Non-seizure benefits of long-term fenfluramine treatment in pediatric 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 problems, 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 Israel[5] 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]

Objective

To report an interim analysis of the impact of long-term fenfluramine on seizure frequency, cognition, and adaptive behavior in a Danish cohort of pediatric patients with DS.

METHODS

- Retrospective evaluation of pediatric patients with a clinical diagnosis of DS and *SCN1A* pathogenic variant treated with fenfluramine between February 2017 to October 2023
- Findings are contextualized using outcomes from a Swedish cohort not treated with fenfluramine (without formal statistical comparison)[7]
- Seizure frequency was collected from seizure diaries as reported by caregivers; change from baseline (pre-fenfluramine) in frequency of generalized tonic-clonic seizures (GTCS) is reported
- Incidence of valvular heart disease (VHD) or pulmonary arterial hypertension (PAH) is reported
- Neuropsychological evaluation was performed once and included:

Cognitive score level

Bayley Scales of Infant and Toddler Development (Bayley-IV), or the Wechsler Intelligence Scales (WIS) adapted to age

Adaptive behavior scores

Vineland Adaptive Behavior Scales (VABS-III)

RESULTS

Parameters	Danish patients treated with fenfluramine (n = 20)	Swedish patients[7] not treated with fenfluramine (n = 42)
Age at last follow-up, median years (range)	12.7 (4–23)	9 (1–19)
Female, n (%)	8 (40)	19 (45)
Proved *SCN1A* variant, n (%)	20 (100)	40 (95)
Age at DS diagnosis, median years (range)	1.3 (0.7–14)	2.4 (0.5–10)
Number of previously tried ASMs, median (range)	5.5 (3–14)	6 (1–20)
Previous use of sodium-channel blockers, n (%)	5 (25)	26 (62)
Fenfluramine treatment period, mean months (range)	55 (21–99)	N/A
Mean dose of fenfluramine at last follow-up, mg/kg/day (range)	0.53 (0.18–0.8)	N/A

Table 1. *Danish and Swedish[7] key cohort descriptions.* No Danish patients were treated with sodium-channel blockers at the time of assessment. ASM: anti-seizure medication, DS: Dravet syndrome, N/A: not applicable.

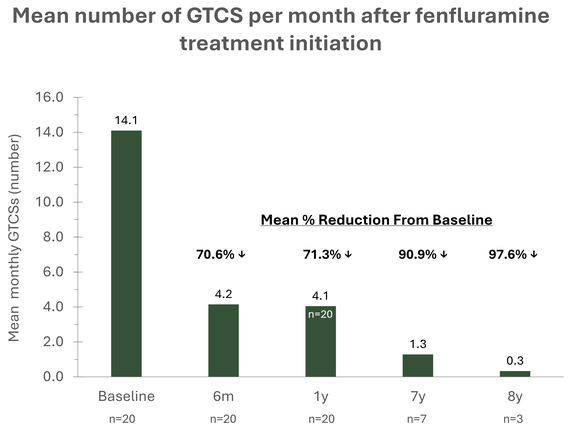

Figure 1. *Danish cohort mean number of GTCSs per month at last month prior to indicated time.* The monthly frequency of GTCSs was collected by electronic medical records and seizure. After 6 months of fenfluramine treatment, a 70.6% reduction was observed which continued to increase throughout the study period. Time points are displayed at equal intervals for readability, though actual time between them varies. GTCS: generalized tonic-clonic seizures, m: months, y: years.

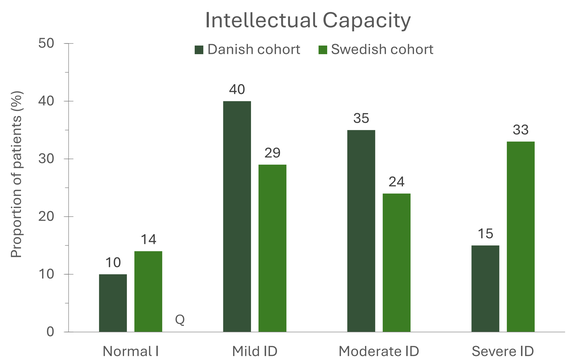

Figure 2. *Intellectual function assessment of patients with DS treated with fenfluramine (Danish cohort) and without fenfluramine (Swedish cohort[7]).* Patients were evaluated by Bayley-IV or WIS adapted to age to determine intellectual capacity. Normal IQ: 70+, Mild ID: 50–69; Moderate ID: 35–49; Severe ID: 20–34. DS: Dravet syndrome, ID: intellectual disability.

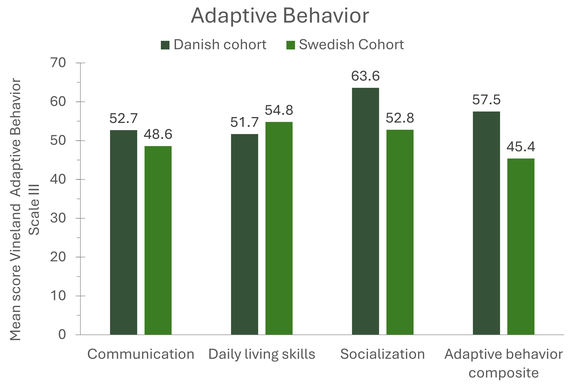

Figure 3. *Adaptive Behavior, measured by Vineland Adaptive Behavior Scale III, in patients with DS treated with fenfluramine (Danish cohort) and without fenfluramine (Swedish cohort[7]).* Higher scores indicate better adaptive behavior and are classified as follows: "High" (domain and ABC Standard Scores of 130–140), "moderately high" (domain and ABC Standard Scores of 115–129), "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). ABC: adaptive behavior composite, DS: Dravet syndrome.

CONCLUSIONS

In Danish pediatric patients with DS treated with standard of care including fenfluramine:

GTCS reduction
- 71.3% after 1 year (N=20)
- 97.6% long-term reduction (8 years, n=3)

VHD/PAH
- No cases of VHD or PAH were observed

Intellectual capacity
- **50%** normal / mild intellectual disability
- **43%** normal / mild intellectual disability (without fenfluramine, Swedish cohort)
- **15%** severe intellectual disability
- **33%** severe intellectual disability (without fenfluramine, Swedish cohort)

Adaptive behavior composite
- **57.5** mean value
- **45.4** mean value (without fenfluramine, Swedish cohort)

Socialization
- **63.6** mean value
- **52.8** mean value (without fenfluramine, Swedish cohort)

PATIENT IMPACT

At the last follow-up, these results suggest that fenfluramine added to standard of care treatment:
- May reduce GTCS burden over time
- May improve intellectual capacity
- May improve adaptive behavior
- May improve socialization skills

LIMITATIONS & FUTURE STEPS

- Limitations:
  - Baseline data were not available
  - Swedish cohort patients who did not receive fenfluramine were more numerous, diagnosed later in life and received contraindicated ASMs; thus, no formal comparisons were made between the two cohorts
  - One-fourth of Danish patients had previously received sodium-channel blockers, compared to >50% of untreated Swedish patients
  - While Danish cohort size is limited, it includes all patients with DS treated with fenfluramine in Denmark, providing a valuable complement to existing evidence
- Additional analyses of non-seizure and seizure outcomes are needed to delineate the potential long-term effect of fenfluramine treatment on these parameters

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