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Treatment with fenfluramine in patients with Dravet syndrome has no long-term effects on weight and growth

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ABSTRACT

Objective: Appetite disturbance and growth abnormalities are commonly reported in children with Dravet syndrome (DS). Fenfluramine (Fintepla) has demonstrated profound reduction in convulsive seizure frequency in DS and was recently approved for use in DS in the US and EU. Prior to its use in epilepsy, fenfluramine was approved to suppress appetite in obese adults. Here, we evaluated the impact of fenfluramine on weight and growth in patients with DS treated for ≥12 months or ≥24 months and compared the results with growth curves in normative reference populations and published historical controls among patients with DS.

Methods: Historical control data from a recent study of 68 patients with DS show decreases in height and weight *Z*-scores of ~0.1 standard deviation (SD) for every 12-month increase in age (Eschbach K. Seizure. 2017;52:117–22). Anthropometric data for fenfluramine were extracted from an open-label extension (OLE) study of eligible patients with DS (2–18 y/o; fenfluramine dose: 0.2–0.7 mg/kg/day). *Z*-score analyses were based on the Boston Children's Hospital algorithm and assessed potential impact of fenfluramine on growth at OLE baseline, at Month 12, and at Month 24. A mixed-effect model for repeated measures (MMRM) estimated changes in height and weight over time. Height and weight *Z*-scores were also analyzed by dose group (0.2–<0.3 mg/kg/day, 0.3–<0.5 mg/kg/day, and 0.5–0.7 mg/kg/day), averaged over time.

Results: At the time of analysis, 279 patients were treated with fenfluramine for ≥12 months; 128 were treated for ≥24 months. Relative to the reference population with DS, fenfluramine treatment for ≥12 months or for ≥24 months had minimal impact on height or weight over time as assessed by *Z*-score analyses. No substantial dose-dependent changes from baseline were observed at Month 12 nor at Month 24. MMRM showed that patients treated with fenfluramine for ≥12 months ($N = 262$) had an estimated change in *Z*-score per year of −0.056 for height and −0.166 for weight. For patients with data from all three time points (baseline, 12 months, and 24 months; $N = 110$), estimated changes in *Z*-scores per year were −0.025 for height and −0.188 for weight. MMRM projections based on normative reference growth curves were comparable to growth data from historical control populations with DS.

Significance/Conclusion: Long-term treatment with fenfluramine had minimal impact on the growth of patients with DS as demonstrated by differences in *Z*-scores for height and weight at 12 months and at

Abbreviations: ASM, antiseizure medication; BMI, body mass index; CDC, Centers for Disease Control and Prevention; DS, Dravet syndrome; FFA, fenfluramine; IGF-1, insulin-like growth factor-1; MMRM, mixed-effect model for repeated measures; OLE, open-label extension; RCT, randomized controlled trial.

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24 months. Changes in *Z*-scores for height and weight were consistent with published reports on patients with DS.

1. Introduction

Fenfluramine (Fintepla) has been demonstrated to provide profound and sustained reductions in convulsive seizure frequency in three randomized, placebo-controlled phase 3 clinical studies and in one long-term open-label extension study (OLE) of children and young adults with Dravet syndrome (DS) [1-3], a rare pediatric encephalopathy characterized by pharmacoresistant seizures of multiple types and neurocognitive deficits [4]. Dravet syndrome is associated with many comorbidities, including developmental delays, cognitive impairment, and sudden unexpected death [5,6]. Beyond seizures and neurocognitive deficits, patients with DS also exhibit growth delays, short stature, orthopedic misalignment, and crouching, and some have abnormal endocrine function [7,8].

Fenfluramine was originally approved as an anorectic agent to treat obesity in adults; thus appetite suppression and weight decrease are potential side effects [9]. Decreased appetite was observed at the most clinically effective dose in 38–44% of patients in the short-term fenfluramine randomized controlled clinical trials (RCTs) [1,2]. However, this effect tended to taper gradually, with most patients who initially lost weight resuming weight gain on treatment over time [10]. Poor appetite is also a common feature in patients with DS [6]; in the fenfluramine clinical trials, decreased appetite was observed in 5–11% of placebo-treated controls [1,2].

In children with DS, the underlying genetic pathology (*SCN1A* deficiency) and progressive developmental delay resulting from the evolving epileptic encephalopathy may contribute to pathologies beyond seizures [11], and these pathologies could be exacerbated further by poor nutrition [11]. Underlying endocrine dysfunction occurs in some patients with DS, suggesting that DS pathophysiology may involve more systems than was previously reported [7]. Impaired growth in children is defined by height-for-age greater than 2 standard deviations below the standards set by the World Health Organization's Child Growth Standards [7,12]. In a recent study of 68 patients with DS, Eschbach reported decreases in height and weight *Z*-scores of ~0.1 standard deviation (SD) for every 1-year increase in age [7]. *Z*-score expresses weight-for-age and height-for-age as the number of SDs (*Z*-score) below or above American Centers for Disease Control (CDC) reference growth curve mean or median values [13].

Because of fenfluramine's historical use to control weight in obese adults, the objective of this analysis was to evaluate the impact of fenfluramine on weight gain and growth in a long-term OLE, using analysis of *Z*-scores as compared to healthy age-matched controls, and, more important, as compared to age-matched patients with DS not being treated with fenfluramine.

2. Materials and methods

2.1. Study design

Patients with DS (2–18 y/o) who completed one of three phase 3 placebo-controlled clinical studies and were eligible enrolled in the OLE (Study 1503: NCT02823145) [10]. Regardless of the dose patients received during RCTs, all patients who entered the OLE started at a dose of 0.2 mg/kg/day and were titrated to effect (0.2–0.7 mg/kg/day fenfluramine) [10]. The maximum daily dose allowed during the OLE was 26 mg/day, except if patients were receiving concomitant stiripentol, in which case, the maximum daily dose was 0.4 mg/kg/day but did not exceed 17 mg/day. At database lock, height and weight data were extracted for patients at OLE baseline, at Month 12, and at Month 24.

This study complied with current International Council for Harmonisation Good Clinical Practice guidelines, as described in International Council for Harmonisation Topic E6 Guidelines. The protocol was approved by applicable regulatory authorities and an independent ethics committee or institutional review board at each participating institution. All patients or their legal representatives provided written informed consent before enrollment.

2.2. Statistical analysis

Z-score analyses assessed the potential impact of fenfluramine on growth at OLE baseline, at Month 12, and at Month 24. *Z*-scores were determined by the Boston Children's Hospital algorithm using height, weight, age, gender, body surface area, and body mass index (BMI) (http://zscore.chboston.org). Growth rates were estimated as described [7]. Briefly, measurements for longitudinal height and weight were transformed to age- and sex-specific *Z*-scores based on CDC 2000 growth charts. Height and weight *Z*-scores were analyzed in separate mixed-effect models for repeated measures (MMRMs) with a random intercept and slope for age with unstructured covariance. Each subject's predicted mean height and weight were transformed to their corresponding percentiles of standard normal distribution and were plotted versus age. MMRM estimated changes in height and weight over time. Percentiles were calculated by transforming predicted mean *Z*-scores, and individual patient data were plotted relative to CDC height and weight norms on published growth charts [13]. All analyses were conducted in the Statistical Analytical Systems (SAS) environment (Cary, NC, ver. 9.4).

3. Results

3.1. Patients

At the time of analysis (October 14, 2019), 279 patients were treated with fenfluramine for ≥12 months and 128 patients were treated with fenfluramine for ≥24 months. Evaluable patients had height and weight data available for analysis at baseline (i.e., the start of the OLE) and at Month 12 ($N = 262$) or Month 24 ($N = 110$). More patients in both groups were male (53%–54%). At baseline, both groups were comparable in mean age (10 years), weight (31–33 kg), height (129–131 cm), and BMI (18 mg/m^2) (Table 1). The most common antiseizure medications (ASMs) in the ≥12-month group were valproate (74%), clobazam (70%), stiripentol (25%), topiramate (25%), levetiracetam (23%), and clonazepam (11%). The most common ASMs were comparable in the ≥24-month group (Table 1). As expected, fewer patients were taking concomitant stiripentol in the ≥24-month group (15%) than in the ≥12-month group (25%). Patients entered the OLE on a rolling basis as they exited the phase 3 studies. Concomitant stiripentol was an exclusion criterion in the earliest study and an inclusion criterion in the second study. Thus, fewer patients taking concomi-

Table 1
Baseline characteristics for evaluable patients with data at baseline and after ≥12 months or ≥24 months of fenfluramine treatment.

	≥12 months (n = 262)	≥24 months (n = 110)[a]
Sex, n (%)		
Female	120 (46)	52 (47)
Male	142 (54)	58 (53)
Age		
Mean (SD)	10 (5)	10 (5)
Median (range)	10 (2–19)	9 (2–18)
Weight, kg		
Mean (SD)	33 (17)	31 (17)
Median (range)	27 (12–108)	25 (12–108)
Height, cm		
Mean (SD)	131 (23)	129 (23)
Median (range)	131 (87–196)	129 (89–181)
BMI, kg/m^2		
Mean (SD)	18 (4)	18 (4)
Median (range)	17 (12–40)	17 (12–40)
Most common concurrent ASM (≥10% of patients), n (%)		
Valproate (all forms)	194 (74)	76 (69)
Clobazam	184 (70)	70 (64)
Stiripentol[b]	66 (25)	17 (15)
Topiramate	66 (25)	28 (25)
Levetiracetam	61 (23)	27 (25)
Clonazepam	30 (11)	13 (12)

ASM, antiseizure medication; BMI, body mass index; SD, standard deviation.
[a] Patients entered the open-label extension study from one of 3 phase 3 studies on a rolling enrollment basis. At the time of analysis, more patients had completed 12 months of treatment than 24 months of treatment due to rolling enrollment—not attrition.
[b] Stiripentol was an exclusion criterion in the first (earliest) and third (latest) studies; stiripentol was an inclusion criterion in the second (later) study.

tant stiripentol had reached 24 months in the OLE at the time of data analysis.

3.2. Z-score analyses

Relative to the reference population, fenfluramine treatment for ≥12 months or ≥24 months resulted in minimal impact on height or weight over time in patients with available data (Table 2). Height and weight Z-scores were also analyzed by three fenfluramine dose groups (0.2–<0.3 mg/kg/day, 0.3–<0.5 mg/kg/day, and 0.5–0.7 mg/kg/day), averaged over time (Table 3). No substantial dose-dependent changes from baseline were observed at Month 12 nor at Month 24 in any dose group. Predicted height and weight percentiles over time were plotted based on CDC growth chart height and weight norms (Fig. 1) [13]. Differences in Z-scores for height and weight over time were minimal for patients treated with fenfluramine and matched published predictions for patients with DS [7]. In MMRM models, patients with ≥12 months (N = 262) of fenfluramine treatment had an estimated change in Z-score per year of −0.056 for height and −0.166 for weight (Fig. 2). For patients with data at all three time points (baseline, 12 months, and 24 months; N = 110), estimated changes in Z-score per year were −0.025 for height and −0.188 for weight.

Predicted 0.5-, 1-, and 2-year height and weight for a child started on fenfluramine at age 8 were compared with published data in patients with DS whose regimens did not include fenfluramine [7] (Fig. 2). Predictions were based on changes in Z-score per year in MMRM models at ≥12 months (N = 262) of fenfluramine treatment. Estimates were based on a starting weight of Z = −0.09 (weight) and Z = −0.45 (height) for an 8-year-old child (data from Eschbach 2017). Predictions were estimated from CDC growth curves using Z-score predictions of −0.10/yr for height and −0.09/yr for weight (as published in Eschbach et al., for patients with DS) or rates predicted by MMRM models for 1-year fenfluramine data (Z = −0.056/yr for height; Z = −0.166/yr for weight). Results for patients taking fenfluramine were similar to 2-year predictions based on Eschbach 2017 height and weight data for children with DS (Fig. 2). Comparable results were obtained with 2-year fenfluramine data (Z = −0.025/yr for height; Z = −0.188/yr for weight; data not shown).

Table 2
Summary of Z-scores for height and weight after ≥12 months or after ≥24 months of fenfluramine treatment.

	Z-score height	Z-score weight
≥12 months, N	279	
Baseline (n = 271)	−0.7 ± 1.2	−0.4 ± 1.5
Month 12 (n = 267)	−0.8 ± 1.3	−0.8 ± 1.4
Change from baseline to Month 12 (n = 262)	−0.1 ± 0.4	−0.4 ± 0.6
≥24 months, N	128	
Baseline (n = 123)	−0.7 ± 1.2	−0.5 ± 1.5
Month 24 (n = 115)	−0.7 ± 1.2	−1.0 ± 1.5
Change from baseline to Month 24 (n = 110)	0.0 ± 0.5	−0.5 ± 0.7

Data show mean ± standard deviation (SD).

3.3. Managing weight loss and decreased appetite

Standard clinical practice was followed to manage weight loss and decreased appetite in these patients. Table 4 summarizes interventions provided for patients who presented with weight loss and/or decreased appetite. Dietary interventions and adjustments in concomitant ASM doses were the interventions most commonly reported.

4. Discussion

In three randomized placebo-controlled trials, fenfluramine has demonstrated profound clinically meaningful reductions in convulsive seizure frequency, which, in open-label trials, show a durable and sustained effect [1-3]. Before its use in epilepsy, fenfluramine had been approved and prescribed for weight loss in adult obese patients. Because patients with DS often have poor appetite and have been reported to have short stature and growth delay [7], monitoring the effects of fenfluramine on weight and growth of patients with DS was an important element of the extensive safety monitoring described in the phase 3 program. Results of this study demonstrate that long-term treatment with fenfluramine had minimal impact on the growth of patients with DS, as demonstrated by differences in Z-score for both height and weight at baseline and at the end of 12 months and 24 months of treatment. Changes in Z-scores for height and weight were consistent with prior literature [7], suggesting that fenfluramine treatment did not further impair growth and development in these children with DS.

With increasing age, patients with DS become increasingly divergent from normal growth curves for each age group, as reported in historical controls [7]. Changes in Z-scores for every year of age were −0.01 for height and −0.09 for weight in this recent study of growth in children with DS [7]. Growth abnormalities in children with DS may not be attributable to weight loss alone; in fact, Eschbach et al found that height failure started at a younger age than weight failure and thus concluded that this pattern refutes the possibility that insufficient caloric intake is causative. Eschbach et al found endocrine dysfunction in some patients, including low insulin-like growth factor-1 (IGF-1) and low testosterone [7]. A recent survey of caregivers of patients with DS supports these conclusions [6], with up to 68% reporting appetite

Table 3
Summary of *Z*-scores for height and weight by fenfluramine dose group at Month 12 and at Month 24.

	FFA average dose level (0.2–<0.3 mg/kg/day)		FFA average dose level (0.4–<0.5 mg/kg/day)		FFA average dose level (0.5–<0.7 mg/kg/day)	
	Z-score height	*Z*-score weight	*Z*-score height	*Z*-score weight	*Z*-score height	*Z*-score weight
Change from baseline to Month 12	−0.1 ± 0.4	−0.3 ± 0.6	−0.1 ± 0.4	−0.3 ± 0.6	−0.1 ± 0.5	−0.5 ± 0.6
N	63		91		108	
Change from baseline to Month 24	−0.0 ± 0.6	−0.3 ± 0.7	0.1 ± 0.6	−0.5 ± 0.7	0.0 ± 0.5	−0.6 ± 0.7
N	21		31		58	

Change from baseline in mean ± SD.
FFA, fenfluramine; SD, standard deviation.

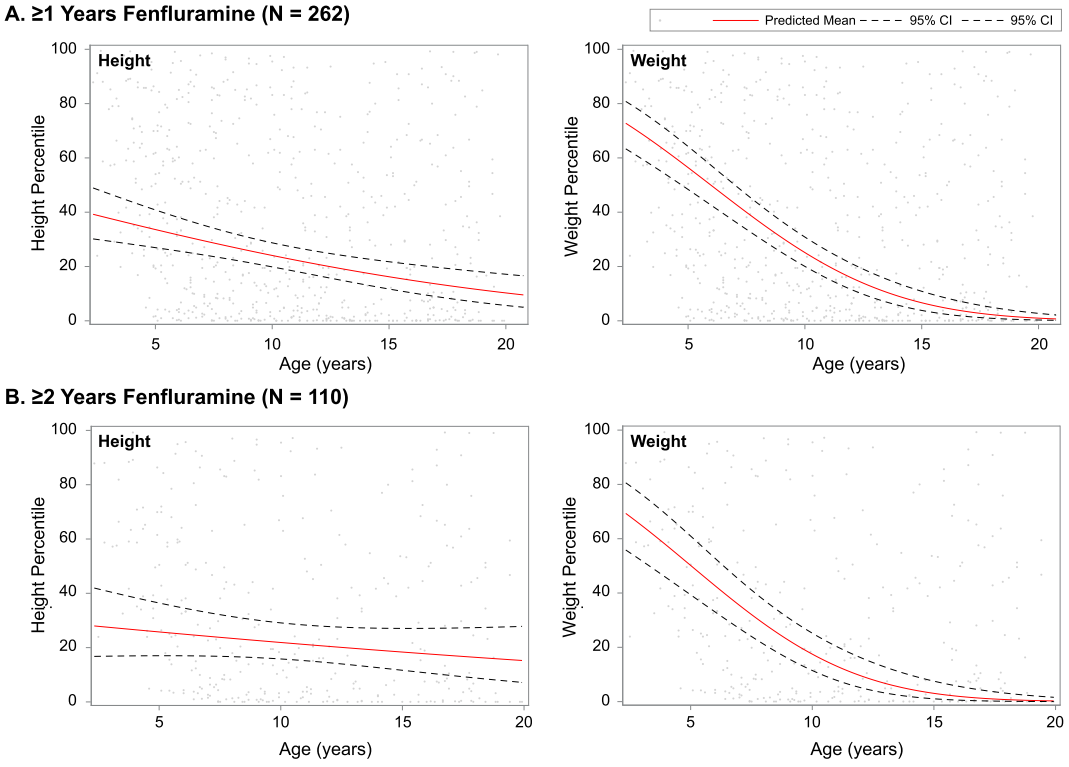

Fig. 1. Predicted mean height and weight percentiles by age over time after (A) ≥1 year or (B) ≥2 years of fenfluramine treatment. Population percentiles over time are based on American CDC growth charts. Each point represents an individual patient measurement. Predicted means (red lines) and upper and lower 95% CIs (dashed black lines) are calculated by mixed-effect models for repeated measures over time. CDC, Centers for Disease Control and Prevention; CI, confidence interval.

disturbances in patients under their care. Further, approximately 9% reported delayed puberty, and an additional 9% reported precocious puberty. Delayed puberty was also reported with greater prevalence in patients with *SCN1A* mutations (33%) [7], a pathogenic variant that is present in up to 85% of cases with DS [14].

Long-term ASM use has been associated with nutrient deficiencies that may affect normal growth in those with epileptic encephalopathies. Patients with DS may be taking multiple concurrent ASMs and still treatment in those patients may fail to achieve adequate seizure control [15]. Topiramate, stiripentol, ethosuximide, and high-dose valproic acid—common concomitant ASMs for patients with DS—have been associated with anorexia [7,16,17].

Our anthropometric data after 1–2 years of fenfluramine treatment suggest that fenfluramine-treated patients experience growth comparable to other children with DS. Notably, patients who reported decreased appetite did not necessarily lose weight in the pivotal phase 3 clinical trials. Although some patients in the pivotal studies experienced decreased appetite and weight loss [1], many experienced resolution of this weight loss with long-term treatment. Recent reports on fenfluramine use at median treatment duration of 256 days (~0.7 years) [10] and for up to 3 years further support our findings and suggest that most patients who initially lose appetite or weight eventually stabilize over time [10].

Given that the underlying pathology of DS contributes to deficits and growth abnormalities, managing growth and endocrine issues is a frequent concern among clinicians and parents/caregivers: 39% (87/223) of caregivers surveyed reported failure to thrive, slow growth, being underweight, and small stature as concerns [6]. Decisions on managing a patient's nutrition must balance seizure risk with optimal nutritional requirements. Decreased appetite is seen with other ASMs [7,16-18], but common dietary interventions or ASM adjustments can be used to manage these

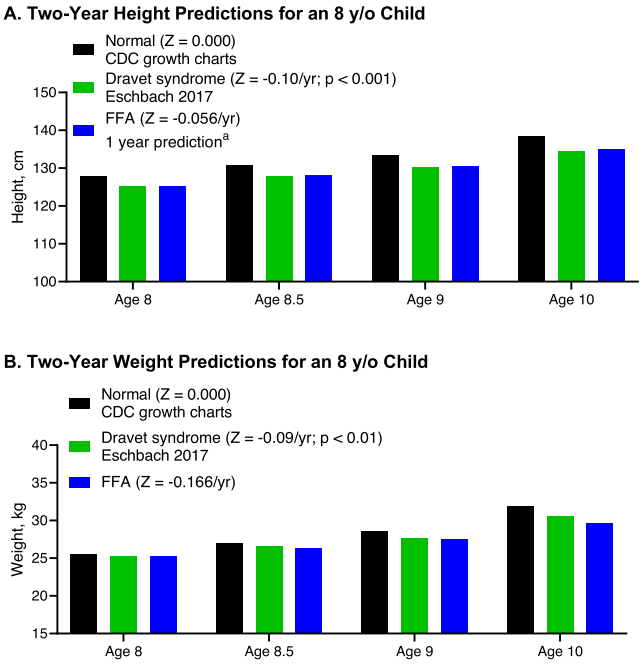

Fig. 2. Predicted (A) 2-year height and (B) 2-year weight for an 8-year-old child started on fenfluramine are comparable to published data for patients with DS (Eschbach 2017). *p* values in Eschbach 2017 were calculated from a linear mixed regression model (patients with DS versus healthy population based on CDC growth curves). [a]Changes in *Z*-score per year are based on MMRM models at ≥12 months of FFA treatment. CDC, Centers for Disease Control and Prevention; DS, Dravet syndrome; FFA, fenfluramine; MMRM, mixed-effect model for repeated measures.

Table 4
Management of weight loss and decreased appetite.

Dietary Interventions
Increase calorie-dense foods
Eliminate low-fat versions of foods (e.g., whole milk vs skim milk)
Increase caloric consumption
Add nutritional supplements (e.g., PediaSure, Boost)
Consider temporary nasogastric tube with medication adjustments if weight loss persists
Concomitant ASM Adjustments
Monitor therapeutic levels of ASMs
Monitor for increasing valproate levels and adjust for seizure control balanced with weight/growth
Reduce doses of ASMs that cause anorexia while maintaining appropriate level of seizure control

Data were provided by study investigators and reflect standard clinical practice for managing abnormalities in weight and growth.
ASM, antiseizure medication.

occurrences (Table 4). For example, clinicians can consider increasing calorie-dense foods and transitioning away from low-fat versions of everyday foods (e.g., skim milk) while incorporating high-fat alternatives (e.g., whole milk). Further, applying more butter to food items can increase caloric consumption. It should be noted that insulin is required for fat deposition. Thus, it has been recommended that pediatric patients with poor weight gain can benefit from high glycemic refined carbohydrates for fat deposition. However, this might not be suitable for patients on a ketogenic diet for seizure control and could provoke loss of ketosis and the possibility of worsening seizures. Therefore, especially for children on a ketogenic diet, some dietitians recommend that daily dietary supplementation with 1–2 cans of a nutritional supplement (e.g., PediaSure, Boost) can also be helpful. Decreased appetite can be further managed by reducing doses of background (concomitant) ASMs that can cause anorexia, particularly if they appear to have been associated with insufficient seizure control or are used at higher doses. If weight loss persists, gastrostomy tube placement may need to be considered.

During the entire phase 3 program, dropout rates related to decreased appetite or weight loss were under 1% (2/330, 0.6%; 1/330, 0.3%, respectively). Early loss of appetite and weight loss tended to resolve over time, with approximately 40% of patients who had lost 7% or more of their body weight stabilizing during the OLE [10].

This study has limitations. First, the study relies on mathematical, model-based projections of anthropometric data over time based on data obtained in clinical trials. Real-world clinical scenarios over time may vary from projections. Second, the study relies on population-level data based on CDC growth curves. Changes in growth observed in the population of patients with DS may be due to the *SCN1A* deficiency itself or to changes related to epileptic encephalopathy that develop over time. As fenfluramine is investigated in other patient populations (e.g., Lennox-Gastaut syndrome, CDKL5 deficiency disorder), comparative anthropometric studies may provide important insight into its potential differential effects on specific genetic disorders. Some of the concurrent ASMs taken by ≥10% of patients in this study are known to cause weight loss or decreased appetite (e.g., topiramate, stiripentol, high-dose valproate). Subanalyses of patients on individual or combinations of ASMs were not conducted due to small sample size with inadequate statistical power. Finally, our study measures only weight and height as surrogate markers for failure to thrive. Additional metrics, such as growth hormone concentrations, may be considered for analysis in future studies.

5. Conclusions

Our data demonstrate that long-term treatment with fenfluramine in patients with DS resulted in minimal impact on weight and growth over that expected in a population of patients with DS. The underlying pathogenesis of DS predisposes these children to endocrine abnormalities leading to failure to thrive. Anthropomorphic parameters should be monitored, and appropriate interventions taken, during routine clinical care of these patients. However, our data support the finding that fenfluramine treatment for ≥1 year or for ≥2 years does not exacerbate further growth inhibition in these patients.

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Author contributions

AGN, JS, BC, EW, OD, RN, KGK, MSP, TP, RD, ARG, GF, and BSG conceptualized the study and contributed to design. ML, AA, RMC, ARG, GF, and BSG contributed to data analysis. All authors contributed to data interpretation. ARG drafted the manuscript. All authors reviewed and critically revised the content and approved the final draft.

Declaration of competing interests statement

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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