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ORIGINAL RESEARCH

Efficacy and Safety of Fenfluramine in Epilepsy: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Fenfluramine (FFA) is an amphetamine derivative that promotes the release and blocks the neuronal reuptake of serotonin. Initially introduced as an appetite suppressant, FFA also showed antiseizure properties. This systematic review aimed to assess the efficacy and safety of FFA for the treatment of seizures in patients with epilepsy.

Methods: We systematically searched (in week 3 of June 2022) MEDLINE, the Cochrane Central Register of Controlled Trials, and the US National Institutes of Health Clinical Trials Registry. Randomized, double- or single-blinded, placebo-controlled studies of FFA in patients with epilepsy and uncontrolled seizures were identified. Efficacy outcomes included the proportions of patients with ≥ 50% and 100% reductions in baseline seizure frequency during the treatment period. Tolerability outcomes

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included the proportions of patients who withdrew from treatment for any reason and suffered adverse events (AEs). The risk of bias in the included studies was assessed according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. The risk ratio (RR) along with the 95% confidence interval (CI) were estimated for each outcome.

Results: Three trials were identified and a total of 469 Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) subjects were randomized. All three trials were judged to be at low risk of biases. In patients with DS, the RRs for ≥ 50% and 100% reductions in convulsive seizure frequency for the FFA group compared to placebo were 5.61 (95% CI 2.73–11.54) and 4.71 (95% CI 0.57–39.30), respectively. In patients with LGS, the corresponding RRs for ≥ 50% and 100% reductions in drop seizure frequency were 2.58 (95% CI 1.33–5.02) and 0.50 (95% CI 0.031–7.81), respectively. The drug was withdrawn for any reason in 10.1% and 5.8% of patients receiving FFA and placebo, respectively (RR 1.79, 95% CI 0.89–3.59). Treatment discontinuation due to AEs occurred in 5.4% and 1.2% of FFA- and placebo-treated patients, respectively (RR 3.63, 95% CI 0.93–14.16). Decreased appetite, diarrhoea, fatigue, and weight loss were AEs associated with FFA treatment.

Conclusion: Fenfluramine reduces the frequency of seizures in patients with DS and LGS. Decreased appetite, diarrhoea, fatigue, and weight loss are non-cardiovascular AEs associated with FFA.

Keywords: Epilepsy; Seizures; Dravet syndrome; Lennox–Gastaut syndrome; Fenfluramine

Key Summary Points

Adjunctive fenfluramine (FFA) reduces the frequency of convulsive seizures in patients with Dravet syndrome.

Adjunctive FFA reduces the frequency of drop seizures in patients with Lennox–Gastaut syndrome.

Non-cardiovascular adverse events associated with FFA include decreased appetite, diarrhoea, fatigue, and weight loss.

INTRODUCTION

Epilepsy is one of the most common chronic disorders of the brain. The management is mainly symptomatic, and most patients reach sustained freedom from seizures. Around one-third of people with epilepsy, however, continue to experience seizures despite adequate treatment [1, 2]. Uncontrolled epilepsy is often disabling and associated with significant psychological and social dysfunction, impaired quality of life, and risk of premature death [3]. There remains, hence, the urgent need to search for new therapeutic options.

Fenfluramine (3-trifluoromethyl-*N*-ethylamphetamine) (FFA) has a long-standing history. The drug was introduced in the early 1960s as an appetite suppressant with less stimulating side effects than existing amphetamines. The anorectic effect was thought to be mediated by serotonergic mechanisms, as FFA both promotes the release of serotonin (5-HT) and blocks its neuronal reuptake [4, 5]. The drug was approved for the short-term treatment of obesity, but safety concerns arose in the 1980s when its use

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was associated with the occurrence of pulmonary hypertension and valvular heart disease in some individuals given up to 220 mg per day [6, 7]. The medication was, hence, withdrawn from the US market in 1997.

The antiseizure effects of FFA were first described in the 1980s by Aicardi and Gastaut in three adolescent patients with intractable self-induced photosensitive epilepsy [8] and later reported in small case series and observational studies of children with intractable and self-induced epilepsy [9]. In 2002, a Belgian Royal Decree was issued to grant compassionate use approval of FFA in paediatric patients with intractable epilepsy and to allow patients with Dravet syndrome (DS) to be treated under a treatment protocol [10]. Some of these patients with DS have been given FFA for up to 30 years with reductions in seizure frequency and no evidence of cardiopulmonary disease [10–12]; the mean doses reported in the two cohorts of Belgian patients were 0.27 mg/kg and 0.35 mg/kg per day [13].

In 2020, FFA was approved by the US Food and Drug Administration (FDA) for the treatment of seizures associated with DS in patients aged 2 years and older, and by the European Medicines Agency (EMA) for the treatment of seizures associated with DS as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older. In March 2022, the FDA approved the use of FFA for the treatment of seizures associated with Lennox–Gastaut syndrome (LGS) in patients 2 years of age and older. In December 2022, the Committee for Medicinal Products for Human Use of the EMA adopted a new indication for FFA as an add-on therapy for seizures associated with Lennox–Gastaut syndrome for patients aged 2 years and older.

This study systematically evaluated and synthesized the evidence about the efficacy and safety of FFA as a treatment for seizures in patients with epilepsy. This could allow us to appreciate the effects of FFA across different epileptic syndromes and assess the tolerability profile based on a larger population dataset.

METHODS

Search Strategy

The results were reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statements [14]. We systematically searched (in week 3 of June 2022) MEDLINE (accessed by PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), and the US National Institutes of Health Clinical Trials Registry (http://www.clinicaltrials.gov). Additional data were sought in the assessment report on FFA by the EMA/Committee for Medicinal Products for Human Use (http://www.ema.europa.eu/). The search strategy included the terms "fenfluramine", "epilepsy", and "seizure"; no filters, date limitations, or language restrictions were applied. Details of the search strategies are outlined in the Supplementary Information. The protocol was not registered previously.

Eligibility Criteria

Studies were selected when they met the following criteria: randomized, double- or single-blinded, placebo-controlled, parallel-group studies with active and control groups receiving FFA and matched placebo. Participants had to meet the following criteria: any sex, ethnicity, paediatric and/or adult age, diagnosis of epilepsy, and seizures uncontrolled by concomitant antiseizure medications (ASMs).

Outcome Measures

The efficacy outcomes were the proportion of patients with a $\geq$ 50% reduction in monthly baseline seizure frequency, the proportion of patients with seizure freedom or near seizure freedom ($\leq$ 1 seizure), and the longest seizure-free interval; efficacy outcomes were evaluated during the treatment period (titration and maintenance phase). The types of seizures that were defined as primary in any included study were considered for each outcome. The safety and tolerability outcomes included the

proportions of patients who withdrew from treatment for any reason and suffered adverse events (AEs), and those who experienced at least one AE and at least one serious AE; any AE occurring in at least 10% of patients in at least one treatment group across the trials was considered. Changes from baseline to the end of treatment in clinical global impression ratings by both investigators and parents/caregivers were also evaluated. Data about echocardiographic examinations to assess cardiac valve function or structure and any evidence of pulmonary arterial hypertension were narratively reviewed.

Study Selection, Data Extraction, and Assessment of the Risk of Bias

Two authors (P.T.D. and N.F.) independently screened the records identified by the literature search and extracted the following data from the included studies: main study author, year of publication, study design, main inclusion and exclusion criteria, treatment arms, number and demographics of participants, and number of participants experiencing each outcome per randomized group. Any disagreement was solved through discussion with a third review author (R.G.). The risk of bias in the included studies was assessed according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [15].

STATISTICAL ANALYSIS

Heterogeneity among the trials was assessed by using the chi-squared (χ^2) test and the I^2 statistics for heterogeneity [15–17]. Provided no substantial heterogeneity was present ($p > 0.10$), results were synthesized using a fixed effect model; if the probability value was ≤ 0.10, heterogeneity determined the choice of a fixed or random effects model for $I^2 < 40\%$ or $\geq 40\%$, respectively [18–22]. We present heterogeneity statistics for all analyses unless only one trial contributed data and heterogeneity was not applicable. The efficacy analyses performed on the modified intent-to-treat population included all randomized patients who received ≥ 1 dose of FFA or placebo with ≥ 1 week of seizure diary data. Safety and tolerability analyses were performed using data from all randomized patients who received ≥ 1 dose of FFA or placebo. The risk ratio (RR) or mean difference (MD) with their 95% confidence intervals (CIs) were used as the measures of association between treatment and dichotomous/continuous outcomes. Results were presented according to FFA daily doses where sufficient data were available. Data analysis was performed using STATA®/IC 13.1 (StataCorp LP, College Station, TX, USA).

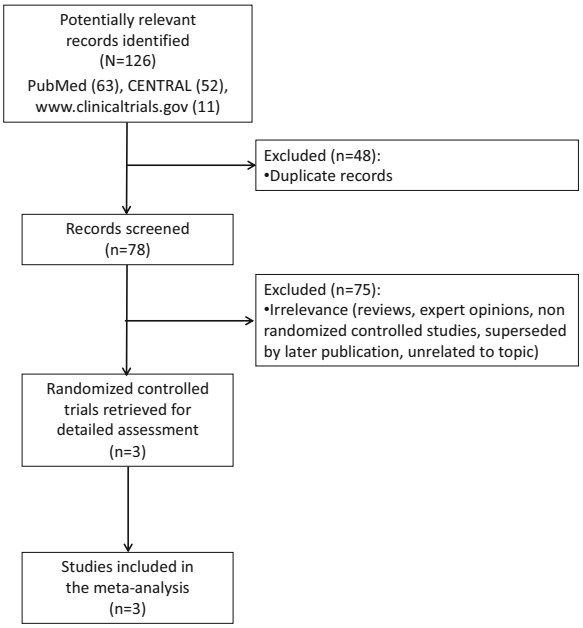
Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Results of the Search and Characteristics of the Included Studies

One hundred and twenty-six records were identified by searching the databases and trial registers. After the removal of duplicates and irrelevant records, three trials were retrieved for detailed assessment and eventually included in the review and metanalysis [23–25] (Fig. 1). All three studies were multinational, double-blind, placebo-controlled, parallel-group, phase III, randomized clinical trials that addressed either the efficacy or safety of FFA administered twice daily as a fenfluramine hydrochloride oral solution in addition to the pre-existing regimen of ASMs. The study by Lagae et al. [23] represents the definitive report of two investigations, one done in the USA and Canada (NCT02682927) and the other in western Europe and Australia (NCT02826863), whose datasets were merged before the unblinding of results and the analysis due to incomplete enrolment of patients with a rare disorder [Dravet syndrome (DS)] in both trials.



Abbreviation: CENTRAL=Cochrane Central Register of Controlled Trials.

Fig. 1 Flow diagram of the study selection process. *CENTRAL* Cochrane Central Register of Controlled Trials

In two trials [23, 24], eligible patients were children aged 2–18 years with a diagnosis of DS; in the study by Nabbout et al. [24], patients had to receive a therapeutically relevant and stable dose of stiripentol in conjunction with clobazam and/or valproic acid. In one trial [25], eligible patients were children and adults aged 2–35 years with a diagnosis of Lennox–Gastaut syndrome (LGS). Details of the studies are provided in Table 1.

The studies included 469 participants: 128 randomized to FFA 0.2 mg/kg/day, 43 randomized to FFA 0.5 mg/kg/day, 127 randomized to 0.8 mg/kg/day, and 171 randomized to placebo. The dose of 0.5 mg/kg/day was determined as the target dose needed to maintain mean patient pharmacokinetic exposures within 10% of that which is expected in patients receiving 0.8 mg/kg/day in the absence of ASMs with the potential for a drug–drug interaction with FFA [24]. Characteristics of the participants are summarized in Tables 2 and 3.

All three trials adopted appropriate methods of sequence generation and allocation concealment. The risk of performance and detection bias was judged to be low, as the FFA and placebo solutions were identical in appearance and taste and neither the investigators nor the patients knew the identity of the study treatment being administered. The risks of attrition and selective reporting bias were also judged to be low, as participants lost to follow-up and withdrawals were few and documented, and there was no suspicion of selective outcome reporting. The manufacturer of FFA was the sponsor of all trials.

Efficacy in Dravet Syndrome

Convulsive seizures were the primary seizure types in both trials that recruited patients with DS; convulsive seizures included hemi-clonic, tonic, clonic, tonic-atonic, generalized tonic–-clonic, secondarily generalized tonic–clonic [focal to bilateral tonic–clonic], and focal with clearly observable motor signs. Reductions of at least 50% in monthly baseline frequency of convulsive seizures occurred in 65/122 (53.3%) patients randomized to add-on FFA and 7/84 (8.3%) of the placebo-treated participants (RR 5.61, 95% CI 2.73–11.54; $p < 0.001$) (chi squared = 1.51, $df = 1$, $p = 0.218$; $I^2 = 34.0\%$] [23, 24]. The overall pooled estimated RR to achieve freedom from convulsive seizures for the add-on FFA group in comparison to add-on placebo was 4.71 (95% CI 0.57–39.30; $p = 0.152$) (chi squared = 0.13, $df = 1$, $p = 0.722$; $I^2 = 0.0\%$). Near seizure freedom was reached by 20/122 (16.4%) patients in the FFA group and none in the placebo arm (RR 13.43, 95% CI 1.82–99.15; $p = 0.011$) (chi squared = 0.03, $df = 1$, $p = 0.866$; $I^2 = 0.0\%$). Data about seizure freedom and near seizure freedom by daily dosage are reported in Table 4.

The weighted MD in the longest seizure-free interval during the treatment period was 15.40 (95% CI 5.28–25.52; $p = 0.003$) days between the 0.2 mg/kg/day FFA and placebo groups, 16.30 (95% CI 7.85–24.76; $p < 0.001$) days between the 0.5 mg/kg/day FFA and placebo groups, and 22.30 (95% CI 13.58–31.02; $p < 0.001$) days between the 0.8 mg/kg/day FFA and placebo arms in favour of FFA.

Table 1 Characteristics of the included studies

Study [reference]	Study design	Main inclusion criteria	Main exclusion criteria	Treatment arms
Lagae et al. (2019) [23]	Phase III Multicentre (USA, Canada, Europe, Australia) Parallel-group, randomized, placebo-controlled clinical trial: 6-week observational baseline period 14-week double-blind treatment period (2-week titration, 12-week stable dosing maintenance)	Aged 2–18 years Clinical diagnosis of Dravet syndrome Convulsive seizures not completely controlled by current regimen of ASMs or other therapies At least 6 convulsive seizures during the baseline period, with at least 2 in the first 3 weeks and at least 2 in the second 3 weeks All medications or interventions for epilepsy were stable for at least 4 weeks before screening and were expected to remain stable throughout the trial	History of pulmonary arterial hypertension, cardiovascular or cerebrovascular disease Current treatment with centrally acting anorectic agents, MAO, or any centrally acting compound with serotonin agonist or antagonist properties Treatment with stiripentol within 21 days before screening Current treatment with carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin or treatment with any of these drugs within the past 30 days Positive result on urine or serum THC panel or whole-blood CBD at the screening	Fenfluramine 0.2 mg/kg/day Fenfluramine 0.8 mg/kg/day Placebo
Nabbout et al. (2019) [24]	Phase III Multicentre (USA, Canada, Europe, UK) Parallel-group, randomized, placebo-controlled clinical trial: 6-week observational baseline period 15-week double-blind treatment period (3-week titration, 12-week maintenance)	Aged 2–18 years Clinical diagnosis of Dravet syndrome Convulsive seizures not completely controlled by current regimen of ASMs or other therapies including stiripentol at a therapeutically relevant dose At least 6 convulsive seizures during the baseline period, with at least 2 in the first 3 weeks and at least 2 in the second 3 weeks All medications or interventions for epilepsy were stable for at least 4 weeks before screening and were expected to remain stable throughout the trial	History of pulmonary arterial hypertension, cardiovascular or cerebrovascular disease Concomitant treatment with centrally acting anorectic agents, MAO, or any centrally acting compound with serotonin agonist or antagonist properties Current treatment with carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin or treatment with any of these drugs within the past 30 days Positive result on urine THC panel or whole-blood CBD at the screening	Fenfluramine 0.5 mg/kg/day Placebo
Knupp et al. (2022) [25]	Phase III Multicentre (USA, Canada, Europe, Australia) Parallel-group, randomized, placebo-controlled clinical trial: 4-week observational baseline period 14-week treatment period (2-week titration, 12-week maintenance)	Aged 2–35 years Clinical diagnosis of Lennox–Gastaut syndrome Seizures that result in drops not completely controlled by current antiepileptic treatments At least 2 seizures per week resulting in drops during the 4-week baseline period All medications or interventions for epilepsy were stable for at least 4 weeks before screening and were expected to remain stable throughout the trial	History of pulmonary hypertension, cardiovascular or cerebrovascular disease Concomitant treatment with centrally acting anorectic agents, MAO, or any centrally acting compound with serotonin agonist or antagonist properties History of hemiclonic seizures in the first year of life Drop seizures only in clusters where individual seizures cannot be counted reliably Positive result on urine or serum THC panel or whole-blood CBD at the screening	Fenfluramine 0.2 mg/kg/day Fenfluramine 0.8 mg/kg/day Placebo

ASM antiseizure medication, *CBD* cannabidiol, *MAO* monoamine oxidase inhibitors, *THC* tetrahydrocannabinol

Table 2 Characteristics of the study participants: Dravet syndrome

Baseline characteristics of participants	Study				
	Lagae et al. [23]			Nabbout et al. [24]	
	Fenfluramine 0.2 mg/kg/day (*n* = 39)	Fenfluramine 0.8 mg/kg/day (*n* = 40)	Placebo (*n* = 40)	Fenfluramine 0.5 mg/kg/day (*n* = 43)	Placebo (*n* = 44)
Age, years					
Mean (SD)	9.0 (4.5)	8.8 (4.4)	9.2 (5.1)	8.8 (4.6)	9.4 (5.1)
Range	2–17	2–18	2–18	2–18	2–19
Patients younger than 6 years	9 (23.1)	11 (27.5)	11 (27.5)	12 (27.9)	12 (27.3)
Male	22 (56.4)	21 (52.5)	21 (52.5)	23 (53.5)	27 (61.4)
BMI (kg/m^2), mean (SD)	19.3 (5.7)	18.5 (3.5)	18.0 (3.8)	17.3 (2.7)	19.1 (4.9)
Number of concomitant ASMs, mean (SD)	2.5 (1.1)	2.3 (0.9)	2.5 (0.9)	3.7 (0.8)	3.4 (0.6)
Concomitant ASMs					
Stiripentol	[a]None	[a]None	[a]None	43 (100.0)	44 (100.0)
Clobazam	24 (61.5)	24 (60.0)	22 (55.0)	40 (93.0)	42 (95.5)
Valproate	24 (61.5)	25 (62.5)	22 (55.0)	38 (88.4)	39 (88.6)
Topiramate	10 (25.6)	11 (27.5)	9 (22.5)	14 (32.6)	7 (15.9)
Levetiracetam	11 (28.2)	4 (10.0)	11 (27.5)	6 (14.0)	5 (11.4)
Baseline convulsive seizure frequency per 28 days					
Mean (SD)	45.5 (99.8)	31.4 (30.6)	44.2 (40.2)	27.9 (36.9)	21.6 (27.6)
Median (range)	17.5 (4.7–623.5)	20.7 (4.8–124)	27.3 (3.3–147.3)	14.0 (3–213)	10.7 (3–163)

Data are number of participants (%) unless otherwise specified
ASM antiseizure medication, *BMI* body mass index, *SD* standard deviation
[a]Concomitant stiripentol not allowed as per study protocol

Efficacy in Lennox–Gastaut Syndrome

In the trial that recruited patients with LGS, drop seizures were the primary seizure types and included the following types: generalized tonic–clonic, secondarily generalized tonic–-clonic [focal to bilateral tonic–clonic], tonic, atonic, or tonic or atonic. Reductions of at least 50% in monthly baseline frequency of drop seizures occurred in 47/176 (26.7%) patients randomized to add-on FFA and 9/87 (10.3%) placebo-treated participants (RR 2.58, 95% CI 1.33–5.02; $p = 0.005$). Adjunctive FFA at either 0.2 or 0.8 mg/kg per day was associated with a significantly greater decrease in baseline drop seizure frequency of 50% or more in comparison with placebo (Table 5). The overall pooled estimated RRs to achieve the freedom and near freedom from drop seizures for the add-on FFA group in comparison to add-on placebo were 0.50 (95% CI 0.031–7.81; $p = 0.617$) and 1.48

Table 3 Characteristics of the study participants: Lennox–Gastaut syndrome

Baseline characteristics of participants	Study		
	Knupp et al. [25]		
	Fenfluramine 0.2 mg/kg/day (*n* = 89)	Fenfluramine 0.8 mg/kg/day (*n* = 87)	Placebo (*n* = 87)
Age, years			
Mean (SD)	13 (8)	13 (7)	14 (8)
Range	3–35	2–35	2–35
Patients younger than 6 years	17 (19.1)	12 (13.8)	9 (10.3)
Male	46 (51.7)	54 (62.1)	46 (52.9)
BMI (kg/m^2), mean (SD)	20 (5)	20 (5)	20 (5)
Aetiology			
Genetic	19 (21.3)	21 (24.1)	15 (17.2)
Structural	11 (12.4)	9 (10.3)	13 (14.9)
Metabolic	3 (3.4)	2 (2.3)	1 (1.1)
Infectious	1 (1.1)	2 (2.3)	3 (3.4)
Immune	0 (0.0)	1 (1.1)	0 (0.0)
Unknown	24 (27.0)	17 (19.5)	22 (25.3)
Number of concomitant ASMs, mean (SD)	3 (1)	3 (1)	3 (1)
Concomitant ASMs			
Clobazam	36 (40.4)	45 (51.7)	38 (43.7)
Valproate	52 (58.4)	46 (52.9)	49 (56.3)
Levetiracetam	17 (19.1)	23 (26.4)	20 (23.0)
Lamotrigine	30 (33.7)	29 (33.3)	29 (33.3)
Rufinamide	17 (19.1)	18 (20.7)	18 (20.7)
Baseline drop seizure frequency per 28 days			
Median (range)	85 (4–2943)	83 (7–1803)	53 (2–1761)

Data are number of participants (%) unless otherwise specified
ASM antiseizure medication, *BMI* body mass index, *SD* standard deviation

(95% CI 0.16–14.05; $p = 0.731$), respectively. Data about seizure freedom and near seizure freedom by daily dosage are reported in Table 5.

Treatment Withdrawal

Across the trials, drug withdrawal for any reason occurred in 30/298 (10.1%) and 10/171 (5.8%) patients receiving FFA and placebo, respectively (RR 1.79, 95% CI 0.89–3.59; $p = 0.102$) (chi squared = 0.98, $df = 2$, $p = 0.612$; $I^2 = 0.0\%$). The RRs to discontinue treatment were 1.21 (95% CI 0.40–3.64; $p = 0.739$) (chi squared = 2.32, $df = 1$, $p = 0.128$; $I^2 = 56.9\%$), 2.39 (95% CI 0.66–8.64; $p = 0.185$), and 2.28 (95% CI 0.97–5.34; $p = 0.059$) (chi squared = 0.06, $df = 1$, $p = 0.800$; $I^2 = 0.0\%$) for FFA at doses of 0.2, 0.5, and 0.8 mg/kg/day, respectively, compared

Table 4 Efficacy of adjunctive fenfluramine in Dravet syndrome

Outcome or subgroup	Number of studies [reference]	Number of pooled events/participants		I^2	Risk ratio (95% CI)	*p* value
		FFA	Placebo			
Reduction of ≥ 50% in convulsive seizure frequency						
FFA 0.2 mg/kg/day	1 [23]	15/39	5/40	–	3.08 (1.24–7.65)	0.016
FFA 0.5 mg/kg/day	1 [24]	23/43	2/44	–	11.77 (2.95–46.89)	< 0.001
FFA 0.8 mg/kg/day	1 [23]	27/40	5/40	–	5.40 (2.31–12.60)	< 0.001
Freedom from convulsive seizures						
FFA 0.2 mg/kg/day	1 [23]	3/39	0/40	–	7.18 (0.38–134.51)	0.188
FFA 0.5 mg/kg/day	1 [24]	1/43	0/44	–	3.07 (0.13–73.30)	0.489
FFA 0.8 mg/kg/day	1 [23]	3/40	0/40	–	7.00 (0.37–131.28)	0.193
Near freedom from convulsive seizures						
FFA 0.2 mg/kg/day	1 [23]	5/39	0/40	–	11.28 (0.64–197.29)	0.097
FFA 0.5 mg/kg/day	1 [24]	5/43	0/44	–	11.25 (0.64–197.44)	0.098
FFA 0.8 mg/kg/day	1 [23]	10/40	0/40	–	21.00 (1.27–346.66)	0.033

CI confidence interval, *FFA* fenfluramine

to placebo. Treatment was discontinued due to AEs in 16/298 (5.4%) and 2/171 (1.2%) patients in the active and control groups, respectively (RR 3.63, 95% CI 0.93–14.16; $p = 0.064$) (chi squared = 0.35, $df = 2$, $p = 0.838$; $I^2 = 0.0\%$). The corresponding RRs for FFA at the doses of 0.2, 0.5, and 0.8 mg/kg/day were RR 3.91 (95% CI 0.45–34.29; $p = 0.218$), 2.05 (95% CI 0.19–21.75; $p = 0.553$), and 6.62 (95% CI 1.20–36.48; $p = 0.030$) (chi squared = 0.19, $df = 1$, $p = 0.665$; $I^2 = 0.0\%$).

Adverse Events and Clinical Global Impression of Improvement

Adverse events were reported in 264/298 (88.6%) and 133/171 (77.8%) patients during treatment with FFA and placebo, respectively (RR 1.15, 95% CI 0.97–1.36; $p = 0.101$) (chi squared = 8.44, $df = 2$, $p = 0.015$; $I^2 = 76.3\%$). Serious AEs were reported by 29/298 (9.7%) and 15/171 (8.8%) participants assigned to FFA and placebo, respectively (RR 1.18, 95% CI

Table 5 Efficacy of adjunctive fenfluramine in Lennox–Gastaut syndrome

Outcome or subgroup	Number of studies [reference]	Number of pooled events/participants		I^2	Risk ratio (95% CI)	*p* value
		FFA	Placebo			
Reduction ≥ 50% in drop seizure frequency						
FFA 0.2 mg/kg/day	1 [25]	25/89	9/87	–	2.72 (1.35–5.48)	0.005
FFA 0.8 mg/kg/day	1 [25]	22/87	9/87	–	2.44 (1.19–5.00)	0.014
Freedom from drop seizures						
FFA 0.2 mg/kg/day	1 [25]	1/89	1/87	–	0.98 (0.06–15.38)	0.987
FFA 0.8 mg/kg/day	1 [25]	0/87	1/87	–	0.33 (0.01–8.07)	0.499
Near freedom from drop seizures						
FFA 0.2 mg/kg/day	1 [25]	2/89	1/87	–	1.96 (0.18–21.17)	0.581
FFA 0.8 mg/kg/day	1 [25]	1/87	1/87	–	1.00 (0.06–15.73)	1.000

CI confidence interval, *FFA* fenfluramine

0.64–2.19; $p = 0.592$) (chi squared = 0.82, $df = 2$, $p = 0.664$; $I^2 = 0.0\%$). The AEs that occurred in at least 10% of patients in at least one treatment group across the trials and the corresponding incidence rates in the FFA-treated versus placebo-treated patients were as follows: blood glucose decreased 4.9% versus 2.4%, bronchitis 4.9% versus 2.4%, decreased appetite 30.5% versus 9.9%, diarrhoea 16.8% versus 5.8%, fall 3.3% versus 4.8%, fatigue 14.4% versus 7.0%, lethargy 12.3% versus 4.8%, nasopharyngitis 14.8% versus 23.8%, pyrexia 12.1% versus 12.9%, seizure 7.4% versus 14.3%, somnolence 12.4% versus 8.8%, upper respiratory tract infection 9.8% versus 9.5%, vomiting 9.4% versus 7.0%, and weight decrease 10.4% versus 2.9%. A change from the baseline of at least 7% was set as the minimum threshold for identifying a clinically meaningful weight decrease. The AEs significantly associated with FFA in the overall analysis were decreased appetite, diarrhoea, fatigue, and weight loss (Table 6). The results by daily dosage are reported in Table 7.

Across the trials, 102/287 (35.5%) patients in the FFA and 17/165 (10.3%) in the placebo group were rated at the end of the treatment period as much improved or very much improved on the Clinical Global Impression-Improvement (CGI-I) scale by their caregiver (RR 3.42, 95% CI 1.42–8.23; $p = 0.006$) (chi squared = 5.91, $df = 2$, $p = 0.052$; $I^2 = 66.2\%$). The corresponding RRs for FFA at doses of 0.2, 0.5, and 0.8 mg/kg/day were 4.73 (95% CI 2.32–9.66; $p < 0.001$) (chi squared = 0.16, $df = 1$, $p = 0.691$; $I^2 = 0.0\%$), 1.59 (95% CI 0.77–3.28; $p = 0.208$), and 6.11 (95% CI 3.04–12.28; $p < 0.001$), respectively (chi squared = 0.09, $df = 1$, $p = 0.760$; $I^2 = 0.0\%$).

When assessed by site investigators, 98/287 (34.1%) patients in the FFA and 16/164 (9.8%) in the placebo arms were rated much improved or very much improved on the CGI-I scale (RR 3.58, 95% CI 2.19–5.87; $p < 0.001$) (chi squared = 1.02, $df = 2$, $p = 0.601$; $I^2 = 0.0\%$).

Table 6 Adverse events for adjunctive fenfluramine versus placebo

Outcome	Number of studies [reference]	Number of pooled events/participants		I^2	Risk ratio (95% CI)	p value
		FFA	Placebo			
Any AE	3 [23–25]	264/298	133/171	76.3%	1.15 (0.97–1.36)	0.101
Any serious AE	3 [23–25]	29/298	15/171	0.0%	1.18 (0.64–2.19)	0.592
Blood glucose decreased	2 [23, 24]	6/122	2/84	-	3.07 (0.66–14.38)	0.155
Bronchitis	2 [23, 24]	6/122	2/84	0.0%	2.31 (0.56–9.55)	0.247
Decreased appetite	3 [23–25]	91/298	17/171	0.0%	3.09 (1.91–5.01)	< 0.001
Diarrhoea	3 [23–25]	50/298	10/171	0.0%	3.00 (1.56–5.77)	< 0.001
Fall	2 [23, 24]	4/122	4/84	0.0%	0.70 (0.16–2.98)	0.627
Fatigue	3 [23–25]	43/298	12/171	45.6%	1.90 (1.03–3.52)	0.041
Lethargy	2 [23, 24]	15/122	4/84	0.0%	2.68 (0.92–7.83)	0.072
Nasopharyngitis	2 [23, 24]	18/122	20/84	41.9%	0.67 (0.36–1.24)	0.197
Pyrexia	3 [23–25]	36/298	22/171	63.9%	1.02 (0.44–2.40)	0.962
Seizure	2 [23, 24]	9/122	12/84	0.0%	0.53 (0.22–1.27)	0.152
Somnolence	3 [23–25]	37/298	15/171	0.0%	1.34 (0.75–2.39)	0.317
Upper respiratory tract infection	2 [23, 24]	12/122	8/84	0.0%	0.97 (0.42–2.27)	0.947
Vomiting	3 [23–25]	28/298	12/171	0.0%	1.25 (0.63–2.46)	0.521
[a]Weight decrease	3 [23–25]	31/298	5/171	0.0%	3.77 (1.48–9.59)	0.005

AE adverse event, *CI* confidence interval, *FFA* fenfluramine

[a]A change from baseline of at least 7% was set as the minimum threshold for identifying a clinically meaningful weight decrease

The corresponding RRs for FFA at the doses of 0.2, 0.5, and 0.8 mg/kg/day were 3.60 (95% CI 1.81–7.17; $p < 0.001$) (chi squared = 0.12, $df = 1$, $p = 0.724$; $I^2 = 0.0\%$), 2.78 (95% CI 1.30–5.93; $p = 0.008$), and 5.09 (95% CI 2.61–9.90; $p < 0.001$), respectively (chi squared = 0.34, $df = 1$, $p = 0.559$; $I^2 = 0.0\%$).

No cases of valvular heart disease or pulmonary arterial hypertension were observed in any patient at any time. Echocardiographic monitoring revealed valvular function within the normal physiological range in all patients throughout the trials; one patient (FFA 0.8 mg/kg/day) had an end-of-study echocardiogram reading as mild aortic regurgitation without changes in valve morphological structure, and a diagnostic transoesophageal echocardiogram revealed absent aortic regurgitation and a normal aortic valve [25].

Table 7 Adverse events for adjunctive fenfluramine versus placebo according to treatment dose

Outcome or subgroup	Number of studies [reference]	Number of pooled events/participants		I^2	Risk ratio (95% CI)	*p* value
		FFA	Placebo			
Fenfluramine 0.2 mg/kg/day						
Any AE	2 [23, 25]	106/128	91/127	81.1%	0.22 (0.87–1.70)	0.249
Any serious AE	2 [23, 25]	8/128	8/127	0.0%	1.00 (0.39–2.57)	0.997
Blood glucose decreased	1 [23]	0/39	0/40	–	–	–
Bronchitis	1 [23]	1/39	0/40	–	3.08 (0.13–73.27)	0.487
Decreased appetite	2 [23, 25]	26/128	12/127	1.3%	12.06 (1.08–3.93)	0.027
Diarrhoea	2 [23, 25]	22/128	7/127	0.0%	3.12 (1.38–7.05)	0.006
Fall	1 [23]	4/39	2/40	–	2.05 (0.40–10.57)	0.390
Fatigue	2 [23, 25]	12/128	10/127	41.4%	1.10 (0.48–2.53)	0.825
Lethargy	1 [23]	4/39	2/40	–	2.05 (0.40–10.57)	0.390
Nasopharyngitis	1 [23]	4/39	5/40	–	0.82 (0.24–2.83)	0.754
Pyrexia	2 [23, 25]	16/128	18/127	0.0%	0.89 (0.48–1.66)	0.708
Seizure	1 [23]	4/39	5/40	–	0.82 (0.24–2.83)	0.754
Somnolence	2 [23, 25]	15/128	12/127	0.0%	1.23 (0.59–2.54)	0.581
Upper respiratory tract infection	1 [23]	8/39	5/40	–	1.64 (0.59–4.58)	0.344
Vomiting	2 [23, 25]	16/128	9/127	0.0%	1.73 (0.78–3.84)	0.176
[a]Weight decrease	2 [23, 25]	7/128	3/127	22.6%	2.09 (0.50–8.70)	0.309
Fenfluramine 0.5 mg/kg/day						
Any AE	1 [24]	42/43	42/44	–	1.02 (0.95–1.11)	0.570
Any serious AE	1 [24]	6/43	7/44	–	0.88 (0.32–2.40)	0.798
Blood glucose decreased	1 [24]	6/43	2/44	–	3.07 (0.66–14.38)	0.155
Bronchitis	1 [24]	5/43	2/44	–	2.56 (0.52–12.48)	0.245
Decreased appetite	1 [24]	19/43	5/44	–	3.89 (1.60–9.48)	0.003
Diarrhoea	1 [24]	10/43	3/44	–	3.41 (1.01–11.55)	0.049
Fall	1 [24]	0/43	2/44	–	0.21 (0.01–4.14)	0.301
Fatigue	1 [24]	11/43	2/44	–	5.63 (1.32–23.92)	0.019
Lethargy	1 [24]	5/43	2/44	–	2.56 (0.52–12.48)	0.245
Nasopharyngitis	1 [24]	7/43	15/44	–	0.48 (0.22–1.06)	0.068
Pyrexia	1 [24]	11/43	4/44	–	2.81 (0.97–8.16)	0.057
Seizure	1 [24]	2/43	7/44	–	0.29 (0.06–1.33)	0.111

Table 7 continued

Outcome or subgroup	Number of studies [reference]	Number of pooled events/participants		I^2	Risk ratio (95% CI)	*p* value
		FFA	Placebo			
Somnolence	1 [24]	3/43	3/44	–	1.02 (0.22–4.79)	0.977
Upper respiratory tract infection	1 [24]	4/43	3/44	–	1.36 (0.32–5.74)	0.672
Vomiting	1 [24]	2/43	3/44	–	0.68 (0.12–3.88)	0.666
[a]Weight decrease	1 [24]	9/43	2/44	–	4.61 (1.06–20.10)	0.042
Fenfluramine 0.8 mg/kg/day						
Any AE	2 [23, 25]	116/127	91/127	48.6%	.26 (1.20–1.43)	< 0.001
Any serious AE	2 [23, 25]	15/127	8/127	0.0%	1.83 (0.80–4.20)	0.154
Blood glucose decreased	1 [23]	0/40	0/40	–	–	–
Bronchitis	1 [23]	0/40	0/40	–	–	–
Decreased appetite	2 [23, 25]	46/127	12/127	19.8%	13.62 (2.01–6.52)	< 0.001
Diarrhoea	2 [23, 25]	18/127	7/127	0.0%	2.56 (1.11–5.92)	0.027
Fall	1 [23]	0/40	2/40	–	0.20 (0.01–4.04)	0.294
Fatigue	2 [23, 25]	20/127	10/127	0.0%	1.95 (0.95–3.97)	0.069
Lethargy	1 [23]	7/40	2/40	–	3.50 (0.77–15.83)	0.104
Nasopharyngitis	1 [23]	7/40	5/40	–	1.40 (0.49–4.04)	0.534
Pyrexia	2 [23, 25]	9/127	18/127	25.0%	0.53 (0.24–1.15)	0.108
Seizure	1 [23]	3/40	5/40	–	0.60 (0.15–2.34)	0.462
Somnolence	2 [23, 25]	19/127	12/127	0.0%	1.59 (0.80–3.13)	0.184
Upper respiratory tract infection	1 [23]	0/40	5/40	–	0.09 (0.01–1.59)	0.101
Vomiting	2 [23, 25]	10/127	9/127	0.0%	1.11 (0.46–2.66)	0.819
[a]Weight decrease	2 [23, 25]	15/127	3/127	0.0%	4.74 (1.39–16.19)	0.013

AE adverse event, *CI* confidence interval, *FFA* fenfluramine

[a]A change from baseline of at least 7% was set as the minimum threshold for identifying a meaningful weight decrease

DISCUSSION

Summary of Main Results

Randomized controlled trials provided robust evidence of the efficacy of FFA to treat seizures in patients with DS and LGS when added to an existing antiepileptic treatment. Fenfluramine oral solution given at daily dosages of 0.2, 0.5, and 0.8 mg/kg resulted in a significantly higher rate of patients presenting a reduction in the frequency of convulsive seizures by 50% or more compared with placebo in children with DS. Additionally, a significantly greater proportion of patients treated with FFA experienced no more than one convulsive seizure during the treatment period compared to placebo, and the longest convulsive seizure-free interval was 18 days longer overall in patients with DS treated with FFA compared to placebo. A phase III trial demonstrated a reduction in the drop seizure frequency in patients who used 0.8 mg/kg/day FFA, with a significantly higher rate of responders in comparison to placebo-treated patients.

The clinical global impression of improvement is an outcome measure used to inform about the clinical relevance of a decline in seizure frequency. Both the investigators and the parents or caregivers rated significantly more FFA-treated patients as being much improved or very much improved compared with patients in the placebo arm. Notably, clinical improvement was observed in patients with DS and LGS, which are developmental epileptic encephalopathies characterized by very difficult-to-treat seizures alongside cognitive and behavioural impairment.

Experimental studies suggest that FFA has a dual mechanism of action, enhancing 5-HT_{1D} and 5-HT_{2C} serotoninergic receptors and positively modulating σ-1 receptors. The antiseizure activity of FFA is thought to be due to the restoration of the balance of GABA-mediated inhibition and glutamatergic excitation [26–28]. Interestingly, σ-1 receptors may be also involved in non-seizure comorbidities associated with the pathophysiology of developmental and epileptic encephalopathies. In addition to the significant reductions in seizure frequency, a direct action of FFA in non-seizure outcomes like cognitive functioning cannot be ruled out. In this regard, FFA improved learning deficits in mouse models via σ-1 receptor activity [26, 28] and improved executive functions in patients with DS and LGS [24, 29–31].

The overall rates of treatment discontinuation and occurrence of AEs associated with FFA were similar to those associated with other ASMs in DS and LGS [32–37], and statistically significant differences with placebo emerged when FFA was given at the higher daily dosages. Non-cardiovascular AEs associated with FFA treatment included decreased appetite, diarrhoea, fatigue, and weight loss. Serious AEs were uncommon and occurred with similar frequencies across the active treatment and placebo groups. Fenfluramine was previously marketed as an appetite suppressant, and decreased appetite was the most common AE; it was reported across the trials by 20–44% of the patients randomized to FFA and 5–11% of patients randomized to placebo. Weight loss above the 7% threshold occurred in 5–21% of participants receiving FFA and up to 5% of participants receiving placebo; it is noteworthy that none of the patients experienced weight loss that resulted in trial discontinuation. Interestingly, long-term treatment with FFA for up to 24 months in patients with DS has been shown to have a minimal effect on weight and growth compared with a reference population of historical control patients [38].

Cardiovascular safety is an important endpoint when evaluating patients treated with FFA. In obese adult patients, increasing doses and increasing duration of treatment have been shown to be risk factors for valvulopathy when FFA is used as an anorectic agent. Importantly, an intensive, prospectively defined monitoring program with color Doppler echocardiographic examinations was used before and during all the randomized controlled trials in patients with DS and LGS. In all these trials, no pathological functional changes in cardiac valves and no signs of pulmonary arterial hypertension were identified in any patient at any time. These findings support the cardiovascular safety of FFA at the lower dosages used for seizure

management relative to the higher dosages used for adults with obesity.

Strengths and Limitations

This systematic review with metanalysis provides a comprehensive and updated synthesis of the efficacy and safety of FFA in patients with epilepsy. Compared to available quantitative analyses focusing on FFA [39, 40], this study pooled a larger population, including evidence about LGS, and explored the study outcomes according to the dose of the drug. Some limits, however, need to be acknowledged to correctly interpret the findings. Only three randomized controlled trials met the inclusion criteria, and they have been all sponsored by a single pharmaceutical company. Only AEs occurring in at least 10% of the patients in at least one treatment group across the trials were included; this more stringent criterion was, however, chosen because the limited statistical power of metanalyses when the event rates are too low may result in false evidence of no differences between the active and placebo arms, and this may even be inappropriately interpreted as a reassuring signal of safety when it may not be. Real world studies of larger cohorts of people are warranted to inform about the actual tolerability and safety profile of FFA with respect to uncommon AEs. As the duration of the trials was short, the long-term effectiveness and safety of FFA cannot be fully characterized yet. In this regard, FFA provided a sustained seizure frequency reduction and was generally well tolerated over an extended period in patients who completed the double-blind studies and entered the open-label extension phases [41, 42]. Further, no patient developed valvular heart disease or pulmonary arterial hypertension in the longitudinal assessment up to 36 months [43, 44], supporting the safe cardiovascular profile of FFA that emerged with ongoing echocardiographic examinations during long-term treatment for up to 30 years in Belgium [13]. In addition, this metanalysis cannot inform about the effects of FFA treatment on non-seizure measures like developmental endpoints and the comparative effectiveness with other ASMs.

CONCLUSION

Current treatment strategies for DS and LGS are based on polypharmacy with drugs of different classes and mechanisms of action. The unique pharmacodynamic properties of FFA may provide a new treatment option for patients with these epileptic and developmental encephalopathies. Additional studies are warranted to investigate and understand the clinical activity of FFA in other epileptic conditions [45–48] and its potential to reduce the risk of sudden unexpected death in epilepsy [49, 50].

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