Drug could reduce frequency of seizures for children with Dravet Syndrome

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Children with Dravet Syndrome given fenfluramine experienced a greater reduction in convulsive seizures, compared to patients given a placebo for a 14-week treatment period, according to a randomized

controlled trial published in *The Lancet*.

Dravet syndrome is a rare, treatment-resistant epileptic disorder. It is one of a group of severe epileptic disorders that affect around one in 15,700-22,000 babies born each year. Dravet syndrome is responsible for about 10 percent of childhood onset epilepsy cases, where patients have frequent, debilitating seizures, neurodevelopmental, motor and behavioral problems and high mortality due to sudden unexpected death in epilepsy (SUDEP). Patients with Dravet syndrome have a substantially higher rate of SUDEP compared with the general population of patients with epilepsy. Current therapies are inadequate for most patients, and approximately 45 percent of patients have more than three convulsive seizures per month despite multiple antiepileptic drugs.

Fenfluramine was marketed for weight loss in obese adults, most often in combination with another weight loss drug called phentermine, but voluntarily withdrawn from the market in 1997 because of high rates of heart problems in some individuals given high doses of up to 220mg per day. Evidence of its antiepileptic effects was reported in small case studies and observational studies, in particular in a compassionate use program in Belgium in which Dravet syndrome patients have been treated daily with fenfluramine for up to 30 years with sustained, clinically significant reductions in seizure frequency, without evidence of heart valve disease.

The drug tested in the study is a low dose fenfluramine oral solution. It had been reported to have antiepileptic activity in small case studies and observational studies and in Belgium, child neurologists obtained a Royal Decree to permit ongoing testing in patients with Dravet syndrome. The daily doses used were comparable to those in the Phase 3 study ranging from 0.13 mg/kg per day to 0.69 mg/kg per day.

In the study, two identical 14-week-long phase 3 randomized controlled

clinical trials designed to assess the effectiveness and safety of fenfluramine, compared to placebo—one trial in the U.S. and Canada, and the other in western Europe and Australia. The results of the two trials were merged and analyzed together. They included 119 participants with Dravet Syndrome aged between two and 18 years old (the average age was nine years old). The authors note that patients included in the trial had a high seizure burden, with an average of about 1.5 convulsive seizures per day (around 40 seizures within a 28-day period).

Participants were divided into three groups, receiving either placebo (40 participants), a low dose of fenfluramine (0.2mg per kg per day—39 participants), or a higher dose (0.7mg per kg per day—40 participants). The drug was given orally by parents and caregivers.

Nine patients withdrew before the end of the trial, including three in the placebo group (one for lack of effectiveness, and two for patient or guardian decision) and six in the higher dose group (five for side effects, and one for patient or guardian decision). Additionally, six of the patients in the higher dose group did not tolerate the maximum dose due to side effects and either had the dose reduced (3 patients) or discontinued treatment (three patients). These patients were included in the higher dose group for the analysis.

Comparing patients given the higher dose of fenfluramine (0.7mg per kg per day) with those given placebo, the authors estimated a 62 percent reduction in the mean number of convulsive seizures.

Comparing the patients' level of seizures before and while they were given treatment, the study found that patients given the higher dose had an average 75 percent reduction in frequency of convulsive seizures per 28 days (from 21 before treatment per 28 days to five during treatment). Patients given the lower dose had an average 42 percent reduction (from

18 seizures per 28 days before treatment to 13 during treatment) and the placebo group had an average 19 percent reduction per 28 days (from 27 before treatment per 28 days to 22 during the trial).

Looking at the side effects of the drug, the authors found that 21-38 percent of patients in the active treatment groups had decreases in appetite and weight loss above the 7 percent threshold was observed in 13 percent of patients in the fenfluramine 0.2 mg/kg per day group, and in 20 percent of patients in the fenfluramine 0.7 mg/kg per day group. Other common adverse events seen were diarrhoea, fatigue, lethargy and sleepiness (somnolence).

Scans of the heart during the study revealed no heart valve problems in all patients and no signs were observed of high blood pressure in the arteries of the lungs during the entire trial. The authors noted that cardiac safety of fenfluramine in the current study was limited by the short treatment and observation period of 14 weeks in this trial, and longer term research will still be needed. However, these findings are consistent with those reported with long-term use of fenfluramine in Dravet syndrome in Belgium, where no cases of heart problems have been reported with up to 30 years of fenfluramine treatment.

Study author, Dr. J. Helen Cross, UCL Great Ormond Street NIHR BRC Institute of Child Health, UK, says: "The frequent seizures suffered in Dravet syndrome impact on the lives of patients and their families. The patients in this study had a high baseline seizure burden with an average of approximately 40 seizures per month across all treatment groups. In our clinical trial we saw impressive reductions in seizures in the patients who received fenfluramine compared with those on the placebo, and although further study will need to assess the long-term safety, I am optimistic about what we have seen so far."

Study author, Arnold Gammaitoni, Zogenix, U.S., says: "We believe

fenfluramine, if approved by regulatory authorities, could be an important new treatment option for patients with Dravet syndrome, a condition marked by debilitating seizures, extremely poor neurodevelopmental outcomes, and a significant rate of SUDEP. Since the trial finished, most of the patients from this study have continued treatment in an ongoing, long-term open label extension study, where we have continued to see clinically meaningful reduction of convulsive seizures with no signs of heart valve problems."

The authors note a limitation of their study is that the occurrence of side effects of fenfluramine could have meant patients and their families could guess that they were on the drug, which may have led to bias in the reporting of seizures (ie, it may have been clear from a child's reduced appetite that they were on fenfluramine).

In a linked Comment, Professor Samuel F Berkovic of the Epilepsy Research Centre at the University of Melbourne, Australia, says: "Until recently, infants with severe epilepsy and intellectual disability often received a diagnosis of not much more than that—the cause was usually unknown, treatment was supportive, and families often felt disempowered due to lack of information about the condition."

He continues: "Although these diagnostic and therapeutic advances are welcome, strategies need to improve the overall neurological outcome are needed. A number of therapies are currently under investigation for Dravet syndrome and other epileptic encephalopathies... The transformation of this field from one of hopelessness, if not disinterest, to exciting cutting-edge science with definite therapeutic advances and hope for a major breakthrough is remarkable."

More information: Lieven Lagae et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial, *The Lancet* (2019). DOI:

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