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Review

Individualized treatment approaches: Fenfluramine, a novel antiepileptic medication for the treatment of seizures in Dravet syndrome

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ABSTRACT

Dravet syndrome is a rare and severe encephalopathy that first presents in infancy with seizures refractory to conventional antiepileptic drugs. Forty-five percent of patients report four or more tonic–clonic seizures per month despite multidrug regimens. Fenfluramine, an amphetamine derivative, was initially developed as an appetite suppressant with a serotonergic mechanism of action. Clinical observation of a potential antiepileptic activity in a small homogeneous cohort of patients combined with a genetic workup of these patients led to the hypothesis of fenfluramine as a treatment for seizures in Dravet syndrome. This concept was successfully evaluated in a zebrafish model and led to a Phase 3 trial of fenfluramine to treat seizures in children with Dravet syndrome. Preliminary results of the trial suggest that fenfluramine may be a highly effective, well-tolerated treatment for patients with Dravet syndrome. This short review summarizes the history of use of fenfluramine from the initial clinical observations followed by preclinical studies and subsequent successful clinical trial.

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1. Background

Fenfluramine (3-trifluoromethyl-*N*-ethylamphetamine) is a derivative of amphetamine that was originally developed as an appetite suppressant and was marketed globally for that indication from the mid-1970s to 1997. Its anorectic mechanism of action was believed to involve serotonin because it was known to disrupt vesicular storage of this neurotransmitter as well as inhibit its neuronal reuptake [1].

Early reports began to emerge in the 1980s of the potential utility of fenfluramine in epilepsy when investigators reported its use in intractable self-induced neurological disorders. For example, Aicardi and Gastaut described three cases of children with self-induced photosensitive epilepsy in whom fenfluramine at 60 mg/day reduced the frequency of seizures [2]. Gastaut and Zifkin conducted a pilot study of fenfluramine at 0.5 to 1.5 mg/kg/day in 33 patients with intractable epilepsy and reported that about half of the patients experienced a ≥50% reduction in seizure frequency [3]. Gastaut and colleagues [4] reported that fenfluramine at 1.5–3.0 mg/kg/day was successful in reducing compulsive respiratory stereotypies in children with autism. Based on these observations, Boel and Casaer [5] treated a group of 11 children who were institutionalized with refractory epilepsy and self-induced seizures, most of them with photosensitive or pattern-sensitive seizures. They reported that fenfluramine at 0.5 to 1.0 mg/kg/day added to their current antiepilepsy drug regimen resulted in complete seizure control in 7 patients and >75% reduction in seizure frequency in the remaining 4 patients during a follow-up of 3 years to 8.5 years (median: 5.08 years). Other case reports and small case series demonstrating an antiseizure action of fenfluramine were reported through 1996 (for review see [6]).

2. Fenfluramine and Dravet syndrome

The patient group treated by Boel and Casaer [5] showed some typical features of patients with Dravet syndrome. Dravet syndrome is a rare, severe, and intractable developmental and epileptic encephalopathy typically beginning with prolonged tonic–clonic or hemiclonic febrile seizures in the first year of life [7,8]. Typical features are seizures provoked by temperature, photic or pattern stimulation, or emotion. Nearly all children are cognitively impaired, sometimes with behavioral abnormalities such as self-provocation of seizures. With currently available antiepileptic drugs (AEDs), complete seizure control is rare [9]. In 2001, a group from the Department of Genetics of Antwerp [10] proposed that mutations in *SCN1A*, the gene coding for the α-subunit of a neuronal voltage-gated sodium channel, were a cause of Dravet syndrome. Boel and Casaer had treated the above reported group of 11 patients with extraordinary good response to fenfluramine in the Center of Puderbols, near Antwerp, and 5 of the 11 patients from this cohort were proven to carry a mutation in *SCN1A*. Ceulemans et al. reported on these

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5 patients as part of a cohort of 12 patients with confirmed Dravet syndrome who had been treated with fenfluramine added to their current antiepileptic regimen for a mean duration of 11.3 years (range: 1 to 22 years) at a mean dosage of 0.34 mg/kg/day (range: 0.12 to 0.90 mg/kg/day) [11]. At the time of their initial report, two patients had withdrawn from the study: one because of lack of efficacy and one whose seizures did not return during a withdrawal of fenfluramine caused by a drug shortage. Three other patients had recurrence of seizures during the drug shortage and were controlled again after reintroduction of fenfluramine, supporting a beneficial effect of the drug against their seizures. Of the remaining 10 patients, seven had been seizure-free at their most recent study visit and had demonstrated a mean seizure-free interval of 6.6 years; one had experienced a 75% reduction in seizure frequency; and the remaining two had no change in seizure frequency. The most recent report from this cohort of 10 remaining patients describes an additional 5 years of follow-up, during which three patients were seizure-free and four additional patients had seizure-free intervals of at least 2 years [12]. No clinical and/or echocardiographic signs consistent with pulmonary hypertension or valvulopathy have emerged. These investigators initiated a second cohort of patients with Dravet syndrome treated with fenfluramine in 2011 [13]. Each patient in this cohort started with a 3-month observation period to establish baseline seizure frequency. In the initial report from the cohort, nine patients had been treated with fenfluramine for a period of 0.3 to 5.1 years (median: 1.5 years) at a mean dosage of 0.35 mg/kg/day at the most recent study visit. Within 3 months of starting fenfluramine, median major motor seizure frequency decreased from 15.0 per month to 1.5 per month, representing a median 75% decrease in frequency. The benefit was sustained in the 6 patients who were treated for at least 1 year. The patients in this prospective observation study received regular echocardiographic examinations before and during treatment with fenfluramine. No changes in valve structure or function were observed in any patient. The clinical profile that has emerged with fenfluramine use in this cohort of patients with Dravet syndrome, a group of patients with seizures that are historically refractory to AED treatment, is unique both in terms of the magnitude of seizure reduction and the durability of effect over long periods of time.

The antiseizure efficacy observed in the two studies above has led to the development of fenfluramine as adjunctive treatment in Dravet syndrome in an ongoing Phase 3 program. Preliminary results of the first, randomized, double-blind, placebo-controlled clinical trial of ZX008 (an oral solution of fenfluramine HCl) have been recently reported [14]. A total of 119 patients with Dravet syndrome aged 2 to 18 years were randomized to placebo, ZX008 0.2 mg/kg/day, or ZX008 0.8 mg/kg/day (1:1:1) and were treated for 14 weeks. Daily dosages were divided in half and administered twice daily with food about 12 h apart. The study met its primary endpoint. Compared with placebo, patients in the ZX008 0.8 mg/kg/day group demonstrated a 63.9% greater reduction in monthly frequency of major motor seizures (tonic, clonic, tonic–atonic, generalized tonic–clonic, hemiclonic, and focal with clear observable motor signs) ($P < 0.001$). Patients in the 0.2 mg/kg/day group also experienced an antiseizure benefit with a 33.7% greater reduction in seizure frequency compared with placebo. A ≥50% reduction in monthly convulsive seizure frequency was seen by 70% of patients in the ZX008 0.8 mg/kg/day ($P < 0.001$) and in 41% of patients in the ZX008 0.2 mg/kg/day ($P = 0.001$) compared with 7.5% of patients in the placebo group. The incidence of serious adverse events was similar in each group ranging from 10.0% in the placebo group to 12.5% in the ZX008 0.8 mg/kg/day group. Regular echocardiographic examinations before and during treatment revealed no evidence of cardiac valvulopathy of pulmonary hypertension.

3. Antiseizure mechanism of action of fenfluramine in Dravet syndrome

The potential association between elevated central nervous system serotonin levels and inhibition of epilepsy was first described by Bonnycastle and colleagues in 1957 who described elevation in brain serotonin levels in rats that had been treated with anticonvulsant compounds [15]. Other investigations have shown that agents that increase CNS serotonin levels, like selective serotonin reuptake inhibitors, inhibit seizures in a variety of animal models [16,17] and that depletion of brain levels of serotonin reduces the threshold for evoking seizures in animals [18]. The results of a few small open-label clinical studies have suggested that selective serotonin reuptake inhibitors may reduce seizure frequency [19,20]; however, no randomized clinical trials have been reported, and the reported magnitude of effect in the small studies has been modest compared with that reported with fenfluramine suggesting that additional mechanisms may be involved with fenfluramine's antiepileptic effects.

About 75%–85% of patients with Dravet syndrome have a mutation in the *SCN1A* gene, which codes for a neuronal voltage-gated sodium channel subunit and has been proposed as the cause of Dravet syndrome [21]. Zebrafish larvae that are homozygous for mutant *scn1Lab*, the zebrafish ortholog of human *SCN1A*, exhibit epileptiform motor activity that is attenuated in the presence of fenfluramine [22]. In large-scale screening of over 1000 compounds, only fenfluramine and dimethadione, a T-type calcium channel antagonist, had antiseizure activity in this model [23]. Pharmacologic interrogation of the model has suggested that fenfluramine's antiepileptiform activity is mediated by 5-HT_{1D} and 5-HT_{2C} (and possible 5-HT_{2A}) receptors [22]. The sigma-1 receptor has also been implicated in the activity of fenfluramine in this model [22].

The interaction of fenfluramine with the sigma-1 receptor has been further characterized using the dizocilpine-induced learning impairment mouse model of spontaneous alternation in a Y-maze. In this model, both fenfluramine and the specific sigma-1 agonist PRE-084 attenuated the learning deficit in a dose-related manner [24]. Of interest was the observation that the combination of ineffective doses of fenfluramine and PRE-084 resulted in a response that was similar to the maximal response to higher doses of either agent alone, suggesting a synergistic interaction.

4. Cardiovascular safety and fenfluramine

When fenfluramine was used in adults with obesity, it was associated with an increased risk of primary pulmonary hypertension and cardiac valvulopathy [25,26]. The same type of cardiac morbidity can be seen in patients with carcinoid tumors, suggesting a relevant role of high serotonin levels, which have been shown to interact via the 5-HT_{2B}-receptor [27]. A recent review of controlled studies of patients treated with fenfluramine reported that the prevalence of mild or greater aortic valve regurgitation increased from 3.9% in control patients or at baseline ($n = 1721$) to 9.6% in adult patients treated with fenfluramine for obesity ($n = 3268$) [28]. Similarly, the prevalence of moderate or greater mitral valve regurgitation was 2.5% in control patients and 3.1% in patients treated with fenfluramine. As the 5-HT_{2B} receptor is thought to be responsible for this drug-induced valve disease [29], it is important to note that fenfluramine has no direct action at the 5-HT_{2B} receptor and its antiepileptiform activity in the zebrafish model is not blocked by a 5-HT_{2B}-antagonist [22,30]. However, its metabolite D-norfenfluramine is a potent and full agonist at this receptor [29,30] and has been implicated in cardiac valve disease in patients treated with benfluorex [31].

The published experience of the treatment of Dravet syndrome now includes nearly 100 patients who have been treated for 3 months to 28 years without the emergence of cardiac valve dysfunction [12–14]. The daily dosages of fenfluramine used to treat Dravet syndrome were 5 mg to <30 mg/day, which is below the threshold of 60 mg/day that was associated with a 9-fold higher risk compared with <40 mg/day when used to treat adults with obesity [32] and below the dosages of 60–120 mg/day that were often prescribed to treat adult patients with

obesity. These observations suggest a positive benefit–risk profile for the use of lower dose fenfluramine in children and young adults treated for Dravet syndrome compared with its use at higher doses in an adult population with obesity.

4.1. Other fenfluramine safety reports

In the two cohorts of patients with Dravet syndrome treated with open-label fenfluramine, the most commonly reported adverse events were somnolence, fatigue, and anorexia or loss of appetite [11–13]. The latter adverse events were expected based on fenfluramine's history as a weight loss treatment. Although loss of body weight was not reported in these cohorts, it was noted that several patients exhibited body mass indices substantially below the normal range [12]. In the recently completed Phase 3 clinical trial [14], the most commonly reported adverse events in patients with Dravet syndrome treated with fenfluramine compared with those patients treated with placebo were diarrhea, decreased appetite, fatigue, lethargy, and weight decrease [14].

5. Summary: fenfluramine and precision medicine

The story of fenfluramine as a treatment of refractory seizures in patients with Dravet syndrome started with the idea of treating compulsive behavior that provoked seizures. The clinical observation of an unexpected suppression of a photoparoxysmal response led to the treatment of a homogeneous group of patients with fenfluramine. Some of these original patients were later found to have a mutation of *SCN1A*, which is found in about 85% of patients with Dravet syndrome. The use of the zebrafish model suggested that fenfluramine may be uniquely effective in the treatment of Dravet syndrome.

Dravet syndrome is associated with reduced quality of life [33], and caring for a patient with Dravet syndrome extracts an elevated caregiver burden and high health-related costs [34,35], in part due to the ineffectiveness of currently available AEDs in controlling the disease. Reducing seizure frequency with an effective new AED may reduce some health-related costs of treating Dravet syndrome, particularly those associated with hospitalizations [36], and will likely improve quality of life for patients and caregivers. The development of fenfluramine has combined "old" meticulous clinical observations with a "new" precision medicine approach, which has led to a successful Phase 3 clinical trial with patients with Dravet syndrome in which fenfluramine demonstrated a dose-related reduction in the frequency of convulsive seizures compared with placebo and was generally well-tolerated. Importantly, no cases of cardiac valve dysfunction or pulmonary hypertension have been observed, consistent with data reported from long-term use in a cohort of patients in Belgium. These results combined with the long-term observations of the Belgian cohorts suggest that fenfluramine may represent a novel and effective treatment for Dravet syndrome.

Conflicts of interest

Dr. Polster has received honoraria for consulting from Desitin Arzneimittel GmbH; Novartis International AG; Shire, plc; UCB; and Zogenix International Ltd.

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References

[1] Fuller RW, Snoddy HD, Robertson DW. Mechanisms of effects of D-fenfluramine on brain serotonin metabolism in rats: uptake inhibition versus release. Pharmacol Biochem Behav 1988;30:715–21.
[2] Aicardi J, Gastaut H. Treatment of self-induced photosensitive epilepsy with fenfluramine. N Engl J Med 1985;313:1419.
[3] Gastaut H, Zifkin BG. Antiepileptic effects of fenfluramine: pilot study. Ann Neurol 1987;22:414–5 [abstract].
[4] Gastaut H, Zifkin B, Rufo M. Compulsive respiratory stereotypies in children with autistic features: polygraphic recording and treatment with fenfluramine. J Autism Dev Disord 1987;17:391–406.
[5] Boel M, Casaer P. Add-on therapy of fenfluramine in intractable self-induced epilepsy. Neuropediatrics 1996;27:171–3.
[6] Schoonjans A-N, Lagae L, Ceulemans B. Low-dose fenfluramine in the treatment of neurologic disorders: experience in Dravet syndrome. Ther Adv Neurol Disord 2015;8:328–38.
[7] Dravet C. The core Dravet syndrome phenotype. Epilepsia 2011;52(Suppl. 2):3–9.
[8] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–21.
[9] Aras LM, Isla J, Mingorance-Le Meur A. The European patient with Dravet syndrome: results from a parent-reported survey on antiepileptic drug use in the European population with Dravet syndrome. Epilepsy Behav 2015;44:104–9.
[10] Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene *SCN1A* cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001;68:1327–32.
[11] Ceulemans B, Boel M, Leyssens K, Van Rossem C, Neels P, Jorens PG, et al. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. Epilepsia 2012;53:1131–9.
[12] Ceulemans B, Schoonjans A-N, Marchau F, Paelinck B, Lagae L. Five-year extended follow-up of 10 Dravet patients treated with fenfluramine. Epilepsia 2016;57:e129–34.
[13] Schoonjans A, Paelinck BP, Marchau F, Gunning B, Gammaitoni A, Galer BS, et al. Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome: a prospective study of a new cohort of patients. Eur J Neurol 2017;24:309–14.
[14] Lagae L, Sullivan J, Cross JH, Farfel GM, Galer BS, Gammaitoni A, et al. ZX008 (fenfluramine HCl oral solution) in Dravet syndrome: results of a Phase 3, randomized, double-blind, placebo-controlled trial. Washington, DC: American Epilepsy Society; 2017.
[15] Bonnycastle DD, Giarman NJ, Paasonen MK. Anticonvulsant compounds and 5-hydroxytryptamine in rat brain. Br J Pharmacol Chemother 1957;12:228–31.
[16] Dailey JW, Yan QS, Mishra PK, Burger RL, Jobe PC. Effects of fluoxetine on convulsions and on brain serotonin as detected by microdialysis in genetically epilepsy-prone rats. J Pharmacol Exp Ther 1992;260:533–40.
[17] Hamid H, Kanner AM. Should antidepressant drugs of the selective serotonin reuptake inhibitor family be tested as antiepileptic drugs? Epilepsy Behav 2013;26:261–5.
[18] Bagdy G, Kecskemeti V, Riba P, Jakus R. Serotonin and epilepsy. J Neurochem 2007;100:857–73.
[19] Favale E, Audenino D, Cocito L, Albano C. The anticonvulsant effect of citalopram as an indirect evidence of serotonergic impairment in human epileptogenesis. Seizure 2003;12:316–8.
[20] Specchio LM, Iudice A, Specchio N, La Neve A, Spinelli A, Galli R, et al. Citalopram as treatment of depression in patients with epilepsy. Clin Neuropharmacol 2004;27:133–6.
[21] Bayat A, Hjalgrim H, Moller RS. The incidence of *SCN1A*-related Dravet syndrome in Denmark is 1:22,000: a population-based study from 2004 to 2009. Epilepsia 2015;56:e36–9.
[22] Sourbron J, Smolders I, de Witte P, Lagae L. Pharmacological analysis of the anti-epileptic mechanisms of fenfluramine in *SCN1A* mutant zebrafish. Front Pharmacol 2017;8:191.
[23] Dinday MT, Baraban SC. Large-scale phenotype-based antiepileptic drug screening in a zebrafish model of Dravet syndrome. eNeuro 2015;2:1–19.
[24] Martin P, Maurice T, Gammaitoni A, Farfel GM, Boyd B, Galer BS. Fenfluramine has in vivo acivity as a positive modulator of sigma-1 receptors. Washington, DC: American Epilepsy Society; 2017.
[25] Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. N Engl J Med 1996;335:609–16.
[26] Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997;337:581–8.
[27] Roth BL. Drugs and valvular heart disease. N Engl J Med 2007;356:6–9.
[28] Schoonjans AS, Marchau F, Paelinck BP, Lagae L, Gammaitoni A, Pringsheim M, et al. Cardiovascular safety of low-dose fenfluramine in Dravet syndrome: a review of its benefit–risk profile in a new patient population. Curr Med Res Opin 2017;33:1773–81.
[29] Rothman RB, Baumann MH, Savage JE, Rauser L, McBride A, Hufeisen SJ, et al. Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. Circulation 2000;102:2836–41.
[30] Porter RH, Benwell KR, Lamb H, Malcolm CS, Allen NH, Revell DF, et al. Functional characterization of agonists at recombinant human 5-HT2A, 5-HT2B and 5-HT2C receptors in CHO-K1 cells. Br J Pharmacol 1999;128:13–20.
[31] Andrejak M, Tribouilloy C. Drug-induced valvular heart disease: an update. Arch Cardiovasc Dis 2013;106:333–9.
[32] Li R, Serdula MK, Williamson DF, Bowman BA, Graham DJ, Green L. Dose-effect of fenfluramine use on the severity of valvular heart disease among fen-phen patients with valvulopathy. Int J Obes Relat Metab Disord 1999;23:926–8.

[33] Lagae L, Brambilla I, Mingorance A, Gibson E, Battersby A. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol 2018;60:63–72.
[34] Nabbout R, Auvin S, Chiron C, Irwin J, Mistry A, Bonner N, et al. Development and content validation of a preliminary core set of patient- and caregiver-relevant outcomes for inclusion in a potential composite endpoint for Dravet syndrome. Epilepsy Behav 2018;78:232–42.
[35] Jensen MP, Brunklaus A, Dorris L, Zuberi SM, Knupp KG, Galer BS, et al. The humanistic and economic burden of Dravet syndrome on caregivers and families: implications for future research. Epilepsy Behav 2017;70:104–9.
[36] Strzelczyk A, Schubert-Bast S, Reese JP, Rosenow F, Stephani U, Boor R. Evaluation of health-care utilization in patients with Dravet syndrome and on adjunctive treatment with stiripentol and clobazam. Epilepsy Behav 2014;34:86–91.