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

Amélie Lothe[1]; Delphine Breuillard[2,3]; Kelly G Knupp[4]; Patrick Healy[5]; Jayne Abraham[5]; Rima Nabbout[3,6,7]

1. UCB, Courbevoie, France
2. Necker-Enfants Malades Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Université de Paris Cité, Paris, France
3. Reference Center for Rare Epilepsies, Necker-Enfants Malades Hospital, AP-HP, Member of the European Reference Network (ERN) EpiCARE, Paris, France
4. University of Colorado, Anschutz Medical Campus, Aurora, CO, USA
5. UCB, Smyrna, GA, USA
6. Institut Imagine, U 1163, Paris, France
7. Université Paris Cité, Paris, France

OVERVIEW

QUESTION

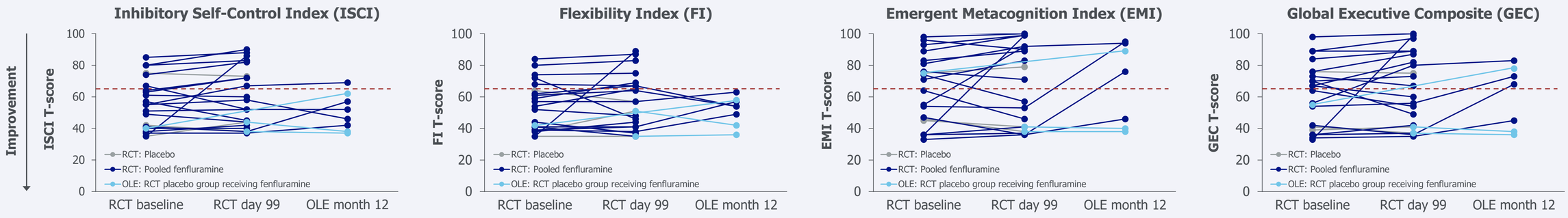
Does treatment with fenfluramine in preschool-aged children with Lennox-Gastaut syndrome (LGS) improve everyday executive function (EEF)?

INVESTIGATION

Post hoc analysis of a randomized 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

Individual trajectories of T-scores showed variable responses



Dotted lines represent T-scores of 65; values ≥65 indicate potentially clinically significant difficulties. OLE, open-label extension; RCT, randomized controlled trial.

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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Background

- Lennox-Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy characterized by multiple types of treatment-resistant seizures, electroencephalogram abnormalities, neurodevelopmental delay, and profound cognitive and often behavioral impairments.[1,2]
- Everyday executive function (EEF) is an important non-seizure domain for patients with LGS and their caregivers and families.[3]
  - A post hoc analysis of adults (18-35 years of age) with LGS in a randomized 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

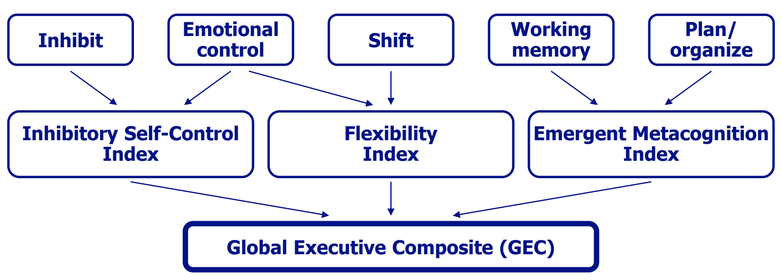
STUDY DESIGN

- In the 14-week RCT (EP0214; NCT03355209), patients with LGS (2-35 years of age) were randomized 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 ≥90% certainty) and worsening (RCI ≥80% certainty) in T-scores from baseline.

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,[e] 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)

[a]At entry into the OLE; [b]Includes atonic, tonic, tonic/atonic, generalized tonic-clonic, and secondarily generalized tonic-clonic seizures resulting in falls; [c]ASMs with a stop date prior to the first randomized dose in the RCT; [d]n=17; [e]For RCT, ASMs reported in ≥25% of any treatment group, and for OLE, reported in ≥25% of patients; [f]Includes valproate semisodium, valproate sodium, and valproic acid. ASM, antiseizure medication; FFA, fenfluramine; NA, not applicable; OLE, open-label extension; RCT, randomized controlled trial.

BRIEF®-P

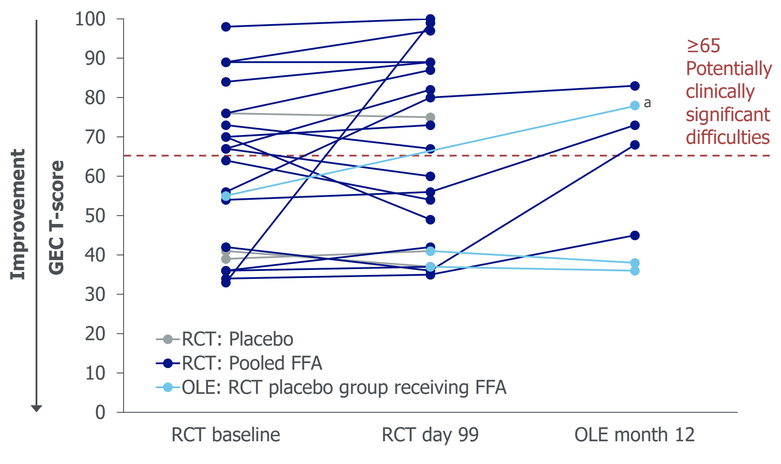
Number of patients experiencing clinically meaningful improvement and worsening from RCT baseline to RCT end of study and OLE month 12

	RCT		OLE
Patients, n	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 ≥90% RCI certainty, 'worsened' if they have an increase from baseline in T-score with ≥80% RCI certainty, and '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. [a]n=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, randomized 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. [a]This 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; EEF, everyday executive function; FFA, fenfluramine; GEC, Global Executive Composite; OLE, open-label extension; RCT, randomized 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

1. Cross JH, et al. *Front Neurol* 2017;8:505.
2. Specchio N, et al. *Epilepsia* 2022;63(6):1398-1442.
3. Kerr M, et al. *Epileptic Disord* 2011;13(suppl 1):S15-S26.
4. Breuillard D, et al. American Epilepsy Society 79th Annual Meeting 2025; Abstract 2.43.
5. Roth RM, et al. Behavior Rating Inventory of Executive Function®—Adult Version. 2005. https://doi.org/10.1037/t86244-000 Accessed July 13, 2026.

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