Five-Year Follow-Up of Fenfluramine as Add-On Treatment in Dravet Syndrome

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INTRODUCTION

- Dravet syndrome (DS) is a severe therapy-resistant epilepsy syndrome that is caused by an SCN1A gene mutation in 70% to 80% of cases
- Health-related quality of life (HRQOL) is significantly lower in DS patients compared with normative data[1]
  - Independent predictors of poor HRQOL included poor seizure control and behavioral, cognitive, and motor problems
- Fenfluramine acts within the central nervous system (CNS) to promote the release of serotonin from neuronal storage vesicles and inhibit its reuptake[2]
  - Fenfluramine has been reported to have antiepileptic activity,[3] although its exact antiepileptic mechanism of activity has yet to be fully elucidated
- Fenfluramine, which had been used in high doses (≥60 mg/day) in combination with phenteramine for weight loss, was withdrawn from the US and European markets in the 1990s/2000s due to reports of valvulopathy and pulmonary hypertension
- In Belgium, regulatory permission was granted to study the use of fenfluramine for the treatment of refractory epilepsy syndromes
  - A retrospective analysis of the initial cohort of 12 DS patients showed that they were treated for 1 to 19 years with fenfluramine at doses ranging from 0.12 to 0.90 mg/kg/day[4]
  - 7 of 10 patients (70%) who continued to be treated demonstrated seizure-free intervals at the final assessment of 1 to 19 years (mean 6 years)
  - Here we present the results of a prospective follow-up study which sought to include patients with a minimum of 4 years of follow-up since the original analysis published in 2012
  - This analysis includes 10 patients from the original cohort (5 years of follow-up) and 2 patients who began treatment in 2011 (4 years of follow-up)

METHODS

Main Inclusion Criteria

- Participation in the original cohort of DS patients treated with fenfluramine[4]
- For new patients:
  - Clinical diagnosis of DS between the ages of 6 months and 50 years
  - Seizures that were refractory to treatment despite use of adequate doses of anti-epileptic drugs
  - Parental or caregiver consent
- Main exclusion criteria: cardiovascular pathologies, glaucoma, treated hypertension

Treatment

- Fenfluramine at doses of 10 mg to 20 mg per day added to current anti-epilepsy treatment regimen
  - Caretakers of new patients documented seizure incidence in a seizure diary for a 3-month period prior to initiating fenfluramine

Assessments

- Study visits every 3 months during the first 2 years; every 6 months thereafter
- Seizure diary kept by parent or caregiver to document seizure type and frequency
- Regular cardiovascular follow-up examinations
  - Echocardiogram every 3 months during Year 1, every 6 months during Year 2, and annually thereafter
  - Standardized protocol for assessing valve thickness
  - 2 cardiologists: one for patients >16 years old and another for patients ≤16 years old

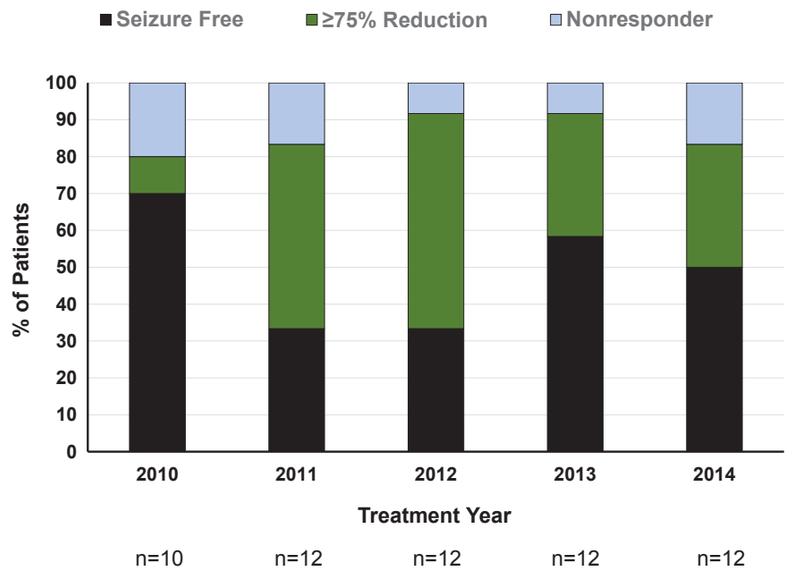
RESULTS

- 10 patients from the original retrospective study
  - 4 male, 6 female
  - Average age = 19 years at study entry
- 2 new patients
  - 1 male, 11 years old at study entry
  - 1 female, 1 year old at study entry
- All patients were treated with valproate, 6/12 were treated with topiramate, and 2/12 were treated with stiripentol
- Maximum fenfluramine dose: 20 mg/day
  - 10 mg/day (5 mg twice daily): 7 patients
  - 15 mg/day (5 mg 3 times daily): 1 patient
  - 20 mg/day (10 mg twice daily or 20 mg once daily): 4 patients

Efficacy

- ≥80% of patients had a ≥75% reduction in seizure frequency in reponse to fenfluramine each year of the study (**Figure 1**)
- No correlation was seen between efficacious dose and body weight or age

Figure 1. Categorical response to fenfluramine in Dravet syndrome patients



- During this 5-year observation period (2010-2014), 3 patients were seizure-free for all 5 years and 5 patients were seizure-free for 2-4 years; 29 of 58 patient-treatment years were seizure-free (50%)

Safety

Cardiovascular

- Valvular thickening
  - Observed at 1 examination in 5 patients and not seen at any other examination
  - Observed 4 times in one patient; patient was normal at most recent examination
  - Observed in 2 patients at most recent examination
- No pulmonary hypertension
- No clinical signs or symptoms associated with valvular thickening

Other Adverse Events

- Loss of appetite (often transient): 5/12
- Mild obesity: 2/12
- Body weight <3rd percentile of normal: 2/12
- Fatigue: 2/12
- Behavioral problems: 2/12
- Somnolence: 2/12

CONCLUSIONS

- Add-on treatment with fenfluramine provided sustained, long-term, clinically significant effectiveness and generally good tolerability in this cohort of Dravet syndrome patients
  - Although some patients experienced changes in response rate during the 5-year period of this observation, at least 80% of patients in any given year maintained a ≥75% reduction in seizure frequency
  - 29 of 58 patient-treatment years (50%) were seizure-free
  - Doses used in Dravet syndrome (≤20 mg/day) were less than had been used in the treatment of obesity (≥60 mg/day was associated with increased risk of valvulopathy[5])
- Fenfluramine exhibits a favorable benefit-risk profile in this patient population and offers a new and possibly effective treatment option

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ACKNOWLEDGEMENT

Professional medical writing and editorial assistance to the authors were provided by Edward Weselcouch, PhD of PharmaWrite, LLC (Princeton, NJ, USA) and was paid for by Zogenix, Inc. (San Diego, CA, USA)

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Presented at the 11th European Paediatric Neurology Society Congress, May 27-30, 2015, Vienna, Austria