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

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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 (≥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

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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
Results of CBD2,3 (39) in the placebo group. These results compare favorably to phase 3 seizure reduction (42
in monthly convulsive seizure frequency.1 At 0.7 mg/kg/d dos-
seizures in children with DS with primary end point reduction
0.2 and 0.7 mg/kg/d) to placebo as treatment for convulsive
hypertension, represents the next most likely candidate to
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Commentary

Dravet syndrome (DS), a rare and severe epileptic encephalo-
pathy 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 (Diaco-
mitt) have received Food and Drug Administration (FDA) indi-
cations for DS with at least 8 additional therapies in various
stages of development. Fenfluramine, a drug previously mar-
keted 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 dos-
ing, 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 CBD2,3 (39%–49% median reduction) and stiripentol4
(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 includ-
ing 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 cogni-
tion, 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 unan-
swered 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%, repre-
senting a considerable burden.5,7 Recorded as “other” sei-
zures, patients treated with high-dose fenfluramine
experienced a 76% reduction, just reaching statistical sig-
nificance (P = .0458) compared to placebo. The relatively
high “other” seizure reduction seen in the placebo group

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follow-up. When new trace mitral or aortic regurgitation arose during the study or during the first 250 days of open-label hypertension or significant cardiac valvulopathy was noted continuing into the open-label phase. No pulmonary arterial grams conducted intermittently throughout the trial and con-

Perhaps more important than the adverse effects present were rhea, decreased appetite, fever, lethargy, and nasopharyngitis. encounters 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. M. Scott Perry

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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