Reintroducing Fenfluramine as a Treatment for Seizures: Current Knowledge, Recommendations and Gaps in Understanding

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Abstract: Despite the introduction of new anti-seizure medications in recent years, approximately one-third of the epileptic population continues to experience seizures. Recently, the anti-obesity medication fenfluramine (FFA) has been successfully repurposed, and it has received approval from various regulatory agencies for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome. The potential antiseizure effects of FFA were initially observed in patients with photosensitive epilepsy in the 1980s but it was not rigorously explored as a treatment option until 30 years later. This narrative review aims to provide an overview of the historical progression of FFA’s use, starting from initial clinical observations to preclinical studies and, ultimately, successful clinical trials in the field of epilepsy.

Keywords: fenfluramine, seizures, Dravet syndrome, drug-resistant epilepsy, serotonin

Introduction

Epilepsy is a common neurological condition, affecting over 70 million individuals worldwide.¹ Despite the introduction of new anti-seizure medications (ASMs) in recent years, approximately one-third of the epileptic population continues to experience seizures.² This drug resistance poses significant challenges in managing epilepsy and improving outcomes for affected individuals.

Recently, the anti-obesity medication fenfluramine (FFA) has been successfully repurposed, and regulatory agencies have approved its use for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome.³⁴ This narrative review aims to provide a comprehensive analysis of fenfluramine’s mechanism of action as an antiseizure medication, its clinical pharmacology, and relevant clinical studies. Special emphasis is placed on evaluating its efficacy in reducing seizures and examining potential adverse effects.

Materials and Methods

A Pubmed search was conducted to identify pertinent articles published from January 1985 to July 2023. Papers were searched using the following terms: “fenfluramine”, “Dravet syndrome”, and “Lennox-Gastaut syndrome”. Priority was given to systematic reviews, followed by randomized controlled trials and observational studies, without excluding any paper for its nature. A narrative review format was chosen. Additional articles were identified through manual searches of the reference lists of relevant articles.

Fenfluramine as an Appetite Suppressant

FFA (3-trifluoromethyl-N-ethylamphetamine) is a derivative of amphetamine that was initially introduced in France in 1963. It was primarily used as an antidepressant and later gained popularity as an appetite suppressant. In 1973, FFA received...
approval for use in the United States where it has been prescribed both as a standalone medication and in combination with
phentermine. FFA is a chiral molecule with a single stereogenic center (Figure 1). It has been marketed as a racemic mixture
(Pondimin®) and as the individual d-enantiomer, also known as dexfenfluramine or (+)-fenfluramine (Redux®).

**Pharmacokinetics**

After oral administration, FFA is rapidly absorbed from the gastrointestinal tract and reaches peak plasma concentration
within 3–5 hours. The absolute oral bioavailability of FFA is estimated to be between 75% and 83%, and it is not
significantly affected by food intake. FFA is metabolized primarily in the liver by CYP1A2, CYP2B6, CYP2D6,
CYP2C9, CYP2C19, and CYP3A4/5 to yield the major active metabolite norfenfluramine and several other minor
inactive metabolites. Both FFA and its metabolites are eliminated through renal excretion, with an elimination half-
life of 20 hours for FFA and 24–48 hours for norfenfluramine. The plasma concentration of FFA and its metabolites can
vary significantly among individuals. A study evaluating FFA plasma concentration in 61 patients (49 with Dravet
syndrome and 7 with Lennox-Gastaut syndrome) found that younger patients had lower concentrations when adjusted for
weight, suggesting faster clearance in children.

**The Fen-Phen Combination**

In 1984, it was reported that the anorexic effects of FFA could be enhanced while minimizing some of its side effects by
combining it with smaller doses of phentermine, another appetite suppressant that had been available in the United States
since 1959. Phentermine is a stimulant that primarily acts on the central nervous system by promoting the release of
noradrenaline and dopamine. Although the combined use of fenfluramine and phentermine, known as fen-phen, did not
receive specific approval from the FDA, it gained significant popularity, with approximately 18 million prescriptions
filled in 1996 alone, mostly for overweight women.

**Fenfluramine: Withdrawal from the Market**

FFA was withdrawn from the market in 1997 due to accumulating evidence that its chronic use could result in
a significant incidence of valvulopathy. The European literature reported two cases of primary pulmonary hypertension
(PPH) associated with the use of FFA in 1981. Subsequent reports further suggested a potential link between FFA and
PPH. In 1996, a case-control study compared 95 patients with PPH with 355 healthy controls. The study found that the
prolonged use of anorexic drugs, particularly dexfenfluramine, for a duration of 3 months or more, was associated with
an odds ratio of 23.1 for developing pulmonary hypertension.

According to an estimate by Manson and Faich, the absolute risk of primary pulmonary hypertension associated
with FFA was approximately 28 cases per million person-years of exposure. A year later, on July 8, 1997, the perception
of fenfluramine’s benefit-to-risk balance underwent a significant shift due to a report involving 24 women who developed
valvular heart disease after being exposed to the fenfluramine-phentermine combination for a period ranging from 1 to 28
months. In most patients, the maximum daily dose of FFA taken prior to the diagnosis of valvular disease was either 40
or 60 mg, although two patients were exposed to as little 20 mg, and two received very high doses (120 and 220 mg
each). Following this report, health professionals quickly became aware of the issue, and by September 30, 1997, the
FDA had received 144 individual spontaneous reports (including the 24 cases reported earlier) involving FFA or
dexfenfluramine with or without phentermine in association with valvulopathy.

![Figure 1 Structure of fenfluramine.](https://doi.org/10.2147/NDT.S417676)
Although the risk of cardiovascular toxicity is generally believed to be dose-dependent, the presence of confounding factors makes it challenging to establish an exact relationship with dosage. The most robust evidence for a dose-response relationship comes from an evaluation of 74 fen-phen patients reported to the FDA who met the FDA’s criteria for valvulopathy. Among these patients, 73 were female, the median daily dose of fenfluramine was 60 mg, and the median duration of exposure was 11 months. Within this small cohort, the proportion of patients with severe valvulopathy (defined as individuals requiring valve replacement surgery or having severe aortic or mitral regurgitation) increased from 20% (3/17) for doses below 40 mg/day to 23% (3/13) at 40 mg/day, 65% (24/37) at 60 mg/day, and 71% (5/7) at doses above 60 mg/day.

**The Mechanisms of Fenfluramine’s Cardiovascular Toxicity**

Several lines of evidence suggest that FFA-induced valvulopathy is the result of excessive serotonergic stimulation of cardiac valve tissue. Specifically, the activation of 5-HT$_{2B}$ receptors by 5-HT has been shown to promote DNA synthesis and cell-cycle progression in valve interstitial cells, leading to valve damage. Recent evidence has further highlighted the crucial role of 5-HT$_{2B}$ receptor stimulation in the development of fenfluramine-induced valvulopathy. A study demonstrated that the increase in mitral valve thickening and endothelial cell density (which are considered early indicators of mitral valve remodelling) caused by 28-day treatment with d-norfenfluramine in mice, is fully prevented by the selective 5-HT$_{2B}$ receptor antagonists SB204741, as well as by the deletion of 5-HT$_{2B}$ receptors.

The relationship between 5-HT$_{2B}$ receptor activation and cardiac valvulopathy is supported by numerous studies. One of these relates to the observation that cardiac valvulopathy is caused by drugs with different pharmacological profiles and chemical structures, such as FFA, benfluorex, pergolide, and cabergoline. These drugs share the common ability to bind to and activate 5-HT$_{2B}$ receptors. In contrast, other serotonergic drugs with low or moderate affinity for 5-HT$_{2B}$ receptors, such as ropinirole and lorcaserin, have not been associated with the development of valvulopathy.

While 5-HT$_{2B}$ receptor stimulation is recognized as a crucial factor in the development of FFA-induced valvulopathy, it is important to acknowledge that other factors are likely to contribute to this condition as well. These include the stimulation of 5-HT$_{2A}$ receptors, serotonylation of the cytoskeletal protein filamin-A, and the interplay of genetic predisposition and individual risk factors.

Another adverse cardiovascular effect that has been reported with high-dose FFA is pulmonary arterial hypertension (PAH). FFA’s serotonergic overactivity can induce proliferation of pulmonary artery smooth muscle cells, which contributes to the development of PAH. The increased serotonergic activity can also cause vasoconstriction of the pulmonary artery. Additionally, other factors such as nitric oxide deficiency have been suggested to play a role in the development of PAH.

**Fenfluramine Repurposing from Weight Loss to Epilepsy**

The anticonvulsant activity of FFA was first recognized in the 1980s, when it was tested in individuals and in small groups of patients with treatment-resistant epilepsies. More specifically, Aicardi et al and Clemens were among the first to present data from case reports and small case series demonstrating a significant reduction in seizure frequency when FFA was added to the existing treatment regimen. It should also be noted that Gastaut et al reported the reduction of compulsive respiratory stereotypies in children with autism, when treated with FFA at doses ranging from 1.5 to 3 mg/kg/day.

The initial pilot study conducted by Gastaut and Zifkin involved the assessment of 33 individuals with intractable epilepsy who were administered FFA at a dose ranging from 0.5 to 1.5 mg/kg/day. The results of the study revealed that almost half of the participants experienced a reduction in seizure frequency of at least 50%. Importantly, no echocardiographic findings indicating pulmonary hypertension or valvular dysfunction were reported. Among the observed side effects in this patient population, the most common were sleepiness, fatigue, and loss of appetite, with or without weight loss.

The potential use of FFA as an antiepileptic treatment is based on the hypothesis that 5-HT receptors, which are widely distributed throughout the central nervous system, can interact with different types of ion channels, thereby...
influencing neuronal excitability. Both clinical and animal studies have demonstrated that serotonergic neurons possess anticonvulsant effects, and patients treated with selective serotonin reuptake inhibitors (SSRIs) may experience a reduction in seizure frequency. Furthermore, recent radioligand binding assays have revealed that FFA exhibits modulatory activity at sigma-1 receptors. These receptors are highly expressed in deeper laminae of the cortex, the olfactory bulb, nuclei of the mesencephalon, hypothalamus, and Purkinje cells in the brain. This modulation of sigma-1 receptors, in addition to FFA’s serotonergic activity, has been observed both in vitro and in vivo.

Mechanisms of Fenfluramine’s Anti-Seizure Activity
Experimental studies suggest that FFA exerts its antiseizure activity by enhancing serotonergic transmission and positively modulating sigma-1 receptors (Figure 2). The anticonvulsant effect of FFA is believed to be associated with restoring the balance between GABA-mediated inhibition and glutamatergic excitation.

Serotonergic Transmission
FFA is known to enhance serotonergic neurotransmission by disrupting the vesicle storage of 5-HT and by preventing its reuptake. FFA achieves this through two main mechanisms. Firstly, it interacts with the serotonin transporter, inhibiting the reuptake of 5-HT. Additionally, FFA prevents the movement of 5-HT from the cytoplasm into vesicles, resulting in the release of cytoplasmic 5-HT outside the cell via 5-HT carriers. These actions contribute to elevated levels of extracellular 5-HT. The inhibitory effects of increased brain 5-HT levels on seizures in rats were observed as early as 1957. Under experimental conditions, exposure to various anticonvulsants, such as phenytoin and carbamazepine, has been shown to increase extracellular 5-HT levels. Additionally, SSRIs, which are known to increase 5-HT levels, have been found to have a positive impact on seizure management.

![Figure 2](https://doi.org/10.2147/NDT.S417676)
Aside from the indirect effect of increasing extracellular 5-HT levels, various in vitro and in vivo studies have demonstrated that FFA is capable of acting as an agonist of multiple serotonin receptors including 5-HT$_{1A}$, 5-HT$_{1D}$, 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$.

**Sigma-1 Pathway**

Beyond its serotonergic activity, FFA interacts with other receptors, most notably sigma-1 receptors, which are a subtype of plasma membrane-localized opioid receptors. While the serotonergic activity of FFA at 5-HT receptors primarily enhances GABAergic signaling, its interaction with sigma-1 receptors reduces glutamatergic excitability. Interestingly, sigma-1 receptors have been implicated not only in seizure control but also in the pathophysiology of non-seizure comorbidities associated with developmental and epileptic encephalopathies. In this regard, FFA ameliorated learning deficits in mouse models via sigma-1 receptor activity and improved executive functions in patients with Dravet syndrome and LGS.

**GABAergic Neurotransmission**

The impairment of GABAergic neurotransmission is a major contributor to epileptogenesis in various preclinical models. FFA has been shown to enhance GABAergic neurotransmission through its effects on 5-HT release at GABAergic synapses and stimulation of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors. Additionally, FFA has demonstrated the ability to restore the dendritic arborization of GABAergic neurons in a zebrafish model of Dravet syndrome. These findings suggest that FFA’s effects on GABAergic neurotransmission may contribute to its antiepileptic properties.

**Fenfluramine in Experimental Models of Epilepsy**

Fenfluramine in experimental models of epilepsy has demonstrated significant antiepileptic effects. In the mutant $scn1La$ zebrafish model of Dravet syndrome, FFA was found to greatly reduce the occurrence of seizures, as evidenced by Zhang and Sourbron. Dinday et al conducted a screening of approximately 1000 compounds and found that FFA-treated $scn1La$ mutant zebrafish exhibited a suppression of spontaneous electrographic seizure activity. In rodent models, FFA has shown efficacy in reducing tonic seizures induced by pentylenetetrazol, as reported by Lazarova et al. Additionally, FFA was investigated in the DBA/1 mouse model of sudden unexpected death in epilepsy, where it demonstrated a dose-dependent reduction in seizure incidence and severity. These findings collectively support the antiepileptic potential of FFA in various animal models.

**Fenfluramine in Dravet Syndrome**

Dravet syndrome is a severe, treatment-resistant epileptic encephalopathy presenting within the first year of life and is characterized by a high seizure burden and significant behavioural, motor, and neurodevelopmental abnormalities. The long-term outcome of Dravet syndrome has been considered to be consistently poor, both in regard to developmental outcome and seizure control. Available antiepileptic drugs do not achieve adequate seizure control in most Dravet syndrome patients, making the identification of new drugs a critical need.

In 2012, Ceulemans et al conducted a retrospective study involving 12 patients with Dravet syndrome. During the course of the study, two patients discontinued treatment. However, the remaining ten patients were followed up for a period of 11 years, during which they received adjunctive FFA at a mean dosage of 0.34 mg/kg/day. Among these ten patients, seven achieved seizure freedom for at least one year. To date, data from two prospective, double-blind, placebo-controlled trials are available, and they both confirm the efficacy and safety of low dose FFA in Dravet syndrome.

In a first study, two different dosages of FFA (0.2 and 0.7 mg/kg/day) were compared to placebo. The percentage of patients who achieved a 50% reduction in seizures was 68% in the 0.7 mg/kg/day group, 38% in the 0.2 mg/kg/day group, and only 12% in the placebo group. The drug was well tolerated, with 38% of children in the highest dosage group experiencing appetite problems. Importantly, prospective cardiac follow-up did not reveal any cardiac issues in patients receiving FFA.
In another randomized clinical trial, a total of 87 pediatric patients were randomly assigned to receive either FFA 0.4 mg/kg day in addition to their treatment regimen or a placebo medication. The results revealed that the number of patients who achieved a 50% reduction in seizures was 54% in the FFA arm compared to only 5% in the placebo arm. These findings strongly suggest that low-dose FFA can be a safe and effective treatment option for individuals with Dravet syndrome.

**Fenfluramine in Lennox-Gastaut Syndrome**

Lennox-Gastaut syndrome (LGS) is a severe developmental and epileptic encephalopathy that typically begins in childhood and has a significant impact on the quality of life of patients and their families. It is considered a rare disease, with an estimated incidence rate of 0.1 to 0.28 per 100,000 people overall and an incidence rate of 2 per 100,000 in children. LGS accounts for approximately 2–5% of all childhood epilepsies, with a slightly higher occurrence in males. LGS usually manifests before the age of 12, with a peak onset between 3 and 5 years of age. Although rare, there have been reports of late-onset cases. LGS has a diverse range of clinical presentations that can evolve and change over time. Tonic seizures are a hallmark of LGS. Alongside tonic seizures, other common seizure types observed in LGS include atypical absences and tonic or atonic drop attacks. The treatment of LGS can be particularly challenging due to the refractory nature of seizures and the associated cognitive and behavioral impairments. Currently available treatments often have limited efficacy and may be associated with significant side effects. Therefore, there is a critical need for the development of novel and effective treatments that can effectively reduce seizures and improve the overall quality of life for individuals with LGS.

Lagae et al reported FFA’s effectiveness in LGS in an open-label prospective Phase 2 study. The study included 13 patients with LGS who experienced more than four convulsive seizures per month. Among them, 10 patients completed 20 weeks of FFA treatment at a dose of 0.8 mg/kg/day (maximum 30 mg/day). The results showed a median reduction of seizures by 53% in the overall patient group. Among the ten patients who completed the study, there was a 60% reduction in seizures. Additionally, >50% seizure reduction was observed in eight (62%) patients. Long-term efficacy was evaluated in nine patients, and the median reduction of seizures was 58%. Among these patients, 67% achieved a ≥50% reduction in seizures, and 33% achieved a ≥75% reduction.

A multicenter, double-blind, placebo-controlled RCT was conducted in 263 LGS patients (2–35 years old) with ≥2 drop seizures/week. The patients were randomly assigned to receive FFA 0.7 mg/kg/day, FFA 0.2 mg/kg/day or placebo. 25.3 and 28.1% of patients treated respectively with FFA 0.7 mg/kg/day and FFA 0.2 mg/kg/day had a ≥50% reduction in monthly drop seizures, compared with 10.3% of placebo. Overall, FFA therapy was well tolerated. Most frequent adverse events (at least 10%) included decreased appetite, somnolence, fatigue, vomiting, diarrhea and pyrexia. No cases of valvular heart disease or pulmonary arterial hypertension were reported.

**Fenfluramine in Other Epileptic Syndromes**

The efficacy of FFA in epilepsies other than Dravet syndrome and LGS is unknown, although recent clinical trials suggested its potential utility in other epilepsy syndromes (Table 1).

CDKL5 deficiency disorder (CDD) is a rare neurodevelopmental and epileptic encephalopathy characterized by infantile-onset epilepsy and severe developmental delays. Most individuals with CDD develop refractory epilepsy with multiple seizure types. In a study conducted by Devinsky et al, the efficacy of FFA was evaluated in six patients with CDD who had failed 5–12 ASMs. These patients were treated with FFA at a dosage of 0.4 mg/kg/day (n = 2) or 0.7 mg/kg/day (n = 4). The results showed a median 90% reduction in seizure frequency, indicating a significant antiseizure effect of FFA in this patient population.

FFA was also assessed in a study involving children and young adults with Sunflower syndrome. Nine patients were treated with FFA for a 4-month period, with a maximum dose of 0.7 mg/kg/day. After 3 months of FFA treatment, eight patients showed a ≥30% reduction in seizure activity. Notably, no cases of cardiac valvulopathy or pulmonary hypertension were observed during the study.
Furthermore, a phase 2 clinical trial (NCT04289467) is underway to investigate the efficacy of FFA in patients with refractory infantile spasms. In this trial, patients will be treated with a dosage of 0.8 mg/kg/day FFA for a duration of 21 days.77

### Efficacy of Fenfluramine Beyond Seizures
Recent data suggest that FFA confers clinical benefit beyond seizure reduction alone, including improvements in everyday executive function and a reduction of sudden unexpected death in epilepsy (SUDEP).80 Both clinical trials and animal studies have shown that FFA can improve survival rates.81,82 Notably, the SUDEP mortality rate among Dravet syndrome patients who received FFA in Phase III studies was significantly lower than pre-treatment rates (1.7 deaths per patient-years after FFA compared to 11.7 deaths per patient-years pre-FFA treatment).81

Moreover, FFA was found to improve executive functioning, including regulation of emotions and behaviour, in some patients with Dravet syndrome as well as in those with LGS.50,51,83 According to survey data from caregivers of patients with Dravet syndrome, FFA treatment is associated with meaningful improvements in cognition, focus, alertness, speech, behaviour, sleep, and motor function.84

![Table 1: Main Results from Clinical Trials for Fenfluramine (FFA) Use in Pharmacoresistant Epilepsies](https://doi.org/10.2147/NDT.S417676)
The mechanisms behind these effects remain under investigation. However, some evidence supports a potential role for the 5-HT$_4$ and sigma-1 receptors. The interaction of FFA with 5-HT$_4$ receptors might have beneficial effects on cognitive functions, as evidence suggests that 5-HT$_4$ receptor agonism enhances learning and memory.

**Safety of Fenfluramine**

FFA was generally well tolerated as a low-dose adjunctive treatment for seizures in patients with Dravet syndrome or LGS, both in the short term (14–15 weeks) and in the longer term (up to 3.5 years). Common adverse effects were decreased appetite, diarrhea, pyrexia, nasopharyngitis, lethargy, and drowsiness. Cardiovascular safety is an important endpoint when evaluating patients treated with FFA. A meta-analysis reported an approximately 20-fold higher risk of aortic valve disease and approximately five-fold higher risk of mitral valve disease following exposure to FFA.

The study conducted by Li et al demonstrated that there is an increased risk of valvulopathy with higher doses of FFA. Patients taking a dose of $\geq$60 mg/day had a relative risk of valvulopathy of 9.2 compared to patients taking a dose $<40$ mg/day.

Additionally, the risk of valvulopathy is higher in certain populations, such as women, the elderly, and those who have been exposed to these agents for a longer duration. For example, the incidence rate of clinically symptomatic valvulopathy is 7.1 per 10,000 individuals with less than 4 months of exposure, whereas it increases to 35 per 10,000 individuals with more than 4 months of exposure.

In the context of evaluating FFA for the treatment of Dravet syndrome and LGS, comprehensive monitoring programs with color Doppler echocardiographic examinations (performed at baseline, after $\approx$ 6–8 weeks of treatment and at study end in the core studies, and at study entry, after 4–6 weeks of treatment, and then at 3-month intervals in the open label extension studies) were implemented in all randomized controlled trials. These monitoring programs were designed to prospectively assess cardiac valve function and identify any signs of pulmonary arterial hypertension. In all these trials, no pathological functional changes in cardiac valves or signs of pulmonary arterial hypertension were observed in any patient at any point during the trials. These findings provide evidence to support the cardiovascular safety of FFA at the lower dosages used for seizure management compared to the higher dosages used in the treatment of obesity in adults.

Several factors may have contributed to the differences in the incidence of cardiac valve dysfunction between the clinical studies conducted shortly after the withdrawal of FFA in 1997 and the current studies of patients with Dravet syndrome treated with FFA: 1) Patient Population: The patients included in the clinical studies conducted after the withdrawal of fenfluramine were primarily obese adults who were using FFA as an appetite suppressant for weight loss. These individuals were older, overweight or obese, and predominantly female. In contrast, the patients in the recent studies were children and adolescents with Dravet syndrome who had normal or low body mass index (BMI). 2) Dose of fenfluramine: The dose of FFA used in the current studies of patients with Dravet syndrome was significantly lower compared to the doses used for weight loss purposes. The maximum doses used in the Dravet syndrome studies were 17 or 26 mg/day, whereas doses of 60–120 mg/day or higher were typically used for weight loss. 3) Cardiac Evaluation: In the clinical studies after the withdrawal of FFA, the adult patients were not evaluated for baseline cardiac valve function before initiating treatment. Additionally, they were not screened for risk factors for valve disease. In contrast, all patients in current studies underwent pretreatment echocardiograms to evaluate their baseline cardiac valve function. These factors, including the differences in patient population, FFA dose, and cardiac evaluation protocols, likely contributed to the variations in the incidence of cardiac valve dysfunction observed between the studies.

**Dosage and Administration of Fenfluramine**

Oral fenfluramine has received approval in the EU and the USA for the treatment of seizures associated with Dravet syndrome and LGS in patients aged $\geq$2 years. In the EU, it is used as an add-on therapy to other ASMs, while in the USA, it can be used both as monotherapy and as an add-on therapy.

FFA is available as an oral solution, taken twice daily with or without food. The recommended starting dosage in patients with Dravet syndrome or LGS who are not receiving stiripentol is 0.2 mg/kg/day. This dosage is gradually increased at 7-day intervals, first to 0.4 mg/kg/day and subsequently to 0.7 mg/kg/day (maximum daily dosage of 26 mg).
For patients with Dravet syndrome or LGS who are already receiving stiripentol, the recommended starting dosage of FFA is also 0.2 mg/kg/day, and the up-titration is done after 7 days to a maintenance dosage of 0.4 mg/kg/day (maximum daily dosage of 17 mg).

**Conclusion**

Despite the introduction of various novel ASMs, drug resistance remains one of the major challenges in epilepsy treatment. It is important to consider that drug resistance is very probably not caused by a single mechanism in all patients but is rather more likely due to several mechanisms, which may even occur together in the same patient. The search for novel ASMs remains an active area of research, with ongoing studies focusing on identifying new molecular targets, developing innovative therapeutic approaches, and repurposing existing medications for new therapeutic indications.

FFA had been used extensively in the past as an appetite suppressant, but it was withdrawn from the market in 1997 due to its association cardiac valvulopathy. More recently, double-blind placebo-controlled trials established its efficacy in the treatment of convulsive seizures associated with Dravet syndrome and of drop seizures associated with LGS.

FFA acts via multiple receptors to exert its therapeutic effects for the treatment of seizures, although the exact mechanisms are still being elucidated. While FFA has been widely recognized as a potent serotonin-releasing agent, its pharmacological mechanism is likely to be more complex than a 5-HT-driven response alone.

It is important to highlight that FFA repositioning as an ASM and its use at lower doses in the treatment of Dravet syndrome and LGS have been shown to be beneficial for seizure management, while vigilant monitoring for cardiovascular adverse events remains crucial. The use of FFA in children with Dravet syndrome and LGS has shown an overall favourable safety profile, with mostly mild side effects. In the treatment of Dravet syndrome and LGS, it is administered at comparatively lower doses (maximum 17–26 mg/day) compared to its previous use as an appetite suppressant, where higher doses (typically 60–120 mg/day), often in combination with phentermine, were employed. Further research and long-term studies are needed to better understand the safety and tolerability of FFA in the pediatric population. Regular monitoring of cardiac function and conducting routine evaluations can help detect any potential cardiovascular issues early and guide clinical management.

**Abbreviations**

5-HT, Serotonin; ASMs, Anti-seizure medications; CDD, CDKL5 deficiency disorder; FFA, Fenfluramine; LGS, Lennox-Gastaut syndrome; PPH, Primary pulmonary hypertension; SSRIs, Selective serotonin reuptake inhibitors; SUDEP, Sudden unexpected death in epilepsy.

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