

Association of Fenfluramine Treatment and Everyday Executive Function in Preschool-Aged Children With Lennox-Gastaut Syndrome

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Background

- Lennox-Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy characterised by multiple types of treatment-resistant seizures, electroencephalogram abnormalities, neurodevelopmental delay, and profound cognitive and often behavioural impairments.^{1,2}
- Everyday executive function (EEF) is an important non-seizure domain for LGS patients and their caregivers and families.³
- A post hoc analysis of adults (18-35 years of age) with LGS in a randomised controlled trial (RCT) and its open-label extension (OLE) demonstrated caregiver-reported improvement in EEF as measured by Behavior Rating Inventory of Executive Functioning® (BRIEF®) following fenfluramine treatment.⁴
- There is a lack of published BRIEF® data in children with LGS.

Objective

- To evaluate fenfluramine-associated EEF changes in preschool-aged children with LGS.

Methods

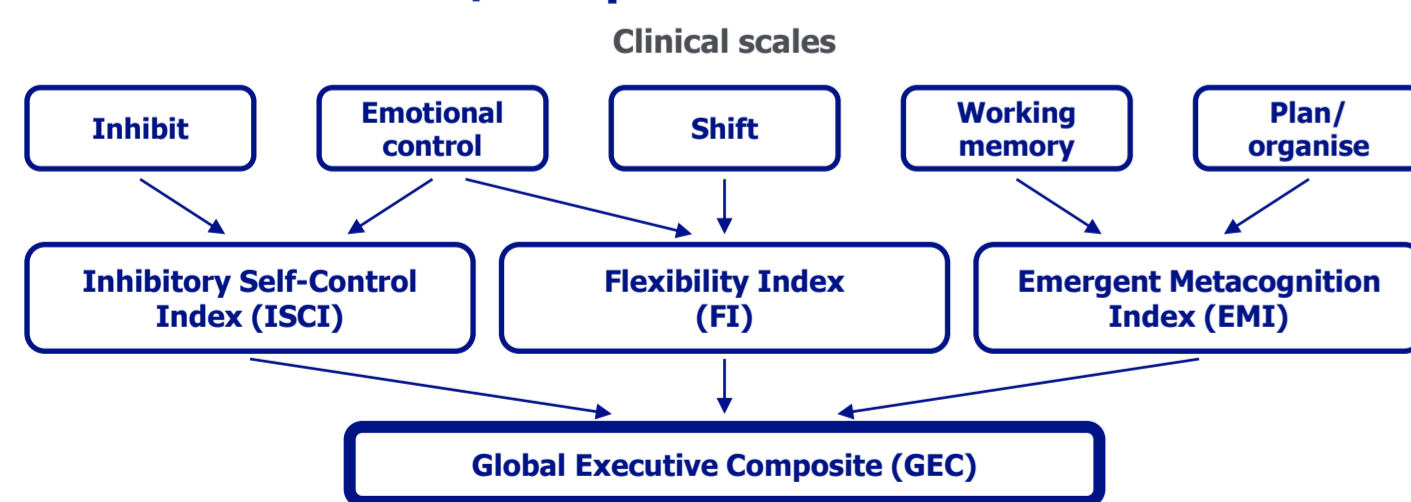
STUDY DESIGN

- In the 14-week RCT (EP0214; NCT03355209), patients with LGS (2-35 years of age) were randomised to receive fenfluramine 0.7 mg/kg/day (maximum 26 mg/day), fenfluramine 0.2 mg/kg/day, or placebo.
- Patients who completed the RCT were eligible to enter the OLE.
- Patients who received placebo in the RCT were transitioned to fenfluramine 0.2 mg/kg/day and flexibly titrated up to 0.7 mg/kg/day (maximum 26 mg/day) based on effectiveness and tolerability after month 1.

ANALYSES

- In this post hoc analysis, preschool-aged children (2 to <6 years of age) with caregiver-completed BRIEF®-Preschool Version (BRIEF®-P) at RCT baseline and:
 - RCT end of study (day 99) were included in the RCT analyses.
 - OLE month 12 were included in the OLE analyses.
- BRIEF®-P Indexes/Composite include the Inhibitory Self-Control Index, Flexibility Index, Emergent Metacognition Index, and Global Executive Composite (GEC).

BRIEF®-P Indexes/Composite



BRIEF®-P, Behavior Rating Inventory of Executive Functioning®-Preschool Version.

- BRIEF®-P raw scores were transformed into T-scores based on a normative sample according to the Professional Manual.¹
- Higher BRIEF®-P T-scores are associated with greater caregiver-perceived impairment in EEF.
- BRIEF®-P T-scores ≥ 65 are defined as potentially clinically significant and suggest difficulties in EEF.⁵
- Reliable change indexes (RCIs) were used to determine clinically meaningful improvement (RCI $\geq 90\%$ certainty) and worsening (RCI $\geq 80\%$ certainty) in T-scores from baseline.

Overview

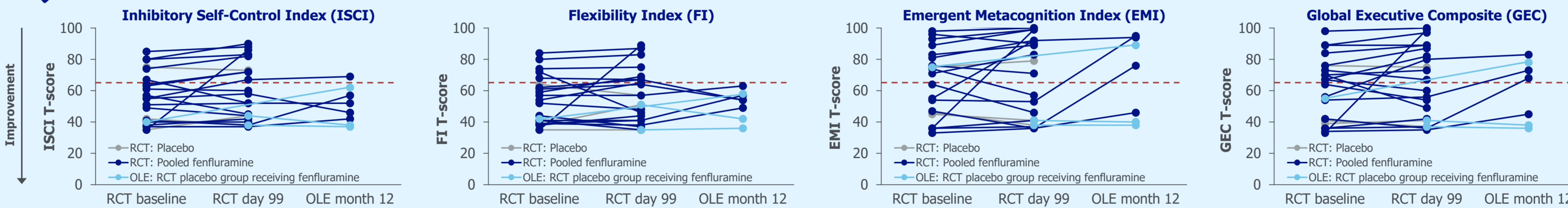
QUESTION

Does treatment with fenfluramine in preschool-aged children with Lennox-Gastaut syndrome (LGS) improve everyday executive function (EEF)?

INVESTIGATION

Post hoc analysis of a randomised controlled trial (RCT) and its open-label extension (OLE). EEF was examined via Behavior Rating Inventory of Executive Functioning®-Preschool Version (BRIEF®-P) Indexes/Composite. Preschool-aged children with LGS in the study were rated on the BRIEF®-P by caregivers; T-scores from baseline, end of RCT, and OLE month 12 were used.

RESULTS



CONCLUSIONS

The results of this post hoc analysis show the dynamics of individual patient evolutions and may suggest a degree of fenfluramine-associated EEF numerical improvement in preschool-aged children 2 to <6 years of age with LGS. However, results should be interpreted with caution due to the small sample size.

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Results

- In the RCT, 21 caregivers completed BRIEF®-P assessments at baseline and end of study.
 - Eight caregivers completed BRIEF®-P assessments at RCT baseline and OLE month 12.

Demographics and baseline characteristics

	RCT		OLE
	POOLED FFA (n=18)	PLACEBO (n=3)	FFA (n=8)
Age, mean (SD), years	3.8 (1.0)	3.0 (1.0)	3.6 (0.7) ^a
Female, n (%)	11 (61.1)	2 (66.7)	4 (50.0)
Weight, mean (SD), kg	17.2 (2.7)	16.2 (2.6)	16.6 (3.1) ^a
Baseline frequency of seizures associated with a fall^b per 28 days, median (range)	206.41 (12.0-2289.0)	374.18 (338.0-388.9)	211.50 (12.0-557.0)
Number of prior ASMs^c			
Median (range)	4.0 (1-11) ^d	7.0 (2-10)	NA
Mean (SD)	5.3 (3.3) ^d	6.3 (4.0)	
Number of concomitant ASMs			
Median (range)	3.0 (1-4)	3.0 (1-4)	3.0 (2-4)
Mean (SD)	2.6 (0.8)	2.7 (1.5)	3.0 (0.8)
Concomitant ASMs, n (%)			
Clobazam	11 (61.1)	0	4 (50.0)
Lamotrigine	7 (38.9)	0	4 (50.0)
Levetiracetam	3 (16.7)	2 (66.7)	1 (12.5)
Phenobarbital	1 (5.6)	1 (33.3)	2 (25.0)
Rufinamide	2 (11.1)	2 (66.7)	2 (25.0)
Topiramate	5 (27.8)	1 (33.3)	2 (25.0)
Valproate^f	6 (33.3)	2 (66.7)	4 (50.0)

^aAt entry into the OLE; ^bIncludes atonic, tonic, tonic/atonic, generalised tonic-clonic, and secondarily generalised tonic-clonic seizures resulting in falls; ^cASMs with a stop date prior to the first randomised dose in the RCT; ^dn=17; ^eFor RCT, ASMs reported in $\geq 25\%$ of any treatment group, and for OLE, reported in $\geq 25\%$ of patients; ^fIncludes valproate semisodium, valproate sodium, and valproic acid. ASM, antiseizure medication; FFA, fenfluramine; NA, not applicable; OLE, open-label extension; RCT, randomised controlled trial.

BRIEF®-P

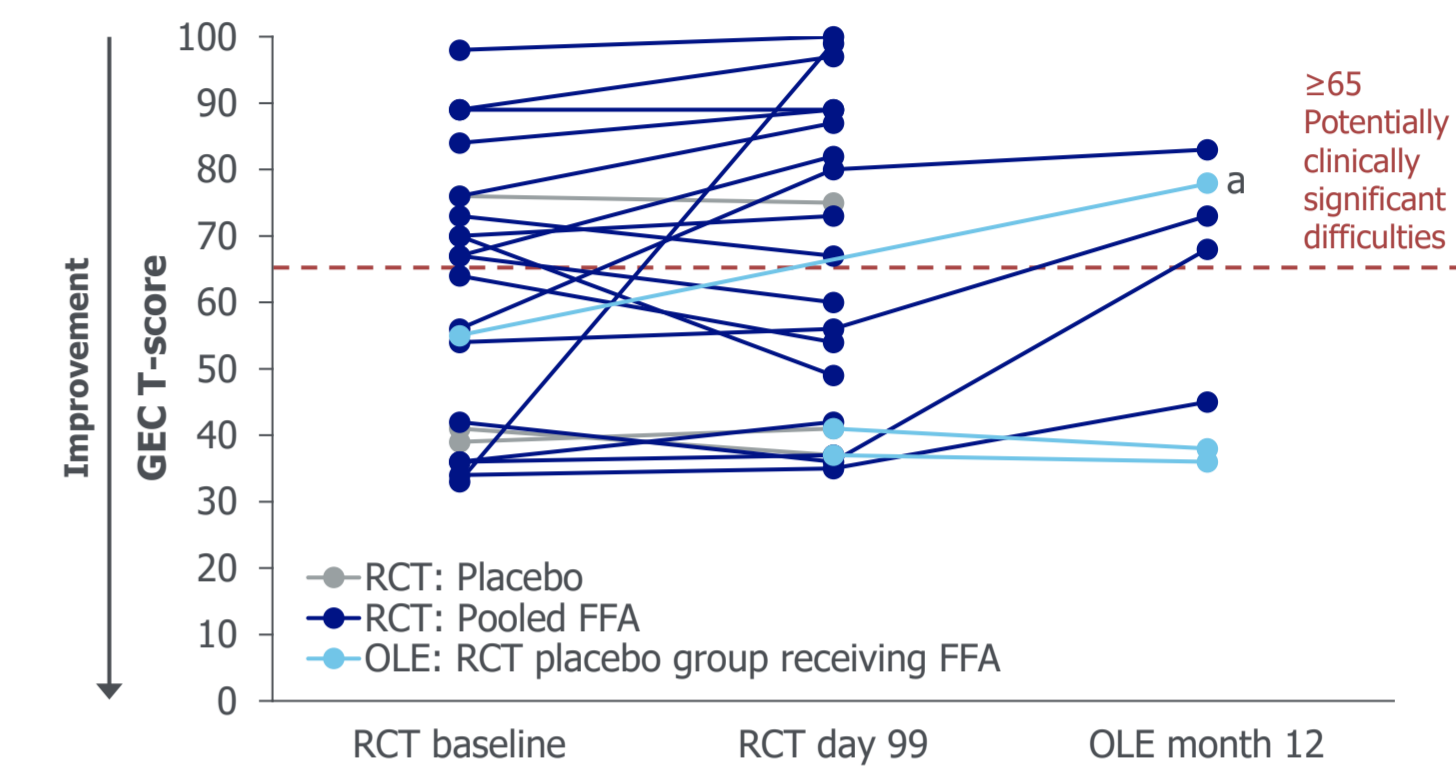
Number of patients experiencing clinically meaningful improvement and worsening from RCT baseline to RCT end of study and OLE month 12

	RCT		OLE
	POOLED FFA (n=18)	PLACEBO (n=3)	FFA (n=8)
Improved			
Inhibitory Self-Control Index	2	0	1
Flexibility Index	1	0	1
Emergent Metacognition Index	3	1	1 ^a
Global Executive Composite	3	0	0 ^a
Worsened			
Inhibitory Self-Control Index	6	1	3
Flexibility Index	4	1	4
Emergent Metacognition Index	5	0	5 ^a
Global Executive Composite	6	0	5 ^a
Stable			
Inhibitory Self-Control Index	10	2	4
Flexibility Index	13	2	3
Emergent Metacognition Index	10	2	1 ^a
Global Executive Composite	9	3	2 ^a

Patients are considered 'improved' if they have a reduction from baseline in T-score with $\geq 90\%$ RCI certainty, 'worsened' if they have an increase from baseline in T-score with $\geq 80\%$ RCI certainty, 'stable' otherwise. Higher T-scores on the BRIEF®-P are associated with greater caregiver-perceived impairment on EEF. Percentage of patients is not shown due to the low number of patients. ^an=7. BRIEF®-P, Behavior Rating Inventory of Executive Function®-Preschool Version; EEF, everyday executive function; FFA, fenfluramine; OLE, open-label extension; RCI, reliable change index; RCT, randomised controlled trial.

- In the RCT:
 - Clinically meaningful improvement on BRIEF®-P GEC was reported in 3 patients receiving fenfluramine (n=18) and in 0 patients receiving placebo (n=3).
 - Clinically meaningful worsening was reported in 6 and 0 patients, respectively.

Individual patient trajectories on GEC T-scores from baseline to RCT end of study and OLE month 12



RCT end of study is defined as day 99 of the RCT. Higher T-scores on the BRIEF®-P are associated with greater caregiver-perceived impairment on EEF. ^aThis patient had a completed BRIEF®-P at RCT baseline and OLE month 12, without a completed BRIEF®-P at RCT end of study. BRIEF®-P, Behavior Rating Inventory of Executive Functioning®-Preschool Version; FFA, fenfluramine; GEC, Global Executive Composite; OLE, open-label extension; RCT, randomised controlled trial.

- Individual trajectories of GEC T-scores showed variable responses.

Limitations

- Results should be interpreted with caution due to the small sample size.
- These data are difficult to interpret due to a lack of understanding of the natural course of EEF impairment in children with LGS.
 - Over time, patients with LGS experience developmental slowing, plateauing, or regression.² BRIEF®-P scores in children 2 to <6 years of age are therefore expected to progressively worsen over time.

Conclusions

- The results of this post hoc analysis show the dynamics of individual patient evolutions and may suggest improvement in caregiver-perceived everyday executive function in some preschool-aged children (2 to <6 years of age) with LGS.
- Additional analyses and larger samples would be needed to better understand the impact of fenfluramine on everyday executive function.

References

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