You Can Teach an Old Drug New Tricks

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Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial

Nabbout R, Mistry A, Zuberi S, et al. *JAMA Neurol.* 2020;77(3):300-308. doi:10.1001/jamaneurol.2019.4113.

Importance: Fenfluramine treatment may reduce monthly convulsive seizure frequency in patients with Dravet syndrome who have poor seizure control with their current stiripentol-containing antiepileptic drug regimens. Objective: To determine whether fenfluramine reduced monthly convulsive seizure frequency relative to placebo in patients with Dravet syndrome who were taking stiripentol-inclusive regimens. Design, Setting, and Participants: This double-blind, placebo-controlled, parallel-group randomized clinical trial was conducted in multiple centers. Eligible patients were children aged 2 to 18 years with a confirmed clinical diagnosis of Dravet syndrome who were receiving stable, stiripentol-inclusive antiepileptic drug regimens. Interventions: Patients with 6 or more convulsive seizures during the 6-week baseline period were randomly assigned to receive fenfluramine, 0.4 mg/kg/d (maximum, 17 mg/d), or a placebo. After titration (3 weeks), patients' assigned dosages were maintained for 12 additional weeks. Caregivers recorded seizures via a daily electronic diary. Main Outcomes and Measures: The primary efficacy end point was the change in mean monthly convulsive seizure frequency between fenfluramine and placebo during the combined titration and maintenance periods relative to baseline. Results: A total of 115 eligible patients were identified; of these, 87 patients (mean [standard deviation], age 9.1 [4.8] years; 50 [57%] male patients; mean baseline frequency of seizures, approximately 25 convulsive seizures per month) were enrolled and randomized to fenfluramine, 0.4 mg/kg/d (n = 43), or placebo (n = 44). Patients treated with fenfluramine achieved a 54.0% (95% CI, 35.6%-67.2%; $P < .001$) greater reduction in mean monthly convulsive seizure frequency than those receiving the placebo. With fenfluramine, 54% of patients demonstrated a clinically meaningful ($\geq$50%) reduction in monthly convulsive seizure frequency versus 5% with placebo ($P < .001$). The median (range) longest seizure-free interval was 22 (3.0-105.0) days with fenfluramine and 13 (1.0-40.0) days with placebo ($P = .004$). The most common adverse events were decreased appetite (19 [44%] patients taking fenfluramine vs 5 [11%] taking placebo), fatigue (11 [26%] vs 2 [5%]), diarrhea (10 [23%] vs 3 [7%]), and pyrexia (11 [26%] vs 4 [9%]). Cardiac monitoring demonstrated no clinical or echocardiographic evidence of valvular heart disease or pulmonary arterial hypertension. Conclusions and Relevance: Fenfluramine demonstrated significant improvements in monthly convulsive seizure frequency in patients with Dravet syndrome whose conditions were insufficiently controlled with stiripentol-inclusive antiepileptic drug regimens. Fenfluramine was generally well tolerated. Fenfluramine may represent a new treatment option for Dravet syndrome.

Fenfluramine Hydrochloride for the Treatment of Seizures in Dravet Syndrome: A Randomised, Double-Blind, Placebo-Controlled Trial

Lagae L, Sullivan J, Knupp K, et al. *Lancet.* 2019;394(10216):2243-2254. doi:10.1016/s0140-6736(19)32500-0

Background: Dravet syndrome is a rare, treatment-resistant developmental epileptic encephalopathy characterized by multiple types of frequent, disabling seizures. Fenfluramine has been reported to have antiseizure activity in observational studies of photosensitive epilepsy and Dravet syndrome. The aim of the present study was to assess the efficacy and safety of fenfluramine in patients with Dravet syndrome. Methods: In this randomized, double-blind, placebo-controlled clinical trial, we enrolled children and young adults with Dravet syndrome. After a 6-week observation period to establish baseline monthly convulsive seizure frequency (MCSF; convulsive seizures were defined as hemiclonic, tonic, clonic, tonic–atonic, generalized tonic–clonic, and focal with clearly observable motor signs), patients were randomly assigned through an interactive web response system in a 1:1:1 ratio to placebo, fenfluramine 0.2 mg/kg/d, or fenfluramine 0.7 mg/kg/d, added to existing antiepileptic agents for 14 weeks. The primary outcome was the change in mean monthly frequency of convulsive seizures during

the treatment period compared with baseline in the 0.7 mg/kg/d group versus placebo; 0.2 mg/kg/d versus placebo was assessed as a key secondary outcome. Analysis was by modified intention to treat. Safety analyses included all participants who received at least one dose of study medication. This trial is registered with ClinicalTrials.gov with 2 identical protocols NCT02682927 and NCT02826863. Findings: Between January 15, 2016, and August 14, 2017, we assessed 173 patients, of whom 119 patients (mean age 9·0 years, 64 [54%] male) were randomly assigned to receive fenfluramine 0.2 mg/kg/d (39), fenfluramine 0.7 mg/kg/d (40), or placebo (40). During treatment, the median reduction in seizure frequency was 74.9% in the fenfluramine 0.7 mg/kg group (from median 20.7 seizures per 28 days to 4.7 seizures per 28 days), 42.3% in the fenfluramine 0.2 mg/kg group (from median 17.5 seizures per 28 days to 12.6 per 28 days), and 19.2% in the placebo group (from median 27.3 per 28 days to 22.0 per 28 days). The study met its primary efficacy end point, with fenfluramine 0.7 mg/kg/d showing a 62.3% greater reduction in mean MCSF compared with placebo (95% CI, 47.7-72·8, $P < .0001$); fenfluramine 0.2 mg/kg/d showed a 32.4% reduction in mean MCSF compared with placebo (95% CI, 6.2-52.3, $P = .0209$). The most common adverse events (occurring in at least 10% of patients and more frequently in the fenfluramine groups) were decreased appetite, diarrhea, fatigue, lethargy, somnolence, and decreased weight. Echocardiographic examinations revealed valve function within the normal physiological range in all patients during the trial and no signs of pulmonary arterial hypertension. Interpretation: In Dravet syndrome, fenfluramine provided significantly greater reduction in convulsive seizure frequency compared with placebo and was generally well tolerated, with no observed valvular heart disease or pulmonary arterial hypertension. Fenfluramine could be an important new treatment option for patients with Dravet syndrome. Funding: Zogenix.

Commentary

Dravet syndrome (DS), a rare and severe epileptic encephalopathy of childhood, has long had treatment guided by expert consensus, yet recently has enjoyed star status among industry seeking DS indications for their compounds. In the last 2 years, both cannabidiol (CBD as Epidiolex) and stiripentol (Diacomit) have received Food and Drug Administration (FDA) indications for DS with at least 8 additional therapies in various stages of development. Fenfluramine, a drug previously marketed for weight loss in adults and removed from the market due to occurrence of cardiac valvulopathy and pulmonary hypertension, represents the next most likely candidate to receive FDA approval for DS on the heels of impressive results from 2 phase 3 trials.

Using a randomized, double-blinded, placebo-controlled design, fenfluramine was compared at 2 doses (base equivalent 0.2 and 0.7 mg/kg/d) to placebo as treatment for convulsive seizures in children with DS with primary end point reduction in monthly convulsive seizure frequency.[1] At 0.7 mg/kg/d dosing, fenfluramine demonstrated an impressive 75% median seizure reduction (42% at 0.2 mg/kg/d) compared to 19% in the placebo group. These results compare favorably to phase 3 results of CBD[2,3] (39%-49% median reduction) and stiripentol[4] (84% median reduction) with notable differences in seizure types studied. Although convulsive seizures were categorized as hemiclonic, tonic, clonic, tonic–atonic, tonic–clonic, and focal with clear motor signs in the fenfluramine trials, only clonic and tonic–clonic were included for stiripentol, and CBD did not include focal seizures in their primary end point. More importantly, patients treated with fenfluramine experienced longer mean durations of seizure freedom compared to placebo and 19% of patients experienced 1 or less seizures during the 14-week trial with the mean pretreatment baseline convulsive seizure frequency 40. This response is not only statistically significant but clinically significant for a population at considerable risk of sudden unexpected death in epilepsy (SUDEP). Although the initial phase 3 trial excluded patients on stiripentol due to absence of available pharmacokinetic data to evaluate dosage adjustments, the second trial exclusively enrolled patients on an antiseizure medication regimen including stiripentol.[5] The study was similarly designed, other than a maximum fenfluramine dose of 0.4 mg/kg/d, and patients enjoyed nearly identical favorable outcome to the initial phase 3 trial.

Although seizure reduction is immensely important for patients with DS, this diagnosis comes with a myriad of other comorbidities that warrant treatment. The duration of these studies was inadequate to determine the long-term impact meaningful seizure reduction may have on cognition, behavior, SUDEP, and sleep, yet results did provide a glimpse of the possibilities. Using the Behavior Rating Inventory of Executive Function to assess negative impact of fenfluramine on cognition, the authors found significant improvements from baseline in the Behavioral Regulatory Index and Global Executive Composite score for patients treated at 0.7 mg/kg/d, while scores declined for those on placebo. This is promising as the treatment paradigm for DS is shifting from seizure reduction to disease modification.

As encouraging as these results are, to truly understand how fenfluramine will fit into DS treatment several unanswered questions will need to be addressed. Both atypical absence seizures and myoclonic seizures were notably absent as primary seizure types measured in these studies. Myoclonic seizures occur in nearly 70% of patients with DS, while atypical absence occurs in at least 50%, representing a considerable burden.[6,7] Recorded as "other" seizures, patients treated with high-dose fenfluramine experienced a 76% reduction, just reaching statistical significance ($P = .0458$) compared to placebo. The relatively high "other" seizure reduction seen in the placebo group

(56%) underscores the difficulty in counting these seizures for study purposes, representing a likely source of considerable bias limiting any meaningful conclusions of efficacy for these seizure types. Additionally, CBD is expected to be a component of many DS treatment plans now that is has received FDA approval, yet patients on any type of CBD were excluded from the trials, as FDA approval of CBD was not achieved prior to the enrollment period. However, CBD has been allowed as concomitant treatment in the Expanded Access Program for fenfluramine and evidence describing this therapeutic combination is likely forthcoming. Finally, a number of medications commonly used to treat comorbidities of DS were excluded from these trials due to similar mechanisms of action. Such treatments include drugs for behavior (ie, SSRI, stimulants), sleep (ie, trazadone), and common ailments such as vomiting (ie, ondansetron), limiting our understanding of how fenfluramine will impact other concomitant treatment plans.

Fenfluramine demonstrated a favorable safety profile. The most frequent adverse effects included those commonly encountered in trials of antiseizure medications—namely diarrhea, decreased appetite, fever, lethargy, and nasopharyngitis. Perhaps more important than the adverse effects present were those that were absent. Cardiac valvulopathy received immense attention throughout treatment with standardized echocardiograms conducted intermittently throughout the trial and continuing into the open-label phase. No pulmonary arterial hypertension or significant cardiac valvulopathy was noted during the study or during the first 250 days of open-label follow-up.[8] When new trace mitral or aortic regurgitation arose during the study, it frequently resolved or remained unchanged on follow-up testing. Although long-term safety data are still being collected, several open-label studies in Europe have supported long-term cardiac safety when used for epilepsy at low dosing.[9,10] Although patients with mitral or aortic regurgitation of any grade at baseline were excluded from the study, these findings would suggest that trace regurgitation is not likely a contraindication to treatment provided there is periodic cardiac follow-up. Weight loss is another expected adverse effect of treatment given the drug's prior indication. Between the 2 trials, 17% of patients experienced weight loss greater than 7% of baseline weight with the majority remaining on therapy. Thus, while appetite suppression and weight loss may occur, it is often tolerable, particularly in the face of considerable efficacy.

Dravet syndrome has reaped the benefits of elevated interest into the epileptic encephalopathies, especially as it pertains to development of new treatments. Fenfluramine, a repurposed old therapy made new again, has benefits that appear to outweigh any potential risks. Even more refreshing is the realization that DS, as devastating an epileptic encephalopathy as it is, is not impenetrable to treatment. Meaningful seizure reduction and seizure freedom are possible, and we should continue working to ensure that outcome for all patients with the disorder.

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Author's Note

Perry has received honoraria for advisory board work with Zogenix and Biocodex. He has served on a speakers' bureau for Biocodex. He receives honoraria as a consultant to Stoke Therapeutics and Encoded Therapeutics.

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