful reduction in GTCS or TCS. This reduction is likely to contribute to other nonseizure benefits such as improvement in comorbidities, decreased use of other ASMs and associated AEs, decrease in health care costs, and potentially a reduction in injuries and risk of premature death (including SUDEP), all of which may translate to improved QOL for patients with these disorders and their families. These data, coupled with 30+ years of experience in the Belgian cohorts and long-term safety data from the DS and LGS clinical trial program, position FFA as a tolerable and effective ASM for management of various DEEs. Future research can aim to further describe FFA's mechanism and efficacy in DEEs and other rare epilepsy syndromes, along with the impact of FFA on behavior, everyday EF, and prevention of premature mortality (e.g., SUDEP).

AUTHOR CONTRIBUTIONS

Antonio Gil-Nagel and Rima Nabbout were involved in data curation, formal analysis, and validation of the studies evaluated. All authors contributed to the conceptualization of the manuscript, were involved in the methodology of this review, critically revised the drafts, and approved the final version for publication.

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DATA AVAILABILITY STATEMENT

Data from noninterventional studies are outside of UCB's data sharing policy and are unavailable for sharing.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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