~50% of epilepsies have some genetic basis [1,2,3]
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* Number of genes tested will vary in each country, ranging from a single gene to over 400+ genes

~ The genetic basis of epilepsy has a range according to country and publication from 14% -24.4%,[2] to 50% [1], to 70-80%[3]

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Fenfluramine as antiseizure medication for epilepsy

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Fenfluramine hydrochloride has classically been described as acting pharmacologically through a serotonergic mechanism. Therefore, it was initially used as an anorectic drug, given that impaired serotonin homeostasis may be associated with increased food intake. Although positive results were documented, cardiovascular concerns resulted in its temporary withdrawal. Nevertheless, a novel role in patients with epilepsy was later suggested by isolated clinical observations. The wide application of genetic testing allowed the classification (predominantly as Dravet syndrom) of patients in whom benefit was seen, while with the development of zebrafish models, its antiepileptic properties were confirmed at a molecular level. Data from randomized clinical trials have shown a beneficial effect of fenfluramine, as an adjunct therapy, on seizure control for children with Dravet syndrome, though there is still uncertainty about the impact on neurodevelopment in these patients. No signs of heart valve disease have been documented to date. Long-term and appropriately designed clinical studies will verify whether fenfluramine is a therapeutic agent of high importance, living up to the promise shown so far.

INTRODUCTION

Neurological disorders in all age groups are characterized by high rates of unmet health needs, as well as resistance to available therapies. This may reflect structural barriers to treatment such as the blood–brain barrier but also the fact that the underlying pathophysiology for most of these disorders has not yet been fully explored.[1] Alternative methods of drug design are an emerging field in current neuropharmacology. Repurposing of known drugs for new indications, based on shared molecular pathology between different entities, has become a popular cost-effective and low-risk strategy for drug development. In parallel, in vitro models of high predictability and databases of results from transcriptomic analysis promise to increase the effectiveness and accuracy of this method.[2]

Epilepsy is now well recognized as a symptom of many underlying causes, more accurately now referred to as the epilepsies. Recognizing the cause, often the result of a genetic mutation, has resulted in increasing recognition for targeting drug repositioning within the central nervous system, while endocrine and metabolic disorders represent relatively common sources of further repositioned therapeutic agents.[3] Fenfluramine is a typical example; although this agent was first launched to help patients with obesity, its concomitant beneficial role in patients with epilepsy has subsequently attracted interest.

Our aim is to summarize the history of therapeutic applications of fenfluramine and provide a literature narrative review about its current emerging use as an antiepileptic agent.

INITIAL USE AS AN ANORECTIC AGENT: A MISSED THERAPEUTIC OPPORTUNITY

It has been long supported by research that impaired serotonin-mediated homeostatic feedback is associated with increased food intake. On this basis, modulation of central serotonergic signalling has been considered as a potential pharmacological target among patients with obesity.[4,5] Fenfluramine (3-trifluoromethyl-N-ethylamphetamine) was first launched in the early 1970s as an agent for appetite suppression, as it is known to act as a serotonin-releasing agent by disrupting vesicular storage of the neurotransmitter and reversing serotonin transporter function. In parallel, its major active metabolite, norfenfluramine, binds to and activates serotonin receptors (5-hydroxytryptamine [5-HT] receptors 2B [5-HT$_{2B}$] and 2C [5-HT$_{2C}$] with high affinity and 5-HT$_{2A}$ receptor with moderate affinity).[6]

Indeed, fenfluramine had been widely used by patients with obesity, either alone or in combination with a trace amine-associated receptor, phentermine, under the trade name Fen-Phen. The starting dosage in obesity was 40mg daily and could be increased gradually over 2 to 4 weeks to 60 to 120mg.[7] Despite its efficacy, fenfluramine was eventually withdrawn from global markets in 1997 at the request of the US Food and Drug Administration following reports of heart valve abnormalities (leaflet thickening, fibrosis, retraction of the valve) and pulmonary

hypertension in adult patients treated for obesity (Fig. 1). The appearance of these adverse events was associated with higher doses of fenfluramine and the concomitant use of phentermine.[8,9] With regard to the underlying pathophysiology, the mitogen properties of serotonin to valve interstitial cells through 5-HT$_{2C}$ receptor (abundant in cardiac tissues) activation may have played a role; although serotonin stimulates DNA synthesis and promotes appropriate heart cell growth in the early stages of development, excess serotonin has been shown to have pathological remodelling effects on mature heart valves.[10]

THE IMPORTANCE OF A 'SECOND CHANCE'
An interesting coincidence is that the cardiovascular safety concerns associated with fenfluramine appeared simultaneously (in the 1980s) with some clinical observations showing a beneficial effect of this agent on seizure management in patients with reflex epilepsies (Fig. 1). More specifically, Gastaut et al., Aicardi et al., and Clemens were the first to present data from case reports and small case series (up to three patients) showing a significant decrease in seizure frequency when fenfluramine was added to the existing treatment plan. The underlying diagnoses included self-induced syncope and self-induced photosensitivity epilepsy, while the dose of fenfluramine ranged from 0.5 to 1.5mg/kg/day with a maximum of 60mg/day.[11–14] The hypothesis behind the potential use of fenfluramine as an antiepileptic treatment lay in the fact that 5-HT receptors are widely expressed in many areas of the central nervous system and are known to interact with different types of ion channel, thus altering their function and the excitability of neurons.

What this paper adds
- Fenfluramine is a very promising repurposed therapy specifically for seizures in Dravet syndrome.
- The long-term effect of fenfluramine on neurodevelopmental prognosis requires further investigation.

Clinical and animal studies have also shown that serotonin neurons have anticonvulsant effects, and patients treated with selective serotonin re-uptake inhibitors may experience improvement in their seizures.[15–17] In addition, recent radioligand binding assays have demonstrated a modulatory activity of fenfluramine at σ1 receptors (highly expressed in deeper laminae of the cortex, olfactory bulb, nuclei of mesencephalon, hypothalamus, and Purkinje cells in the brain) in vitro and in vivo in addition to its serotonergic activity.[18]

It should also be noted that Gastaut et al. found that fenfluramine (1.5–3mg/kg/d) also contributed to the reduction of compulsive respiratory stereotypies in children with autism.[19] The first pilot study was conducted by Gastaut and Zifkin, they assessed 33 individuals with intractable epilepsy receiving fenfluramine at a dose of 0.5 to 1.5mg/kg/day which revealed a reduction in seizure frequency of at least 50% in almost half of them. In parallel, no echocardiographic findings suggestive of pulmonary hypertension or valvular dysfunction were reported, whereas the most frequent side effects encountered in this new patient population were sleepiness, fatigue, and loss of appetite with or without weight loss.[20]

In the meantime, fenfluramine had been withdrawn as a drug to treat obesity. However, Belgian researchers
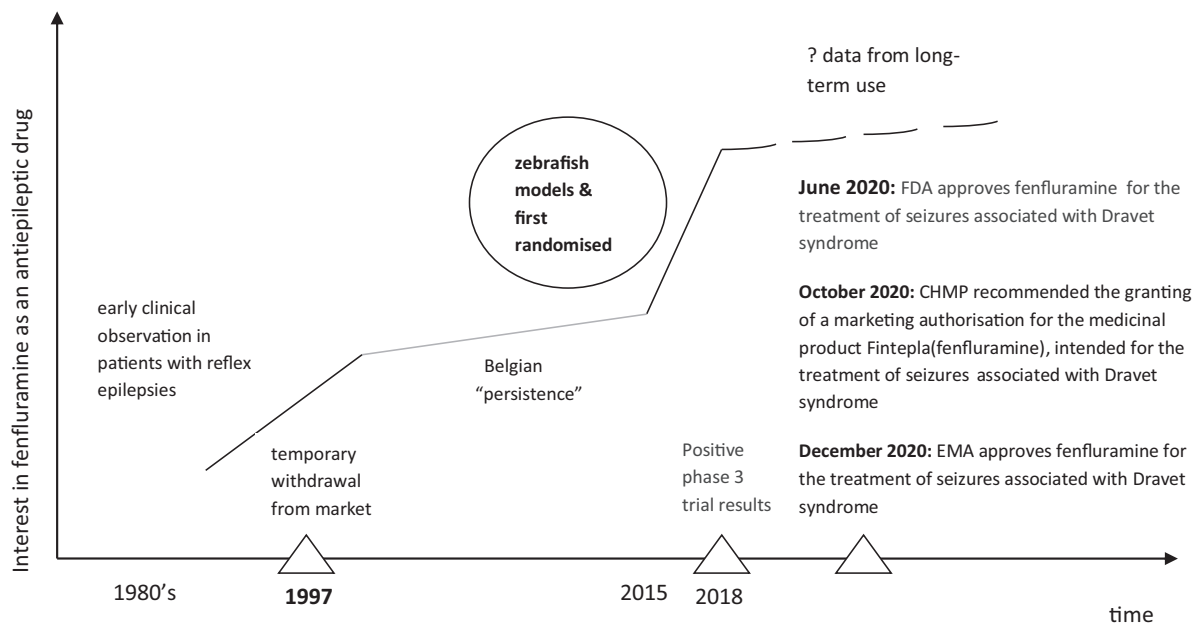

Figure 1: Development of interest in antiepileptic properties of fenfluramine and the hallmarks of its use as an antiepileptic agent. CHMP, Committee for Medicinal Products for Human Use; FDA, Food and Drug Administration.

continued to be interested in its antiepileptic properties and further investigation of this agent was permitted by Belgian governance[21] (Fig. 1). Therefore, over subsequent years, results from more case series provided additional supporting evidence about the positive impact of fenfluramine, as an adjunctive therapy, on seizure control among children and adolescents with intractable self-induced epilepsy.[22,23] In this way, when the door to the clinical use of fenfluramine as an appetite suppressant finally closed, the window of an alternative therapeutic opportunity had already opened (Fig. 1).

A deeper look at the clinical phenotypes of patients included in all the aforementioned studies revealed that several responders shared some common features (i.e. severe developmental and epileptic encephalopathy, early prolonged seizures, behavioural disorders, self-provocation of seizures, epileptic events precipitated by external stimuli), which were compatible with the diagnosis of Dravet syndrome. Therefore, Ceulemans et al. focused on this entity and published the first retrospective analysis of the effect of fenfluramine (daily dose 0.12–0.90mg/kg/d) on seizure control in 12 children and adolescents with Dravet syndrome.[24] Several of these patients had been included in previous published case series and later demonstrated to have an *SCN1A* mutation. According to the results of this analysis, fenfluramine was found to be effective against multiple types of seizure, not only self-induced or photic-induced seizures. It is also worth mentioning that seizure recurrence was noticed in some patients after a temporary discontinuation as a result of its withdrawal from the market, while those children again became seizure-free after restarting the drug.[24]

A DEEPER UNDERSTANDING OF THE PHARMACOLOGICAL PROPERTIES: THE CONTRIBUTION OF ZEBRAFISH STUDIES
Zebrafish models have been demonstrated to be useful in assessing the function of a rapidly increasing number of candidate genes for neurological disorders, including the epilepsies. This is due to a series of specific features of this species: fully sequenced genome, rapid embryonic development, large and transparent embryos developing externally, same major subdivisions of a vertebrate brain as mammals (forebrain, midbrain, hindbrain, spinal cord), and common major neurotransmitter systems (GABA [γ-aminobutyric acid], glutamate, dopamine, norepinephrine, serotonin, histamine, and acetylcholine). Eighty per cent of risk genes associated with human disorders have an orthologous version in zebrafish. With regard to the epilepsies, it should be highlighted that zebrafish larvae exhibit clinical seizures, which can be easily quantified and are also associated with electroencephalographic changes.[25] Zebrafish models for Dravet syndrome have been developed by targeting *scn1Lab*, the zebrafish orthologue of *SCN1A*, used to identify early cellular defects and investigate the potential disease-modifying role of fenfluramine.[26–31]

According to the results of these studies, fenfluramine was found to suppress seizure activity in Dravet zebrafish models[26–31] (Table 1). At the same time, the models confirmed the beneficial role of several antiseizure medications routinely used in patients with Dravet syndrome (e.g.-stiripentol, sodium valproate, clobazam)[30,31] (Table 1). It should be noted that two of these studies additionally demonstrated that zebrafish larvae express the orthologues of all human 5-HT receptor subtypes and revealed that various agonists of those 5-HT receptors (apart from fenfluramine) can exert significant antiseizure activity.[27,29] What would be desirable is evidence for any potential disease-modifying effect of the new therapeutic agent on cellular changes in Dravet syndrome, as this would make a difference from other conventional antiseizure medications. This has been studied by Tiraboschi et al. in a zebrafish model of Dravet syndrome induced by CRISPR/Cas9 mutagenesis. Fenfluramine was identified to modulate the pathophysiological background of the disease; more specifically, it completely restored the decreased dendritic arborization often noticed in this disease.[26] This finding clearly shows the advantage of zebrafish models in revealing early mechanisms predisposing to an epileptogenic state, as well as the potential disease-modifying role of new drug candidates.

THE FIRST RANDOMIZED CONTROLLED TRIALS
After these encouraging findings from small case series, small patient cohorts, and zebrafish models, a systematic large-scale evaluation of the real benefits and risks of this drug in a new patient population was needed and the first clinical trials were designed.[32,33] Dose-finding studies for the co-administration of fenfluramine with stiripentol, clobazam, and valproate were conducted,[34] and phase III trials have been undertaken to investigate the effect of fenfluramine, as an adjunctive therapy, on seizure frequency in children with Dravet syndrome and other developmental epileptic encephalopathies. Currently, data are available for the randomized controlled trials in Dravet syndrome[35,36] while results from phase III trials for Lennox–Gastaut syndrome are still awaited[37] (Table 2).

The primary endpoint in the studies of the effect of fenfluramine in Dravet syndrome was the change in the frequency of convulsive seizures; these are defined as hemiclonic, tonic, clonic, tonic–atonic, generalized tonic–clonic, and focal with clearly observable motor signs. The effect of fenfluramine on absence seizures was not investigated. Fenfluramine was well-tolerated and, as an add-on therapy, contributed to a significant decrease in convulsive seizure frequency in children with Dravet syndrome compared with placebo[35,36] (Table 2). Nabbout et al. also focused on children with Dravet and concomitant use of stiripentol (a standard therapy for Dravet syndrome) and demonstrated that adding fenfluramine to stiripentol-containing antiepileptic regimens significantly contributed to a reduction in the frequency of convulsive seizures.[36] What was striking in both studies was the difference in

Table 1: The effect of fenfluramine on zebrafish models of Dravet syndrome

Reference	Model	Clinical and EEG changes	Cellular changes	Fenfluramine effects	Effect of other agents
Zhang et al.[31]	Homozygous *scn1Lab*$^{-/-}$ mutants (with morpholino antisense oligomers)	Clinical traits: hyperactivity, convulsive seizure-like behaviour, loss of posture, repetitive jerking, myoclonic seizure-like pattern EEG: epileptiform activity	Not described	↓ Locomotor activity ↓ Occurrence of epileptic events, polyspiking discharges, cumulative duration of these events	Similar effects of VPA TOP/CLB/STP: ↓ hyperactivity, not tested with EEG
Dinday et al.[30]	Homozygous *scn1Lab*$^{-/-}$ mutants (chemical mutagenesis)	Whole-body convulsive seizures (determined by swim velocity)	Not described	↓ Mean swim velocity suppression of spontaneous electrographic seizure discharges	VPA/STP/BEN: improvement in both measures PHE/CBM/ETS/DEC/PRI/ VGB/PHEN/TIL: no effect
Sourbron et al.[29]	Homozygous *scn1Lab*$^{-/-}$ mutants (chemical mutagenesis)	Seizure-like locomotor behaviour Corresponding epileptiform brain activity	Not described	Clear locomotor-reducing effect on the homozygous *scn1Lab*$^{-/-}$ mutants	Not applicable
Griffin et al.[27]	Homozygous *scn1Lab*$^{-/-}$ mutants (obtained by natural spawning of adult heterozygous scn1lab)	Multi-spike or poly-spike upward or downward membrane deflections	Not described	Suppression of convulsive swim behaviours in a concentration-dependent manner	Not applicable
Tiraboschi et al.[26]	Homozygous *scn1Lab*$^{-/-}$ mutants (CRISPR/Cas9 mutagenesis)	Seizures Spontaneous EEG discharges with high amplitude and duration	↓ Oligodendrocytes ↓ GABAergic, ↑ glutamergic ↑ astrocytes, ↓ astrocyte maturation ↓ dendritic arborization	Seizure suppression Completely restored dendritic arborization	BEN (e.g. diazepam): ↓ seizures but no effect on cellular defects

Downward- and upward-pointing arrows indicate decrease and increase respectively. EEG, electroencephalogram; VPA, valproic acid; TOP, topiramate; CLB, clobazam; STP, stiripentol; BEN, benzodiazepines; PHE, phenytoin; CBM, carbamazepine; ETS, ethosuximide; DEC, decimemide; PRI, promidone; VGB, vigabatrin; PHEN, phenacemide; TIL, tiletamine.

effect between the fenfluramine-treated groups and placebo, a difference unprecedented in other randomized controlled trials. Lagae et al. were also able to show a marginal beneficial effect of fenfluramine on other seizure types (focal seizures without clearly observable motor signs, absence or atypical absence, myoclonic, atonic, and other or unclassifiable types) as a total, but no separate analysis was undertaken for each type.[35]

Although one small open trial has been published of use in Lennox–Gastaut syndrome suggesting promising results,[37] the outcome of the international randomized controlled trials are awaited.

In addition, Lagae et al. and Nabbout et al. analysed the effect of fenfluramine administration on scores in quality of life scales and in scales related to cognitive and behavioural aspects of Dravet syndrome.[35,36] In the former study, at the end of a 14-week treatment period an improvement was seen in both fenfluramine groups compared with placebo in the Paediatric Quality of Life Inventory (but not in the Quality of Life in Childhood Epilepsy instrument), in the Behavioural Regulation Index, and in the Global Executive Composite. Metacognition index was also improved, but the difference was not significant compared with the placebo group. It should be mentioned that scores of all these indexes

worsened in the placebo group.[35] On the other hand, Nabbout et al. found that significantly more patients receiving fenfluramine than placebo were rated as having any improvement (including being minimally improved) both by investigators and by caregivers in the Clinical Global Impression of Improvement Scale, but no significant differences were recorded between groups on the Quality of Life and Behaviour scales.[36]

A beneficial effect on quality of life is expected and quite plausible, given the considerable decrease in seizure burden. What is interesting is that, in contrast to many conventional antiseizure medications which may negatively impact neurodevelopment, fenfluramine seems from the limited data to possibly exert a protective role and improve aspects of cognition and behaviour in these children. It has been demonstrated in animal models that the serotonergic system is one of the earliest monoamine systems arising during fetal brain development, and serotonin has been proposed to play a crucial role as a developmental signal guiding somatosensory and visual system development; deficits in these processes have been described in several neurodevelopmental disorders both in children and in adults (e.g. autism spectrum disorder, attention-deficit/hyperactivity disorder, developmental coordination disorder).[38] In parallel, human studies have provided

Table 2: Summary of clinical trials for the effect of fenfluramine as an antiepileptic agent in children with epileptic encephalopathy

Reference	Population sample	Method	Primary outcome	Secondary outcomes
Lagae et al.[35]	Dravet syndrome: 173 assessed (2016–2017) 119 assigned (mean age 9y, 64% male) Randomization to one of three groups: 40 (placebo), 40 (fenfluramine, 0.7mg/kg/d), 39 (fenfluramine, 0.2mg/kg/d)	Randomized, double-blind (phase III) Analysis by modified intention to treat Randomization through an interactive web system Safety analysis in all who received at least one dose of study drug Duration: 14wks treatment period (2wks titration+ 12wks maintenance)	The change in mean MFCS during the treatment period vs baseline in the 0.7mg/kg/d group vs placebo: patients in the fenfluramine 0.7mg/kg/d group had a 62.3% greater reduction (74.9% vs 19.2%, $p<0.001$)	**Differences between 0.2–placebo, 0.7–0.2** Mean MFCS during the treatment period vs baseline **Differences between 0.7–0.2, 0.2–placebo, 0.7–placebo** Proportion of patients with ≥25%, ≥50%, ≥75%, or 100% reduction in MCSF Longest seizure-free interval Frequency of rescue medication use Post hoc analysis of patients with ≤1 convulsive seizure Clinical Global Impression of Improvement Scale (caregiver, investigator), Quality of Life in Childhood Epilepsy Scale, Pediatric Quality of Life Inventory, Metacognition Index, Global Executive Composite, Behavioral Rating Inventory of Executive Function **Adverse effects** 65% in placebo group, 95% in the 0.2mg/kg/d group, 95% in the 0.7mg/kg/d group 94%: mild to moderate Most frequent: decreased appetite, diarrhoea, nasopharyngitis, lethargy, somnolence, pyrexia Weight loss ≥7%: 3% in placebo group, 13% in the fenfluramine 0.2mg/kg/d group, 20% in the fenfluramine 0.7mg/kg/d group No cardiovascular complications
Nabbout et al.[36]	Dravet syndrome treated with stiripentol: 115 assessed 87 assigned (mean age 9y 1mo, 57% male) Randomization to one of two groups: 44 (placebo), 43 (fenfluramine, 0.4mg/kg/d)	Randomized, double-blind (phase III) Randomization stratified across ages (<6y, ≥6y) Randomization through an interactive web system Duration: 15wks (titration 3wks and maintenance 12wks)	The change in mean MCSF during treatment period vs period in the fenfluramine vs placebo group: fenfluramine group exhibited 63.1% in MCSF vs 1.1% of placebo ($p<0.001$)	The proportion of patients with no seizures or one seizure during treatment period The proportion with ≥25%, ≥50%, ≥75%, or 100% reduction in seizures from baseline Change from baseline in clinical global impression ratings both by parents/caregivers and by investigators Total days of rescue medication use per 28d Total seizure frequency (including nonconvulsive seizure types) per 28d Quality of Life in Childhood Epilepsy Scale, Pediatric Quality of Life Inventory, Behavior Rating Inventory of Executive Function **Adverse events** Most common: decreased appetite, pyrexia, fatigue, and diarrhoea Discontinuation in three patients Two patients receiving placebo and nine patients receiving fenfluramine experienced weight decreases ≥7% No cardiovascular complications
Lagae et al.[37]	Lennox–Gastaut syndrome: 13 patients enrolled (9 male, 11y 8mo±4y 5mo) 10 completed the core study 9 entered the extension phase 7 completed the extension phase	Non-randomized, phase II, open-label[a] Responders: ≥50% convulsive seizure reduction from baseline Starting dose: 0.2mg/kg/d; every 4wks non-responders were considered for a dose increase by an additional 0.2mg/kg/d until 0.8mg/kg/d (30mg/d maximum); responders stable Core study: 20wks Extension study: up to 15mo At the end of the core study, responders were offered entry into extension study	Number of responders at each study visit: During the core study: 13/13 responders (53% median reduction in convulsive seizures, 60% in 10 completers) At 15 months: 6/9 still responders	**Adverse effects** Most frequent adverse events: decreased appetite, decreased alertness, sleep problems, fatigue, tiredness, sleepiness No cardiovascular complications

[a]A phase III, randomized controlled study is ongoing. MFCS, monthly frequency of convulsive seizures.
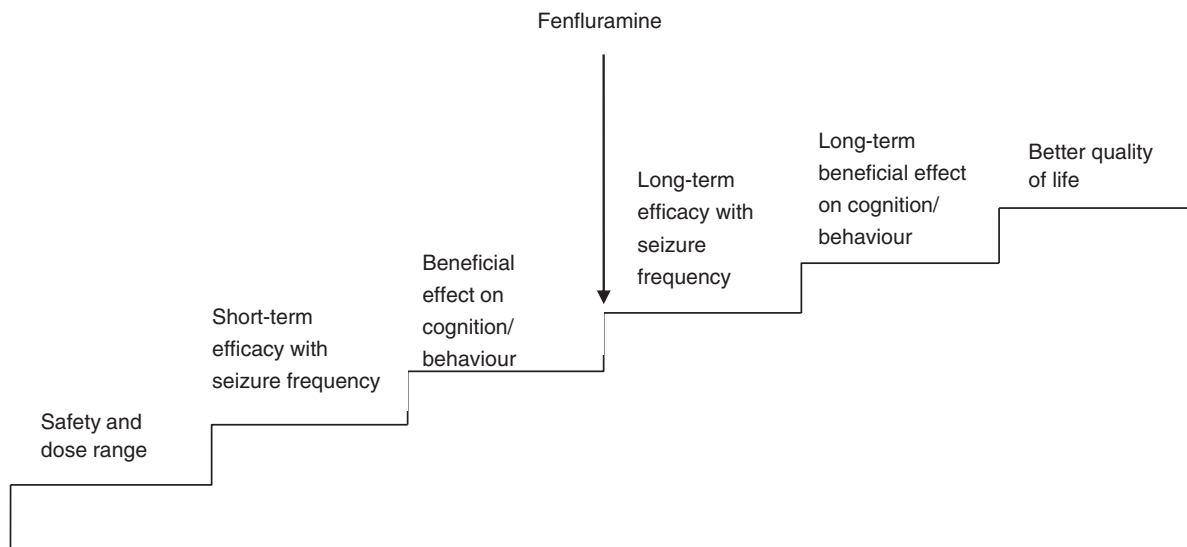
Figure 2: Clinical research on the use of fenfluramine as an antiepileptic agent: what is next?

evidence that prenatal use of selective serotonin re-uptake inhibitors could be associated with negative neurodevelopmental outcomes or behavioural disorders (e.g. autism spectrum disorder).[39] Therefore, the use of a serotonergic therapeutic agent might also have a positive influence on cognition and behaviour.

The most frequent adverse events encountered in the aforementioned studies included decreased appetite, fatigue, somnolence, sleep disorders, diarrhoea, nasopharyngitis, and pyrexia; the most frequent serious adverse event was hospital admission due to status epilepticus[35–37] (Table 2). Although cardiovascular concerns had arisen when fenfluramine was initially used in patients with obesity, it is noteworthy that no cases of pulmonary arterial hypertension or valvular dysfunction were revealed by echocardiographic evaluations in any of the children enrolled in these studies. This could be attributed to the fact that fenfluramine was used at lower doses and most probably the new patient group (paediatric patients with epilepsy) would not be expected to exhibit any of the microscopic histopathological or functional alterations found in patients with adult obesity. The most significant clinical concern was weight loss due to appetite loss, but only a few patients were finally withdrawn because of this.[35,36]

THE FUTURE
Addressing complex needs of children with Dravet syndrome
Dravet syndrome is a drug-resistant developmental and epileptic encephalopathy of childhood characterized by multiple seizure types, cognitive problems, motor difficulties, and behavioural disorders.[40] Most have an underlying *SCN1A* mutation, although it remains a clinical diagnosis. Although current genetics allow consideration of an early diagnosis, effective treatment options are scarce. The prevalence of intellectual dysfunction, behavioural, and motor problems among these children is not negligible and insight from affected families shows that the negative impact on quality of life is significant.[41–43] As has already been mentioned, serotonin can be associated with epileptic activity and seems to play a key role in the pathophysiology of several neurodevelopmental disorders (e.g. attention-deficit/hyperactivity disorder, autism spectrum disorder, motor problems), not necessarily associated with epilepsy.[44]

According to these findings, several clinical manifestations of Dravet syndrome may have a common association with underlying disorders related to serotonin and this could also explain the success of fenfluramine, as recorded in current clinical studies. From this point of view, finding a therapeutic option with a serotonergic mechanism of action could potentially address or at least improve multiple aspects of these encephalopathies and overcome the challenge of undesired drug interactions, while the effect of fenfluramine on widely distributed σ1 receptors should also be considered. The causal relationship between Nav1.1 dysfunction (due to *SCN1A* mutation) and Dravet phenotype is indisputable and, in general, it is rather simplistic to attribute the complexity of the clinical phenotype of those entities to a single factor.[45] Nevertheless, a new research target has emerged, to look behind seizures and explore additional comorbidities, particularly those that are modifiable. In parallel, the effect of fenfluramine on dendritic arborization, as shown in zebrafish models, implies a disease-modifying role. In view of this, the possibility of using the fenfluramine very early after epilepsy onset might need to be considered to understand whether there could be a better outcome if used earlier in life.[26]

Whether fenfluramine will improve comorbidities in children with Dravet syndrome or other epilepsies is a

question that needs to be explored in future large-scale, long-term studies with optimized methodology (Fig. 2). Currently, fenfluramine has been approved by both the US Food and Drug Administration and the European Medicines Agency for use in Dravet syndrome in individuals over 2 years of age.

Designing future clinical trials and … a fairy tale

It was 1942 when Antoine de Saint-Exupery wrote in his novella *The Little Prince* that 'the essential is usually invisible to the eye'. He was referring to feelings, but the example of fenfluramine and its potential beneficial role with regard to cognitive and behavioural aspects in children with Dravet syndrome also reminds us of the fact that countable seizures are not all that matters in patients with epilepsy. Better seizure control achieved after the introduction of a new agent definitely leads to an improvement in intellectual ability and behaviour, but it can also mask negative effects of the antiseizure medication itself on cognition, which may arise after years of treatment.[46] In parallel, from a methodological point of view, it is not often feasible to differentiate a treatment-related adverse event from the progression of the underlying brain disorder. The change in the frequency of convulsive seizures is the most frequently used primary endpoint of epilepsy clinical trials, as it is relatively easy to recognize and record, and the sample-size estimation is based on this parameter.[46,47] Cognitive, behavioural, or emotional aspects, as well as quality of life, have only been assessed as secondary outcomes (e.g. in the large randomized controlled trials[35,36]); therefore, findings may be significantly affected by reduced statistical power. Furthermore, additional aspects of daily functioning, such as feeding problems or speech development, have not been scrutinized until now.

At the same time, published papers may emphasize seizure-related secondary outcomes of doubtful importance in terms of clinical practice (e.g. the proportion of patients with ≥25%, ≥50%, ≥75%, or 100% reduction in seizure frequency).[35,36] Since more cognitive, behavioural, and quality of life-related tools (questionnaires, scales) have now been validated in paediatric populations, the use of these parameters as primary outcomes of epilepsy clinical trials (after effective seizure control has been established) would be an innovative future investigational aim, especially for drugs showing some preliminary positive results, such as fenfluramine. The criterion standard approach seems to be to perform assessments during a baseline period and after new treatment implementation. In that case, additional issues need to be addressed, including the ideal timing of such assessments or the prioritization of aspects studied, and longer trials might be considered.[48,49] The concept of drug repurposing could have a significant contribution to this field, as safety and tolerability data of these medications are already available.

Finally, it is essential to shed light on personal insight and find out what really matters for affected children, their families, as well as healthcare professionals, and to use this knowledge to make informed treatment decisions. Therefore, studies trying to collect data about patients' and carers' ideas, values, emotions, and priorities to identify new starting points, have already been initiated.[50] In this way, when clinical researchers design future epilepsy trials and discuss appropriate endpoints, they might also consider *The Little Prince*.

Expanding the applications of drug repositioning in patients with epilepsy

Fenfluramine is an excellent example of finding new indications for older drugs. Interactive website platforms allow a 'hands-on' approach to future drug development, providing new stimuli for research and accelerating the process of validation of a therapeutic agent. This is of paramount importance for patients with rare neurological conditions, including those with developmental epileptic encephalopathies.[51] At the same time, the advantages and potential applications of the so-called 'drug recycling' in drug industry and clinical practice are too appealing to leave this process to the chance of random discoveries and vigilant spontaneous observations, such as those of the Belgian researchers.

For this reason, new resources for drug repurposing research need to be systematically investigated. A database was recently created by Sivapalarajah et al., based on novel software that allows advanced computational analysis of the literature, which identified a significant number of well-known prescribable drugs (for other conditions) with corroborative evidence of efficacy in experimental models of epilepsy. It is interesting that many of the drugs included in this database target proteins with published evidence of functional relevance in epilepsy (including transcription factors or G protein-coupled receptors), but are not targeted by currently approved antiseizure medications.[52] Meanwhile, the effect of fenfluramine on serotonin metabolism acts as a gentle reminder for us to turn our attention to brain homeostasis and the need to focus on functional genomics of epileptogenesis. Indeed, genomics-based drug repurposing holds promise for further enrichment of available therapies. The concept is based on comparison of gene expression between normal tissues and those with the disease, and generation of a transcriptomic signature which can then be used as a map to guide restorative treatments.[53] This has already been tested in animal models with chronic temporal lobe epilepsy and the wide availability of zebrafish models can help this method to be expanded to additional epilepsy entities, including Dravet syndrome.[54]

CONCLUSION

The history of transition of fenfluramine from obesity to epilepsy reflects the current trends in the development of new antiseizure medication and encourages us to thoughtfully discuss the future of the design of epilepsy clinical trials. It seems that symptom-centred treatments are going to give their place to a biology-based era of therapeutics.

Drug repurposing seems to be a really attractive approach to developing new drugs for neurological disorders, saving significant time and even overcoming regulatory barriers without compromising the quality of the development process. This would be of paramount importance for patients with complex health conditions characterized by low remission rates (e.g. those with epileptic encephalopathy), who very often face the complications of polypharmacy and undesired drug interactions.

It is often said that 'you campaign in poetry, you govern in prose'. This imbalance between planning and implementing is also reflected in the field of drug discovery. In other words, when the initial enthusiasm from revolutionary drug models and promising findings of clinical trials settles down, fenfluramine will have to meet a bigger challenge: improving global functioning and contributing to a better quality of life under real-world conditions and after long-term use.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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