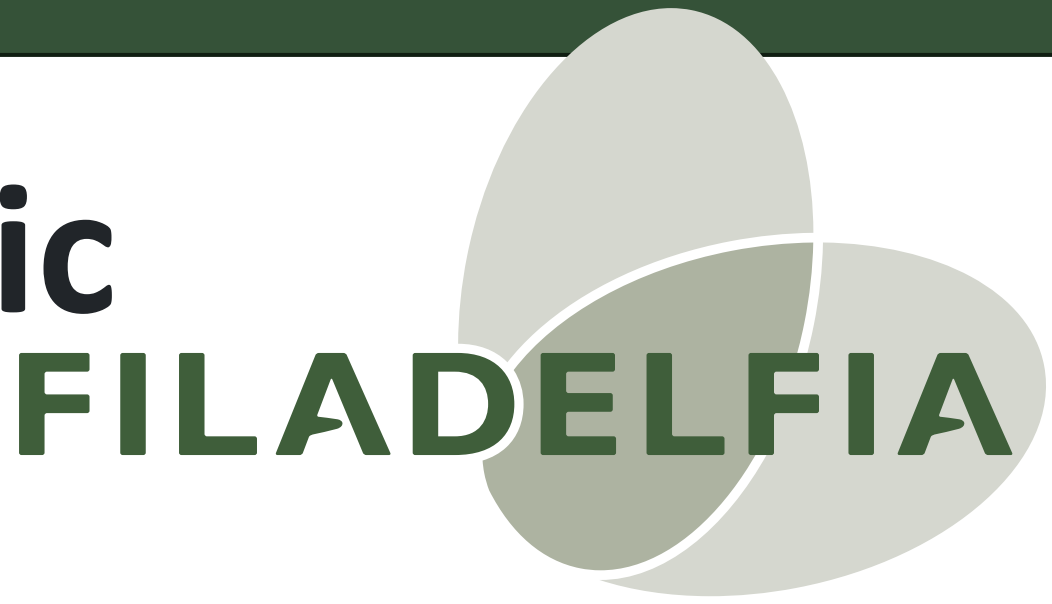


Prospective evaluation of fenfluramine use in a cohort of pediatric and adult patients with Dravet syndrome



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BACKGROUND

Dravet syndrome (DS) is a developmental and epileptic encephalopathy (DEE) characterized by multiple seizure types, intellectual disability, behavioral difficulties, psychiatric comorbidities, poor sleep patterns, and progressive gait impairment.

Fenfluramine is approved for the treatment of seizures associated with DS in the United States,¹ European Union,² United Kingdom,³ Japan,⁴ and Israel⁵ in patients ≥2 years of age. Fenfluramine significantly reduces seizure frequency in patients with DS, and some evidence suggests a beneficial effect on non-seizure parameters.⁶ Real-world data (both non-seizure and seizure outcomes) in adults with DS are particularly limited.

Objective

To describe cognition and adaptive behavior in both adult and pediatric patients with DS, and the first interim results of fenfluramine-associated treatment effect on seizure frequency and non-seizure outcomes.

Parameters at baseline	Adult Patients (n = 5)	Pediatric Patients (n = 5)
Age at last follow up, median years (range)	33 (25–47)	7 (5–19)
Female, n (%)	2 (40)	2 (40)
Verified SCN1A loss-of-function variant, n (%)	5 (100)	5 (100)
Age at DS diagnosis, median years (range)	22 (9–39)	1.5 (1-3.5)
Number of previously tried ASMs, median (range)	10 (8–12)	4 (2-7)
Grade of intellectual disability at baseline	Profound 3/5 (60%) Severe 2/5 (40%)	Normal 1/5 (20%) Mild 2/5 (40%) Moderate 2/5 (40%)
Previous use of sodium-channel blockers, n (%)	5 (100)	0 (0)
Number of concomitant ASMs at baseline, median (range) • Patients treated with stiripentol, n (%)	3.5 (3–4) • 5 (100)	3 (2-4) • 2 (40)
Discontinuations of fenfluramine, n (%) • Adverse effects, n • Lack of efficacy, n	3 (60) • 2 • 1	2 (40) • 0 • 2
Parameters at last follow-up	n = 2	n = 3
Fenfluramine treatment period, median months (range)	16 (15-17)	11.5 (5–31)
Median dose of fenfluramine, mg/kg/day (range)	0.16 (0.15-0.17)	0.45 (0.21-0.7)
Number of concomitant ASMs, median (range) • Patients treated with stiripentol, n (%)	2.5 (2-3) • 1 (50)	1 (1-2) • 0 (0)
Median reduction of GTCS, % (range)	74% (68-80)	100% (100)

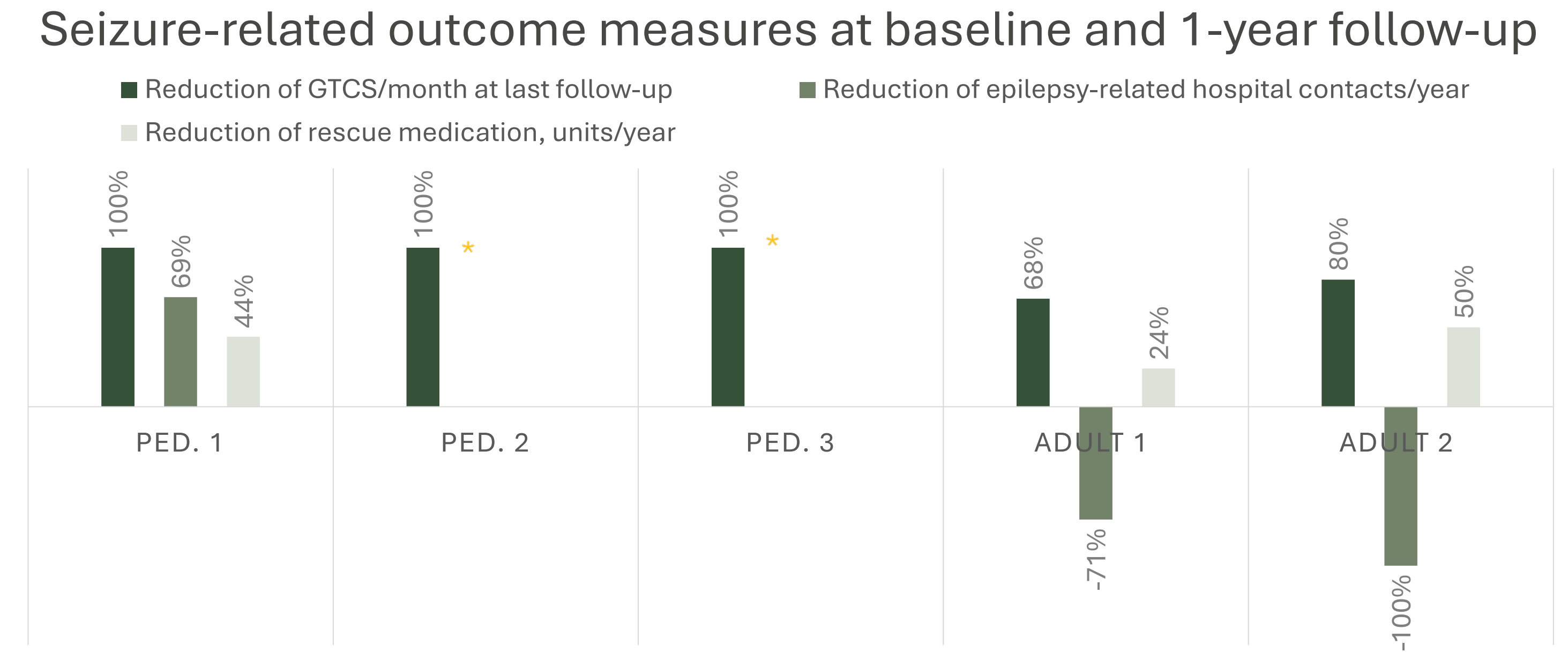


Figure 1. Reduction of epilepsy-related hospital contacts per year, units of rescue medication per year, and mean number of GTCS/month from the initiation of fenfluramine treatment to last follow-up. A marked reduction of monthly GTCS and yearly amount of rescue medication were observed in both pediatric and adult patients. Epilepsy-related hospital contacts increased for both treated adults due to the need for closer follow-up on treatment. *12-month treatment not yet reached. Thus, the reduction in the annual number of epilepsy-related hospital contacts could not be calculated. GTCS: Generalized tonic-clonic seizures. Ped.: Pediatric patient.

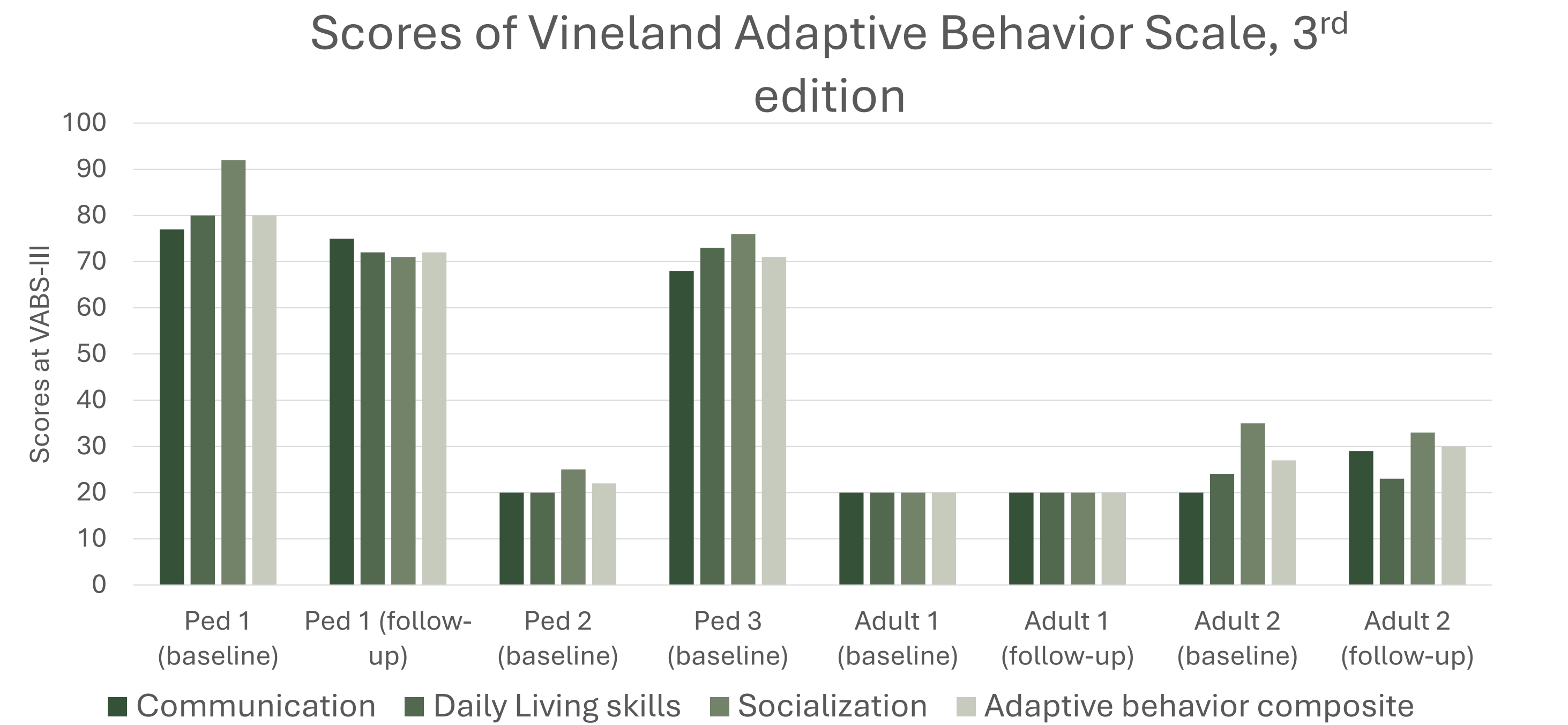


Figure 2. Adaptive Behavior, measured by the Vineland Adaptive Behavior Scale III, in patients with DS at baseline and 1-year follow-up when reached. Higher scores indicate better adaptive behavior and are classified as follows: “Adequate” (domain and ABC Standard Scores of 86–114), “moderately low” (domain and ABC Standard Scores of 71–85), and “low” (domain and ABC Standard Scores of 20–70). Data from patients who discontinued treatment are not included. ABC: adaptive behavior composite, DS: Dravet syndrome.

METHODS

- Prospective evaluation of adult and pediatric patients with a clinical diagnosis of DS and SCN1A pathogenic variant treated with fenfluramine between August 2023 and December 2025
- Neuropsychological evaluation was performed at baseline (pre-fenfluramine) and after 12 months of treatment. The evaluations included:
 - Adaptive behavior scores:** Vineland Adaptive Behavior Scales (VABS-III)
 - Cognitive score level:** Bayley Scales of Infant and Toddler Development (Bayley-IV), or the Wechsler Intelligence Scales (WIS) adapted to age
- Seizure frequency was collected from seizure diaries as reported by caregivers; change from baseline in frequency of generalized tonic-clonic seizures (GTCS) is reported

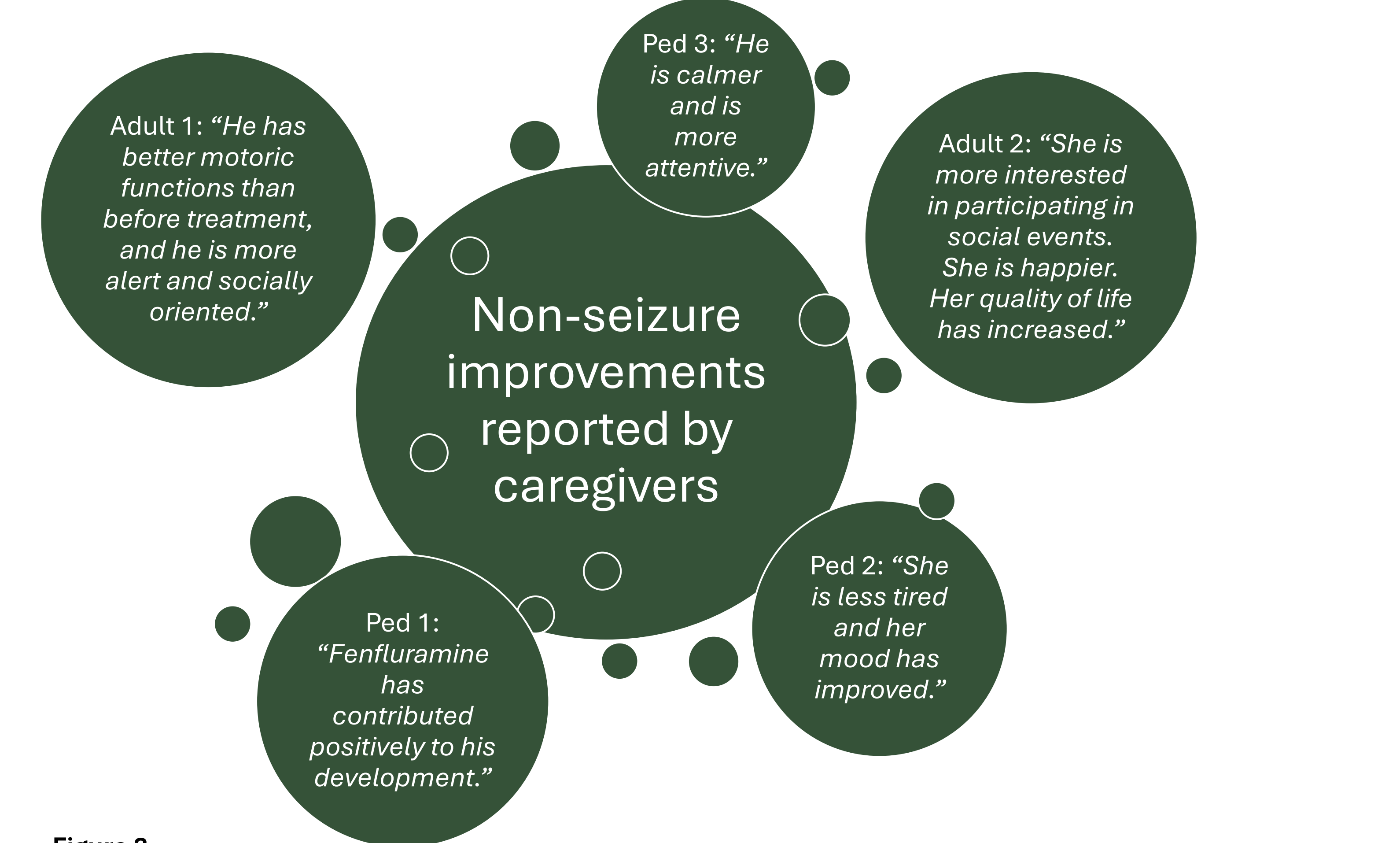


Figure 3. Non-seizure improvements observed by caregivers after initiation of treatment with fenfluramine. Some were not quantifiable by the VABS-III at follow-up evaluations.

CONCLUSIONS

The interim results from this small prospective cohort of adult and pediatric patients with DS treated with fenfluramine suggest:

Intellectual capacity

- Baseline intellectual capacity in the adult cohort (n = 5) was in the severe–profound range, whereas the five pediatric patients were in the normal–mild range.
- Follow-up evaluations indicated that intellectual capacity remained unchanged since initiation of fenfluramine.

Adaptive behavior

- Baseline scores ranged from 20–35 across all domains in adult patients and from 20–95 in pediatric patients.
- Follow-up evaluations showed improvements in some domains, consistent with non-seizure-related benefits reported by caregivers.

GTCS

- A reduction in GTCS frequency within the first 6 months of adding fenfluramine to standard-of-care treatment was observed in both adult and pediatric patients
- Epilepsy-related hospital contacts per year decreased by 69% after one year of treatment in one pediatric patient. However, the need for close monitoring of treatment resulted in an increase in hospital contacts among adult patients.
- The yearly amount of rescue medication decreased by 24–60% among all participants who reached the 1-year follow-up evaluation.

PATIENT IMPACT

- Data suggest that DS is associated with gradual decline in intellectual capacity and adaptive behavior over the disease course
- Fenfluramine is associated with non-seizure improvements reported by caregivers
- A reduction in monthly GTCS and yearly amount of rescue medication was observed in adult and pediatric patients with fenfluramine treatment

LIMITATIONS & FUTURE STEPS

- Limitations
 - The small cohort and treatment of the most severe adult patients might lead to selection bias, limiting the overall conclusions
- Yearly neuropsychological evaluation will determine if fenfluramine might improve intellectual capacity and/or adaptive behavior measured by VABS-III