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Long-term cardiovascular safety of fenfluramine in patients with Dravet syndrome treated for up to 3 years: Findings from serial echocardiographic assessments

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ABSTRACT

Objective: To assess the cardiovascular safety of fenfluramine when used to treat children and young adults with Dravet syndrome.

Methods: Patients with Dravet syndrome who completed one of three phase 3 clinical trials of fenfluramine could enroll in the open-label extension (OLE) study (NCT02823145). All patients started fenfluramine treatment at an oral dose of 0.2 mg/kg/day. The dose was titrated based on efficacy and tolerability to a maximum of 0.7 mg/kg/day (absolute maximum 26 mg/day) or 0.4 mg/kg/day (absolute maximum 17 mg/day) in patients concomitantly receiving stiripentol. Serial transthoracic echocardiography was performed using standardized methods and blinded readings at OLE entry, after 4–6 weeks, and every 3 months thereafter. Valvular heart disease (VHD) was defined as ≥ moderate mitral regurgitation or ≥ mild aortic regurgitation combined with physical signs or symptoms attributable to valve dysfunction. Pulmonary artery hypertension (PAH) was defined as systolic pulmonary artery pressure >35 mmHg.

Results: A total of 327 patients (median age, 9.0 years; range, 2–19 years) have enrolled in the OLE and received ≥1 dose of fenfluramine. The median duration of treatment was 23.9 months (range, 0.2–42.6 months) and the median dose of fenfluramine was 0.44 mg/kg/day. No patient demonstrated VHD or PAH at any time during the OLE.

Significance/interpretation: This study, which represents the largest, longest, and most rigorous examination of cardiovascular safety of fenfluramine yet reported, found no cases of VHD or PAH. These results, combined with fenfluramine's substantial antiseizure efficacy, support a strong positive benefit-risk profile for fenfluramine in the treatment of Dravet syndrome.

1. Introduction

Dravet syndrome is a rare, severe, pharmaco-resistant developmental and epileptic encephalopathy that has its onset in the first year of life and is associated with substantial morbidity and premature mortality [1]. Fenfluramine was recently approved in the United States and European Union/United Kingdom for the treatment of Dravet syndrome, after demonstrating a profound reduction in monthly convulsive seizure frequency (MCSF). In two double-blind clinical trials, patients treated with fenfluramine that was added to their antiseizure medication regimen experienced a 54% and 62% greater reduction in convulsive seizure frequency compared with placebo [2,3]. Moreover, 35% and 50% of patients experienced a ≥75% reduction in MCSF.

Fenfluramine, dosed at 60–120 mg/day, was previously marketed globally as a weight loss drug for the treatment of obese adults and was withdrawn in 1997 following reports of cardiac valvulopathy (defined by the Food and Drug Administration, or FDA, as ≥ moderate regurgitation of the mitral valve and/or ≥ mild regurgitation of the aortic

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valve) in a minority of treated patients [4,5]. Subsequent investigations aimed at assessing the magnitude of this adverse association (reviewed by Schoonjans et al. [6]) reported wildly divergent estimates of the prevalence of cardiac valvulopathy in treated patients (Supplemental Appendix A). Despite the wide range of the prevalence findings, nearly all of the studies suggested a potential link between fenfluramine use and cardiac valvulopathy.

Because of these previous reports of cardiac valvulopathy, it was of critical importance to carefully monitor the cardiovascular safety of fenfluramine for the treatment of Dravet syndrome during the drug development program. The initial report of this surveillance program found no incidence of valvular heart disease (VHD) in 232 patients treated for median 256 days (range 58–634 days) [7]. Here we update the cardiovascular safety observations from the development program, which now has 50% more patients and 1 year longer median exposure to fenfluramine than in the previous report [7].

2. Methods

The study design and methods employed for the assessment of VHD and pulmonary artery hypertension (PAH) have been previously described in detail [7] and will be briefly summarized here. The protocol for this open-label extension study (OLE) was reviewed and approved by the institution review board or ethics committee of each study site prior to initiation of any study activities. Signed consent for study participation was provided by all patients or their legal guardians.

Patients with Dravet syndrome who had completed any of the three double-blind phase 3 clinical trials (NCT02826863, NCT02682927, NCT02926898) were invited to enroll in the OLE study (NCT02823145) provided they met eligibility criteria. Important eligibility criteria included demonstration during the double-blind study of compliance with electronic diary completion ($\geq$90%), study visits, and study drug accountability. Key exclusion criteria included current VHD or pulmonary arterial hypertension; current or history of cardiovascular or cerebrovascular disease; and hypersensitivity to fenfluramine or any components of its formulation. Patients who demonstrated any grade of aortic or mitral valve regurgitation, including "trace" regurgitation, were excluded from the core double-blind, placebo-controlled clinical trials, but patients who exhibited trace aortic or mitral valve regurgitation during the core studies were allowed to enroll in the OLE study.

All patients entering the OLE study were started on 0.2 mg/kg/day given in two equal doses administered about 12 h apart regardless of the dose they received in the core double-blind studies. This dosing scheme allowed maintenance of the blind because the double-blind studies were still active when patients began entering the OLE study. After 4 weeks, the dose could be titrated based on efficacy and tolerability, with increases limited to 0.2 mg/kg/day steps with at least 2 weeks between dose changes. Patients not currently treated with stiripentol had their dose limited to 0.7 mg/kg/day (up to a maximum dose of 26 mg/day) and patients concomitantly treated with stiripentol had their dose limited to 0.4 mg/kg/day (up to a maximum dose of 17 mg/day) to account for a drug-drug interaction between stiripentol and fenfluramine [8,9].

In the OLE study, all patients continued an extensive program of scheduled comprehensive transthoracic echocardiographic (TTE) examinations using standardized views and machine settings (see Supplemental Appendix B for summary). An echocardiography core lab, which operated in accordance with American Society of Echocardiography standards for echocardiography core laboratories as outlined in the 2009 consensus statement [10], was utilized for the cardiovascular safety assessments. Some of the core lab practices included the following: site selection (including training of sonographers and other personnel), development of case report forms, use of an image review charter or site manual describing all aspects of core lab operations, data management (including image transfer, processing, and storage), and continuing image review to ensure site image quality and evaluability. Interpretation of echocardiograms was conducted by board-certified pediatric or adult cardiologists who were blinded to all aspects of the study, including study design and identification of the treatment being tested.

Echocardiographic examinations were performed upon OLE study entry, at study week 4 or 6, and every 3 months thereafter. Single, 12-lead electrocardiography was performed on the same schedule. All echocardiograms were assessed at the echocardiography core lab by two blinded, independent, board-certified cardiologists. A third blinded, board-certified cardiologist provided arbitration in the event of differing assessments of the echocardiograms. Standard criteria, as outlined in American Society of Echocardiography consensus guidelines [11], were used to grade regurgitation of all four cardiac valves as absent, trace, mild, moderate, or severe. Although universally accepted international clinical guidelines for the diagnosis of VHD do not exist, specific criteria were used to establish the diagnosis of VHD. These included a finding of $\geq$ mild aortic regurgitation or $\geq$ moderate mitral regurgitation, combined with physical signs or symptoms attributable to valvular disease, and one or more of the following findings on echocardiography: structural lesion/restriction of valve movement of the aortic or mitral valve, abnormal left ventricular systolic function with depressed left ventricular ejection fraction, left ventricle dilatation, or left atrial enlargement.

A separate analysis for pulmonary and tricuspid valves was conducted in which any observations of $\leq$ mild regurgitation for either valve were considered physiologic. PAH was defined as pulmonary artery systolic pressure (PASP) >35 mmHg and was derived from the peak systolic Doppler-determined tricuspid regurgitation jet velocity, confirmed by follow-up examination.

All patients who had enrolled in the OLE study and had received at least one dose of fenfluramine as of November 30, 2020, were included in this cardiovascular safety analysis. The primary outcome was the number of patients who met the definition of VHD. Secondary outcomes included the prevalence of trace or greater regurgitation of the aortic or mitral valve at each study visit, the effect of the dose of fenfluramine (above or below the mean dose) on valvular regurgitation, and the incidence of PAH. Data are presented using descriptive statistics, including mean $\pm$ SD or median (range) as appropriate.

3. Results

As of November 30, 2020, 327 patients had enrolled in the OLE study and received at least 1 dose of fenfluramine. Baseline characteristics of the study population are presented in Table 1. The median duration of treatment with fenfluramine during the OLE study was 23.9 months (range, 0.2–42.6 months). At OLE study baseline, 35 and two patients demonstrated trace mitral or trace aortic valve regurgitation, respectively. The median daily dose of fenfluramine was 0.44 mg/kg/day. A total of 77 (23.5%) patients have withdrawn prematurely from the study, with the most common reasons cited being lack of efficacy (n = 44) and adverse event (n = 6).

A total of 3308 echocardiograms were conducted (mean $\pm$ SD per patient, 10.1 $\pm$ 3.2) during the study. A total of 281, 262, 191, and 100 patients had echocardiograms at month 6, 12, 24, and 36, respectively. Fig. 1 presents a summary of the transthoracic echocardiography findings during the study. A single patient (0.3%) had a finding of mild mitral regurgitation (a nonpathologic finding) during the study, and no patients demonstrated moderate or greater mitral regurgitation during the study. Similarly, a single patient (0.3%) demonstrated mild aortic regurgitation without physical signs or symptoms associated with valve dysfunction at month 15, a finding that triggered additional investigation. A transesophageal echocardiogram performed 6 weeks later found absent aortic regurgitation and no abnormalities of valve morphology. The patient discontinued fenfluramine 2 weeks later due to lack of efficacy, and the end-of-study TTE performed at that time revealed trace aortic valve regurgitation and no abnormalities of valve morphology. Cardiac follow-up echocardiograms performed 3 and 6 months later

Table 1
Baseline characteristics of patients in the open-label extension study.

Characteristic	
N	327
Age, years	
Mean ± SD	9.2 ± 4.7
Median (min, max)	9.0 (2, 19)
Age group, n (%)	
2 to <6	85 (26.0)
6 to <12	136 (41.6)
12-17	96 (29.4)
≥18	10 (3.1)
Sex, n (%)	
Male	175 (53.5)
Female	152 (46.5)
Race, n (%)	
White	244 (81.9)
Black	5 (1.7)
Asian	30 (10.1)
American Indian or Alaska Native	2 (0.7)
Other	17 (5.7)
Ethnicity	
Hispanic or Latino	39 (11.9)
Not Hispanic or Latino	240 (73.4)
Not reported	40 (12.2)
Unknown	8 (2.4)
Body mass index, kg/m^2	
Mean ± SD	17.9 ± 3.9
Median (min, max)	17.0 (11.8, 38.0)

revealed absent aortic regurgitation on both occasions.

No findings of moderate or greater aortic regurgitation were observed at any time. The point prevalence of mild tricuspid regurgitation ranged from 0% to 2.3% during the study, and the point prevalence of mild pulmonic regurgitation ranged from 0% to 0.7%. Mild tricuspid and pulmonic regurgitation are considered nonpathologic findings. No findings of ≥ moderate regurgitation were observed for the pulmonic or tricuspid valves (Fig. 1).

No cases of PAH were observed in the study. The most recent mean PASP was 15.7 ± 5.0 mmHg in the 294 patients with an evaluable estimate, representing a mean change from baseline of −2.7 ± 6.1 mmHg for the 162 patients with both baseline and most recent measurements. No effects on heart rate, AV conduction, cardiac depolarization, or cardiac repolarization were seen on ECG during treatment with fenfluramine.

4. Discussion

The results of this study extend and confirm previous results in this patient population showing no incidence of VHD or PAH in children and adolescents with Dravet syndrome who have been treated with fenfluramine [2,3,7,12]. A total of 327 patients treated with fenfluramine have now been prospectively followed for up to 36 months with 3308 echocardiograms, without any subject demonstrating echocardiographic evidence of VHD or PAH.

To our knowledge, the present study represents the largest, most rigorous prospective longitudinal assessment of cardiac valve function and morphology in patients receiving fenfluramine. Unlike prior studies that reported an association of fenfluramine and cardiac valvulopathy and PAH when the drug was prescribed in higher doses, and most often with phentermine, to treat adult obesity (as discussed above), all patients in this long-term extension study had at least 1 baseline echocardiographic examination prior to initiating treatment with fenfluramine to exclude patients with any evidence of valve abnormalities or PAH. In addition, regular follow-up echocardiographic examinations were conducted during the entire time of treatment with fenfluramine. Importantly, unlike the older studies, all echocardiographic examinations were done using standardized views and machine settings. Finally, all echocardiograms were read in an echocardiography core laboratory by two independent, board-certified cardiologists who were blinded to all aspects of the study. A third blinded board-certified cardiologist provided arbitration in the event of disagreement between the first two readers.

None of the original studies of fenfluramine, in which the medication was used in doses of 60–120 mg/day and usually given in conjunction with phentermine to treat adult obesity, were considered definitive in establishing the magnitude of the risk of cardiac valvulopathy associated with the use of fenfluramine in obese adults. However, several trends were reported that suggested a causal relationship. These older studies reported that increasing duration of fenfluramine use appeared to be associated with increased risk of valvulopathy in the adult obese population. For example, Dahl et al. [13] reported echocardiography results from 4825 women and 918 men in Utah who reported fenfluramine use. The odds ratio for valve disorders in their study was 1.32 for each 3-month increment in fenfluramine use (95% CI 1.24–1.40). Hopkins and Polukoff [14] conducted a meta-analysis using data from 8 separate studies to estimate the influence of duration of exposure on aortic and mitral valve regurgitation. The effect of duration was strongest on aortic regurgitation ≥ mild starting at 6 months use and increased with increasing duration of use. The trend for mitral regurgitation was smaller and not statistically significant. Jick and colleagues [15] performed a population-based study using data from the UK General Practice Research Database to identify incident clinical valve disease in patients treated with fenfluramine over a 5-year period. In 8903 subjects who were treated with fenfluramine or dexfenfluramine, 11 incident cases of cardiac valve disease were identified, representing a 5-year cumulative incidence of 14.2 per 10,000 subjects (95% CI, 7.8 to 26.2). No cases were found in the 9281 control subjects. In their nested case-control analysis [15], fenfluramine or dexfenfluramine use for ≥4 months was associated with an odds ratio of 7.4 (95% CI, 1.5 to 36) compared with drug use for 1–3 months. Increasing dose of fenfluramine has also been associated with increased risk of valvulopathy. Li and co-workers reported on patients included in the original FDA report and reported that the relative risk of valvulopathy was 9.2 in patients taking ≥60 mg/day compared with patients taking <40 mg/day [16].

Stimulation of serotonin 5-HT$_{2b}$ receptors on cardiac valves during treatment with fenfluramine has been hypothesized as the underlying mechanism responsible for the pathologic changes in valve structure and function in early clinical investigations cited above [17]. However, fenfluramine has minimal affinity for the 5-HT$_{2b}$ receptor [18,19], and circulating serotonin levels are *decreased* during chronic fenfluramine treatment, thus removing serotonin as the causative agent [17]. Nor-fenfluramine, the primary metabolite of fenfluramine, has high affinity for the 5-HT$_{2b}$ receptor [18,19], but no clinical data have been reported supporting its role in valvulopathy.

The observations of the present study stand in stark contrast to prior findings. Importantly, in the fenfluramine for Dravet syndrome development program, more than 85% of patients have been treated with fenfluramine for 6 months or longer and have been followed with a scheduled series of echocardiographic examinations, without any observations of VHD. In addition, within the dose range studied, no influence of dose above or below the median study dose was associated with any echocardiographic signal of increased risk of VHD.

What factors might have contributed to the differences in the incidence of cardiac valve dysfunction between the clinical studies reported shortly after the withdrawal of fenfluramine in 1997, and the findings of the current study of patients with Dravet syndrome treated with fenfluramine? The vast majority (97%) of patients with Dravet syndrome in the present study were children and adolescents (<18 years old at the start of the OLE) with normal or low BMI, compared with the obese adult population previously treated with fenfluramine for its anorectic effect, who were older, overweight or obese, and primarily female. The maximum doses of fenfluramine used in the present study were 17 or 26 mg/day (depending on other antiseizure medication used), whereas patients treated for weight loss typically were treated with 60–120 mg/

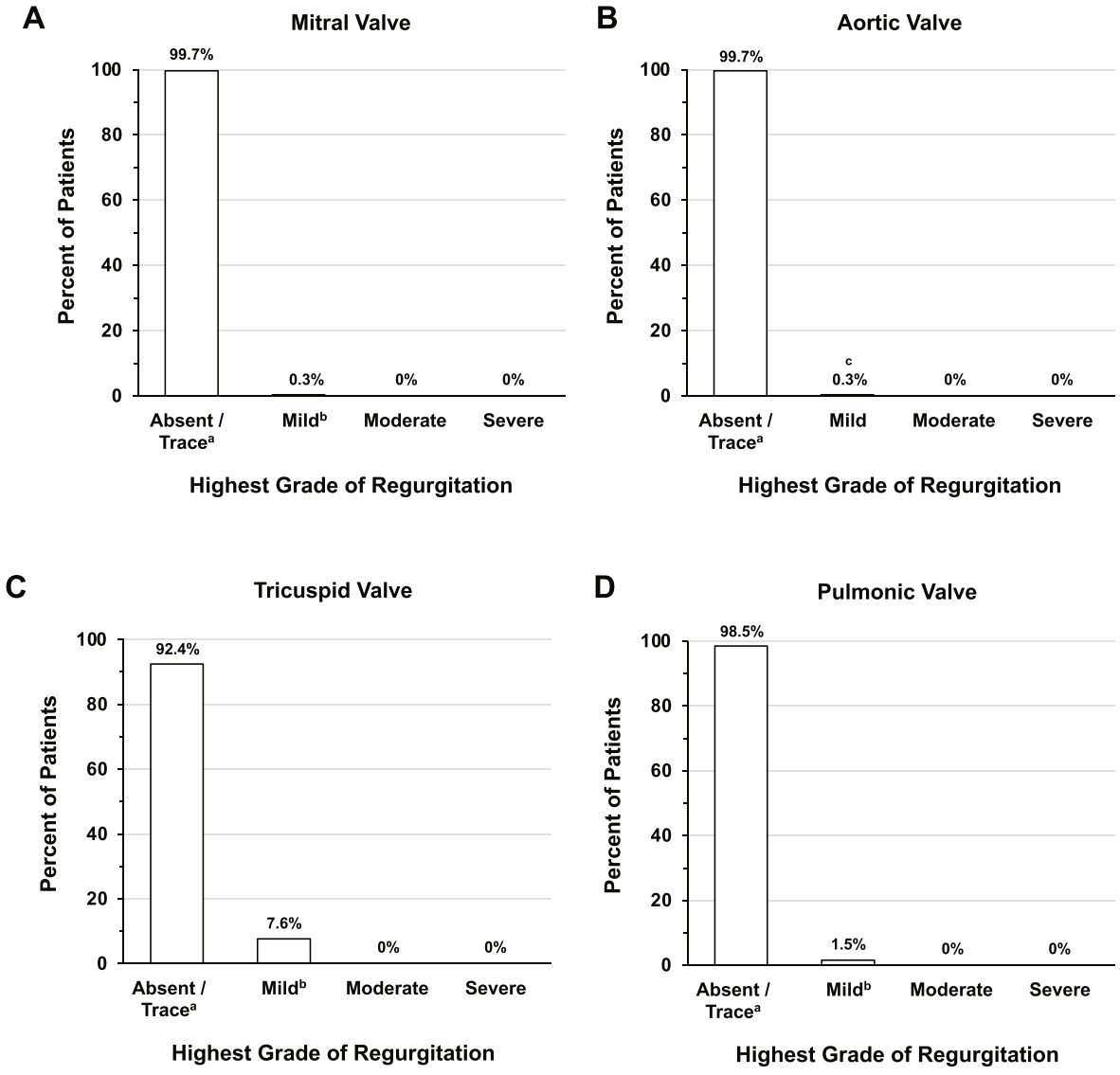

Fig. 1. Highest grade of regurgitation observed during serial transthoracic echocardiography in each patient.
[a]Trace regurgitation is a physiologic, nonpathogenic finding.
[b]Mild regurgitation is considered a nonpathologic finding in mitral, tricuspid, and pulmonic valves.
[c]Further investigation in this patient using transesophageal echocardiography revealed absent aortic regurgitation and normal aortic valve structure.

day or higher. Furthermore, none of the adult patients in studies of patients being treated with the combination of fenfluramine/phentermine for weight loss had pretreatment echocardiograms to evaluate baseline cardiac valve function, nor were they screened for risk factors for valve disease. In contrast, all of the patients with Dravet syndrome who were treated with fenfluramine had pretreatment echocardiograms. Finally, as noted above, all echocardiograms were conducted in a standardized manner and were read at a core echocardiography laboratory following current guidelines by experienced cardiologists who were blinded to the drug identification, dose used, and duration of treatment.

5. Limitations

The variable duration of treatment with fenfluramine of patients at the time of this analysis is a limitation of the study. Because PAH is rare, the relatively small number of patients in this study (n = 327) remains too small to accurately estimate the risk. In addition, the grading of valvular regurgitation was qualitative and possibly subject to interobserver variability. However, the use of an echocardiography core laboratory following established grading criteria should have minimized this issue.

6. Conclusions

This study represents the most rigorous prospective study yet reported of cardiovascular assessment in patients treated with fenfluramine. In 327 patients with Dravet syndrome who were treated with fenfluramine for up to 36 months, and followed with prospective standardized transthoracic echocardiograms, no cases of VHD or PAH were observed. These results, in conjunction with the substantial seizure and nonseizure benefits reported in phase 3 clinical trials, support a continued strong positive benefit-risk profile for use of fenfluramine in the treatment of Dravet syndrome.

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Declaration of competing interests

AA, GMF, ARG, and BSG are employees of, and have ownership interest in, Zogenix, Inc.

PCW is a consultant to Zogenix, Inc.

FJP received research support from Zogenix, Inc.

Author contributions

All authors have agreed to this final version of the paper being submitted to the Journal. All authors participated in the design of the study and the collection, analysis, and interpretation of the data. All authors were responsible for the concept and design of the manuscript, and all authors participated in the drafting of the manuscript, with AA, PCW, and ARG taking lead roles. All authors participated in all stages of drafting of the manuscript and provided critical comments during the review of each version of the manuscript. Each author reviewed and approved the final version of the manuscript for submission to the journal.

Previous presentation

Agarwal A, et al. Serial Echocardiographic Assessment of Patients With Dravet Syndrome Treated With Fenfluramine (Fintepla®) for Up to 3 Years: No Incidence of Valvular Heart Disease or Pulmonary Artery Hypertension. Presented at the American Epilepsy Society Annual Meeting, December 3–7, 2021, Chicago, IL (Poster 3415) and encored at the American Academy of Neurology Annual Meeting, April 2–7, 2022, Seattle, WA.

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Appendices A and B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2022.05.006.

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