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Epilepsy (E Waterhouse, Section Editor)

# Fenfluramine for the Treatment of Dravet Syndrome and Lennox Gastaut Syndrome: A Review

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## Abstract

*Purpose of Review* Treatment-resistant epilepsy comprises approximately 36.3% of neurology clinic-based populations in the USA. Despite new drug development over the past 50 years, the rates of drug-resistant epilepsy remain the same. The need for continued drug trials with novel mechanisms of action remains paramount in patients with drug-resistant epilepsy. In particular, patients with severe epilepsy syndromes such as Dravet syndrome (DS) and Lennox Gastaut syndrome (LGS) continue to be the most severely affected due to the increased rates of status epilepticus and sudden unexpected death (SUDEP).
*Recent Findings* Fenfluramine has recently been FDA-approved for DS and LGS. There is substantial evidence highlighting the efficacy of fenfluramine in the treatment of seizures associated with DS and LGS. There are a growing number of studies investigating alternative uses of fenfluramine for treatment-resistant epilepsies.
*Summary* The completed studies suggest that fenfluramine is both a safe and efficacious adjunctive therapy in the treatment of convulsive seizures and drop seizures associated with DS and LGS. Fenfluramine's suggested mechanism of action and available human evidence likely support its efficacy as an add-on therapy for more seizure types and calls for further research to expand its clinical use.

## Introduction

Treatment-resistant epilepsy comprises approximately 36.3% of neurology clinic-based populations in the USA [1]. Despite new drug development over the past 50 years, the rates of drug-resistant epilepsy remain the same [1]. The need for continued drug trials with novel mechanisms of action remains paramount in patients with drug-resistant epilepsy. In particular, patients with severe epilepsy syndromes such as Dravet syndrome (DS) and Lennox Gastaut syndrome (LGS) continue to be the most severely affected due to the increased rates of status epilepticus and sudden unexpected death (SUDEP) [2]. Fenfluramine has recently been FDA-approved for DS and LGS. The following will summarize the literature and trials regarding fenfluramine.

# History in brief

Fenfluramine (3-trifluoromethyl-N-ethylamphetamine) was initially trialed as an appetite suppressant in France in the 1960s. Its efficacy in appetite suppression and epilepsy is believed to be mediated through serotonergic mechanisms [3–5]. Patients with obesity found fenfluramine to be an effective agent for appetite suppression [6, 7]. However, it was withdrawn from global markets given reports of heart valve abnormalities in the late 1990s [8].

Prior to its withdrawal, fenfluramine was studied in small case reports by Dr. Henri Gastaut and Jean Aicardi. Gastaut and Aicardi commented on efficacy in compulsive behaviors and photosensitive epilepsies [9, 10]. The concept of using fenfluramine in epilepsy was largely forgotten until 2012 when Ceulemans et al. described a small group of patients in Belgium that was permitted to use fenfluramine in refractory epilepsy by Royal Decree [11]. The study reported remarkably good effects as an add-on agent in Dravet syndrome. Interest in fenfluramine was largely rekindled leading to further drug trials and FDA approval for patients with DS and LGS.

# Mechanism of action and interactions

Fenfluramine (3-trifluoromethyl-N-ethylamphetamine) is an amphetamine derivative that acts as an agonist on 5-Ht2 receptors and inhibits the reuptake of serotonin [3]. It has some properties that promote the release of norepinephrine [3]. In high concentrations, it has been shown to release dopamine [3]. The hypothesized efficacy in seizure control is thought to be related to serotonin modulation, although the exact mechanism remains unknown [12, 13]. Fenfluramine is 50% bound to plasma proteins. Its volume of distribution is 11.9L/kg with a coefficient of variation of 16.5% following oral administration in healthy subjects [3]. It is predominantly metabolized by the liver and is highly excreted in urine. Its half-life is estimated to be roughly 20 h in healthy subjects [3]. Its $T^{max}$ to steady state is estimated to be between 4 and 5 h with a bioavailability between 68 and 74% [3].

Fenfluramine is a strong inducer of CYP1A2 and CYP2B6 enzymes [3]. Drugs that also induce CYP1A2 and CYP2B5, such as rifampin, will lower plasma concentration of fenfluramine. Dose adjustment is required with

co-administration of stiripentol plus clobazam as these drugs will inhibit the breakdown of fenfluramine, thereby causing higher than expected plasma concentrations [3]. Drugs and substances with mechanisms of action that effect serotonin may interact with fenfluramine. Co-administration of SSRI's, SNRI's, TCA's, MAO inhibitors, trazodone, dextromethorphan, and supplements like St. John's Wort may increase the risk of serotonin syndrome through increased levels of serotonin.

## Fenfluramine and epilepsy

At the time of this review (August 2022), 2 interventional clinical trials regarding fenfluramine in epilepsy have been completed as per www.clinicaltrials.gov. Six clinical trials were active, recruiting, or had completed enrollment. The available published clinical data on fenfluramine and its role in the management of epilepsy are described and outlined below. A table reference is provided (Table 1).

## Randomized control trials

Two randomized control trials sought to investigate the efficacy of fenfluramine vs placebo. Both studies (NCT02926898 and NCT02682927) investigated fenfluramine in the treatment of DS as an adjunctive agent. The first study (NCT02926898) sought to understand the change in number of convulsive seizures in patients receiving fenfluramine vs placebo from their baseline [14]. Patients were randomized to 0.4 mg/kg/day of fenfluramine vs placebo [14]. Study participants between the ages of 2 and 18 years were included [14]. The participants were required to be diagnosed with DS and be stable doses of clobazam, valproic acid, and/or stiripentol [14]. The study enrolled a total of 87 patients [14]. Once enrolled in the study, the participants were assessed for a 6-week baseline period prior to receiving a 12-week treatment period [14]. Seizure frequency was measured from a seizure diary kept by the parent/caregiver. The participants were then randomized to receive 0.4 mg/kg/day of fenfluramine vs placebo [14]. Fifty-four percent of patients in this study that received fenfluramine demonstrated a clinically meaningful reduction in seizures [14]. A clinically meaningful reduction in seizures was defined as a 50% or greater reduction in the number of monthly convulsive seizures [14]. The median seizure-free interval was 22 days in the fenfluramine treatment arm compared with 13 in the placebo arm [15]. Common adverse events included decreased appetite in the treatment group (44%) vs placebo (11%) [14]. Less common adverse events included fatigue (26 vs 5%), diarrhea (23 vs 7%), and pyrexia (26 vs 9%) [14]. There were no clinical or echocardiographic changes in valvular heart function or pulmonary arterial hypertension.

**Table 1 The published clinical data on fenfluramine and its role**

| NCT number | Title | Conditions | Interventions | Study type | Phase | Funding |
|---|---|---|---|---|---|---|
| NCT02682927 | A Trial of Two Fixed Doses of ZX008 (Fenfluramine HCl) in Children and Young Adults With Dravet Syndrome | Dravet Syndrome | Placebo vs ZX008 | Interventional | Phase 3 | Zogenix |
| NCT02926898 | A Two-Part Study to Investigate the Dose-Ranging Safety and Pharmacokinetics, Followed by the Efficacy and Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children ≥ 2 Years Old and Young Adults With Dravet Syndrome | Dravet Syndrome | Placebo vs ZX008 (0.2 mg/kg/day) vs ZX008 (0.4 mg/kg/day) vs ZX (20 mg/kg/day) | Interventional | Phase 3 | Zogenix |
| NCT03936777 | A Study to Investigate the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution in Children and Adults With Epileptic Encephalopathy Including Dravet Syndrome and Lennox-Gastaut Syndrome | Dravet Syndrome and Lennox Gastaut Syndrome | Drug: ZX008 (fenfluramine hydrochloride) fenfluramine hydrochloride provided in a concentration of 2.5 mg/mL | Interventional | Phase 3 | Zogenix |

**Table 1** (continued)

| NCT number | Title | Conditions | Interventions | Study type | Phase | Funding |
|---|---|---|---|---|---|---|
| NCT03790137 | Treatment of Sunflower Syndrome With ZX008 (Fenfluramine Hydrochloride) in Children and Young Adults (Ages 4–25) | Sunflower Syndrome | Fenfluramine hydrochloride will be supplied to the treatment group as an oral solution in a concentration of 2.5 mg/mL. Subjects will receive their daily dose of fenfluramine hydrochloride in two doses (one in the morning and one in the evening). After a 4-week baseline, subjects that meet enrollment criteria will enter a titration period. The starting dose will be 0.2 mg/kg/day for the first 14 days. The dose will be increased every 2 weeks as tolerated by 0.2 mg/kg/day, to a maximum dose of 0.8 mg/kg/day, or a total maximum dose of 30 mg/day. The subject will remain on a dose of 0.8 mg/kg/day, 30 mg/day, or maximum tolerated daily dose for a 6-week maintenance period | Interventional | Phase 3 | Zogenix |
| NCT03861871 | Fenfluramine in CDKL5 Deficiency Disorder (CDD) | CDKL5 Deficiency Disorder (CDD) | Drug: fenfluramine hydrochloride<br>Oral solution 2.5 mg/mL<br>Other name: ZX008 | Interventional | Phase 2 | NA |
| NCT02655198 | Add-on Therapy With Low Dose Fenfluramine in Lennox Gastaut Epilepsy | Lennox Gastaut Syndrome | Drug: fenfluramine<br>Study of efficacy and safety of add-on fenfluramine at different dosages in refractory Lennox Gastaut patients: 0.2–0.4 and 0.8 mg/kg/day (max 30 mg) | Interventional | Phase 2 | KU Leuven |
| NCT04289467 | Treatment of Refractory Infantile Spasms With Fenfluramine | Refractory Infantile Spasms | Drug: fenfluramine<br>Open-label<br>Other name: fenfluramine hydrochloride | Interventional | Phase 2 | NA |

**Table 1** (continued)

| Sponsored by | Outcome measures | Study start date | Primary completion | Study completion | Results first posted | Last update posted |
|---|---|---|---|---|---|---|
| Zogenix | Change in mean convulsive seizure frequency comparing the baseline with the combined titration and maintenance period for ZX008 0.8 mg/kg/day group compared with placebo group | 1/16 | 7/20 | 7/20 | 2/17/2016 | 1/6/2020 |
| Zogenix | Change from baseline in frequency of convulsive seizures in subjects receiving ZX008 0.2 mg/kg/day as adjunctive therapy compared to placebo | 9/16 | 6/18 | 1/8/2019 | 10/6/2016 | 6/13/2019 |
| Zogenix | Change in adverse events, change in laboratory test results, changes in heart rate, changes in respiratory rate, changes in blood pressure, change in body weight, changes in heart rhythm, change in heart valve function | 4/22/2019 | 4/23 | NA | No results posted | 6/30/2022 |
| Elizabeth Thiele | Change in frequency of absence seizures associated with hand waving. Change in frequency of generalized tonic–clonic seizures | 5/31/2019 | 2/20 | NA | No results posted | 8/21/2019 |

**Table 1** (continued)

| Sponsored by | Outcome measures | Study start date | Primary completion | Study completion | Results first posted | Last update posted |
|---|---|---|---|---|---|---|
| NYU Langone Health | Median monthly convulsive seizure frequency | 10/29/2019 | 12/22 | NA | No results posted | 4/7/2022 |
| Zogenix | Efficacy of add-on FFA in Lennox Gastaut epilepsy: number of responders and seizure-free patients at each FFA dosage (0.2 or 0.4 or 0.8 mg/kg/day) | 1/16 | 9/18 | NA | No results posted | 1/27/2021 |
| University of California, Los Angeles | Number of participants with resolution of epileptic spasms and hypsarrhythmia (if present at baseline) after 21 days of treatment, as determined by overnight video-electroencephalography (EEG) evaluation and caregiver seizure diary | 4/1/2020 | 12/31/2021 | NA | No results posted | 2/28/2020 |

Study NCT02682927 compared the dose response of fenfluramine vs placebo [16]. A total of 119 participants with DS ranging from age 2 to 19 years were randomized to receive 0.7 vs 0.2 mg/kg/day fenfluramine vs placebo [16]. The study used parental/caregiver seizure diary to quantify the number of seizures. Median time to *n*th seizure was longer in the fenfluramine groups vs placebo (fenfluramine 0.7 mg/kg/day 13 weeks, 0.2 mg/kg/day 10 weeks, placebo 7 weeks) [16]. Additionally, the longest duration of convulsive seizure-free days was also lengthened ((0.7 mg/kg/day, 25 days), (0.2 mg/kg/day, 15 days, (placebo, 9.5 days)) [16]. The demonstrated adverse effects were consistent with the first study highlighting decreased appetite, fatigue, diarrhea, pyrexia, and upper respiratory infections [16].

A post hoc analysis from the studies on DS suggested a substantially lower rate of all-cause and SUDEP-related mortality compared with historical natural history cohorts [2].

Study NCT03355209 investigated the efficacy and safety of fenfluramine as an adjunctive therapy in children and adults with LGS [17]. The study aimed to understand the change from baseline in frequency of seizures that result in drops in subjects receiving fenfluramine compared to placebo [17]. A drop seizure includes the following: generalized tonic clonic, focal to bilateral tonic–clonic, tonic, atonic, or tonic or atonic seizures causing loss of upright positioning [17]. Patients aged 2 to 35 years with a confirmed diagnosis of LGS were randomized after a 4-week observation period to receive 0.7 mg/kg/dose of fenfluramine, 0.2 mg/kg/dose of fenfluramine, or placebo [17]. A total of 242 patients completed the trial [17]. Median percent reduction in drop seizure frequency was 26.5 percentage points in patients receiving 0.7 mg/kg/dose of fenfluramine, 14.2 percentage points in patients receiving 0.2 mg/kg/dose of fenfluramine, and 7.6 percentage points in the placebo group [17]. The study also concluded that 25% of patients in the 0.7 mg/kg/dose arm of fenfluramine experienced a 50% or greater reduction in drop seizure frequency, 28% in the 0.2 mg/kg/dose group, and 10% in the placebo group [17]. The study reported a 45.7% reduction in generalized tonic clonic seizure frequency in the 0.7 mg/kg/dose group, 58% in the 0.2 mg/kg/dose group, and a 3.7% increase in the placebo group [17]. Notably, no patients enrolled in the trial experienced valvular heart disease or pulmonary hypertension [17].

## Open label-interventional trials

No open label-interventional trials have reached completion at this time.

## Additional information on safety

Safety concerns have been a major reservation in some groups of neurologists given the drugs' initial withdrawal from the market due to associated valvular dysfunction in the 1990s. Extensive monitoring has been key to

fenfluramine's resurgence to the market for patients with epilepsy. Long-term open safety studies have examined the cardiovascular safety of fenfluramine particularly in patients with DS and have found a low risk of developing cardiac valvulopathy and pulmonary artery hypertension [8, 18]. There have been no reported valvular cardiac adverse events in over 1500 patients treated with fenfluramine [18]. Given the historical information and concerns, the current guidelines recommend an echocardiogram every 6 months for patients taking fenfluramine and once 3–6 months following cessation of the drug [19].

Fenfluramine did not prolong QT interval in adults at a dose of 4 times maximum recommended dose [3].

## Clinical trials: what is on the horizon?

Many clinical trials are on the horizon for fenfluramine. Trials are investigating the utility of fenfluramine in refractory infantile spasms, CDKL5 deficiency disorder, Sunflower syndrome, and children and adults with epileptic encephalopathy.

Fenfluramine in refractory infantile spasms is being studied (NCT04289467) to determine the number of participants with resolution of epileptic spasms and hypsarrhythmia. This open label study will assess patients with overnight EEG 21 days after treatment.

Patients with Sunflower syndrome and CDKL5 deficiency disorder are also being studied in trials (NCT03790137, NCT03861871) using fenfluramine. The study on patients with Sunflower syndrome has planned to assess change in frequency of absence seizures associated with hand waving with an upward titration of fenfluramine starting at 0.2 mg/kg/day for the first 14 days. That dose will then be increased every 2 weeks as tolerated by 0.2 mg/kg/day to a maximum dose of 0.8 mg/kg/day. Patients with CDKL5 DD will use fenfluramine to assess the median frequency of monthly convulsive seizures.

Finally, a study (NCT03936777) in children and adults with epileptic encephalopathy including DS and LGS will monitor changes in adverse events and test results with the use of fenfluramine.

## Conclusion

Fenfluramine's history and re-emergence on the market have created a mixed climate of skepticism and optimism given its initial withdrawal despite remarkable efficacy. The completed studies suggest that fenfluramine is both a safe and efficacious adjunctive therapy in preventing convulsive and drop seizures associated with DS and LGS [9, 20–22]. Fenfluramine suggested mechanism of action and available human evidence likely support its efficacy as an add-on therapy for more seizure types and calls for further research to expand its clinical use.

## Compliance with Ethical Standards

**Conflict of interest**
The authors declare that there is no conflict of interest.

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## Publisher's Note