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Highlights from the symposium

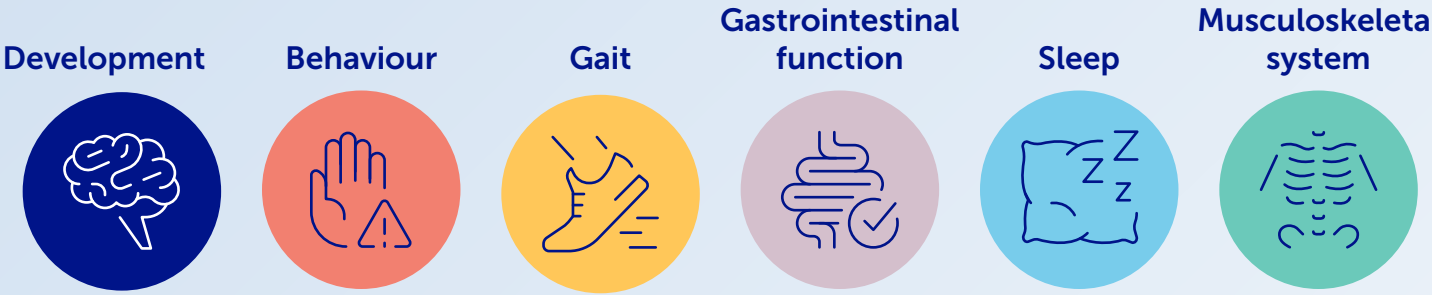
Product information can be found at the end of this document.

Fintepla® ▼ (fenfluramine) is indicated for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.

What are developmental and epileptic encephalopathies (DEEs)?

Symposium Chair Helen Cross described DEEs as disorders where there is developmental impairment related to both the underlying aetiology independent of epileptiform activity and the epileptic encephalopathy[1,2] – for example, Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS).

The impacts of DEEs extend beyond seizures. Comorbidities include impairments in:[2-5]



Click on the links for publications reporting the full 2022 International League Against Epilepsy (ILAE) diagnostic criteria for **DS** and **LGS**.[2,5] **Mandatory criteria** are described below.

Mandatory diagnostic criteria for DS[2]

Seizures	Recurrent focal clonic (hemiclonic) febrile and afebrile seizures (which often alternate sides from seizure-to-seizure), focal-to-bilateral tonic–clonic and/or generalised clonic seizures
Age at onset	1–20 months
Course of illness	Drug-resistant epilepsy and intellectual disability

Adapted from Zuberi SM, et al. Epilepsia. 2022;63(6):1349-97, used under the Creative Commons Attribution (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/). The publication is available at https://doi.org/10.1111/epi.17239.

Mandatory diagnostic criteria for LGS[5]

Seizures	Tonic seizures. In addition, at least one additional seizure type must be present which may include any of the following: • Atypical absence • Atonic • Myoclonic • Focal impaired awareness • Generalised tonic–clonic • Non-convulsive status epilepticus • Epileptic spasms
Electro-encephalogram (EEG)	Generalised slow spike-and-wave complexes of <2.5 Hz (or history of this finding on prior EEG). Generalised paroxysmal fast activity in sleep (or history of this finding on prior EEG)
Age at onset	<18 years
Long-term outcome	Drug-resistant epilepsy and mild to profound intellectual disability

Adapted from Specchio N, et al. Epilepsia. 2022;63(6):1398-442, used under the Creative Commons Attribution (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/). The publication is available at https://doi.org/10.1111/epi.17241.

Why is a diagnosis of a DEE important for patients and families?

Nicola Specchio explained why **diagnosis is critical for timely disease-specific management** and used patient cases to illustrate the **challenges** associated with the early diagnosis of DEEs.

Early syndromic classification

1. Can impact clinical management, e.g., choice of antiseizure medication[5,6]
2. May avoid unnecessary testing[5,6]
3. Shortens the diagnostic journey for families[6]
4. Allows for specific counselling (family planning)[6]
5. Provides opportunities to participate in clinical studies[5,6]
6. May allow for targeted therapy, i.e., precision medicine[5,6]
7. Connects families with each other and with advocacy groups[6]

Patient case – diagnostic process for a 16-year-old male with LGS

Patient profile

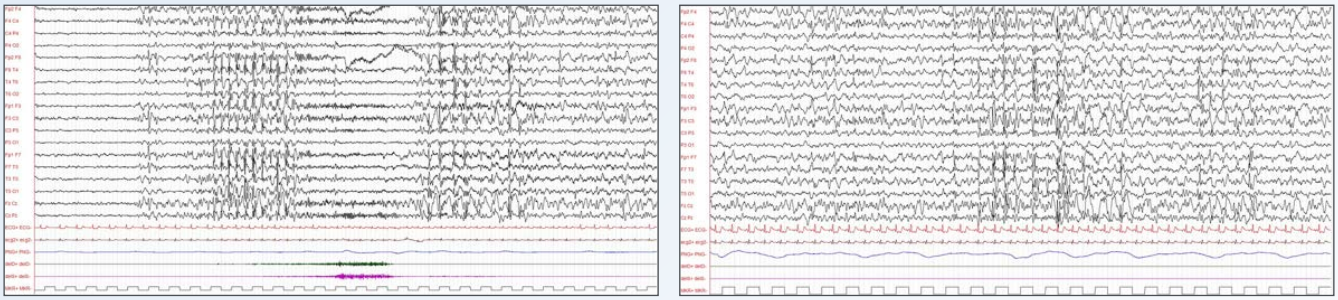
- Early severe impairment in language development and social-emotional reciprocity and displayed repetitive behaviours in his psychiatric evaluation.
- No verbal expression and limited non-verbal communication with poor eye contact, and response to instructions was inconsistent.
- Minor dysmorphic features, and head circumference was in the third percentile.

Clinical presentation

- At the age of 6 years, he developed tonic drop attacks, which was followed by a loss of attained cognitive skills.
- By 8 years of age, he developed multiple types of seizure, including nocturnal tonic seizures, tonic drop attacks, and head drops.

Diagnostic tests

- EEGs were conducted



- Magnetic resonance imaging (MRI), metabolic analysis, next-generation sequencing epilepsy panel, and comparative genome hybridisation-array were normal.
- Whole exome sequencing showed a novel variant c.4818_4819insA (p.Glu1608fs*71) in *SHANK3*, which was classified as 'pathogenic'.

Diagnosis

- The patient was **diagnosed with LGS** as he met the **three most important criteria**: multiple seizure types, slowness of intellectual growth, and specific EEG findings.

This case shows the clinical experience of a real patient case but has been applied to a hypothetical patient. Case studies are representative only and individual patient response may vary. Content is based on the speaker's clinical experience.

What tools are available to help healthcare professionals identify DEEs?

An **electronic decision-assisting tool** is being developed by a group of epilepsy experts to aid the identification of **LGS**. Its digitalisation has been funded by UCB, with no influence on its content, and it is undergoing clinical validation.

The questionnaire is based on the **mandatory, alert, and exclusionary features of the ILAE diagnostic criteria** for LGS.[5] The output of the tool requires further validation by an expert physician for a confirmatory diagnosis.

*If you would like to receive an update when the LGS electronic decision-assisting tool becomes available, please register your interest via this **link** or **QR code***

What are the potential benefits of early diagnosis?

Antonio Gil-Nagel illustrated the importance of **early diagnosis and treatment in DEEs**, and the concept of the **'window of opportunity'**.

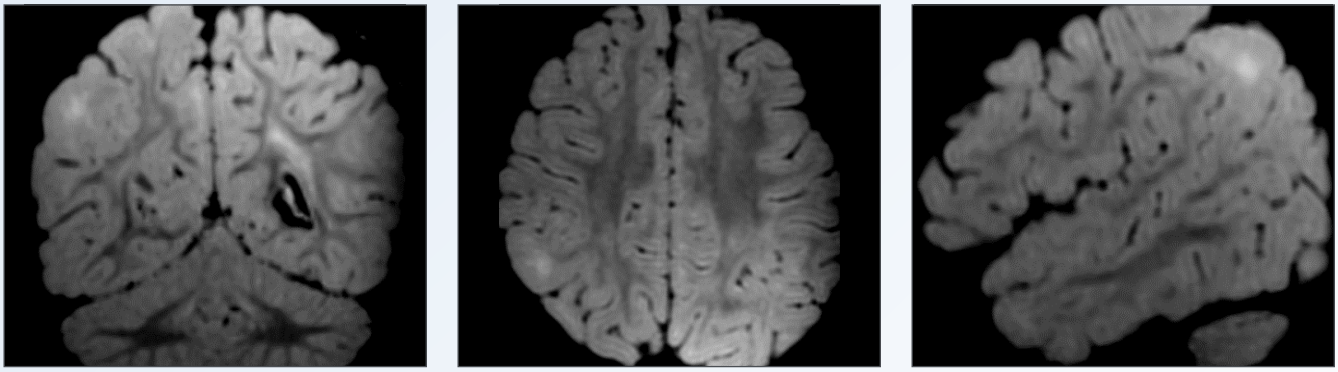
In DS, a **longer duration of inappropriate treatment** in the 5 years after seizure onset has been associated with **poorer cognitive function** versus a shorter duration.[7] **Early diagnosis reduces the risk of inadequate treatment**.

Patient case – 6-year-old male with delayed diagnosis of DS

Clinical presentation

Seizure onset at 4 months old – prolonged right or left arm clonic movements and subsequent Todd paresis.

- ***EEG***
  - *<12 months*: normal.
  - *>12 months*: mild slowing of background, right hemisphere focal and generalised epileptiform activity, and generalised tonic–clonic seizures associated with focal and diffuse electrodecrement.
- ***MRI:*** right parietal white matter cortical and subcortical signal alteration, interpreted as a probable cortical dysplasia.
- ***Previous treatment*** with seven different antiseizure medications.



Brain MRI provided by the patient, prior to epilepsy surgery

Surgery

- ***Surgery at 3 years of age*** – a right parietal type 1 cortical dysplasia was removed.
- Poor response after surgery: **persistent seizures** (multiple secondary bilateral tonic–clonic or tonic seizures per month and many myoclonic seizures per day) and **cognitive regression** (loss of speech, poor visual contact, stereotypes, positional tremor, and ataxia).

Referred to epilepsy centre at 6 years of age

- Diagnosed with **DS** (SCN1A c.3763G>A de novo). Phenotype modification due to concomitant hypoxic-ischaemic encephalopathy.
- **Fenfluramine was initiated at 9.5 years of age** and the patient is currently treated with **fenfluramine and valproic acid**. No adverse events have been reported.
- Since treatment initiation, the patient has been **seizure-free** (4 years), but only a **mild improvement in speech** has been observed.

Clinical case information provided by Dr Antonio Gil-Nagel with permission. Case studies are representative only and individual patient response may vary.

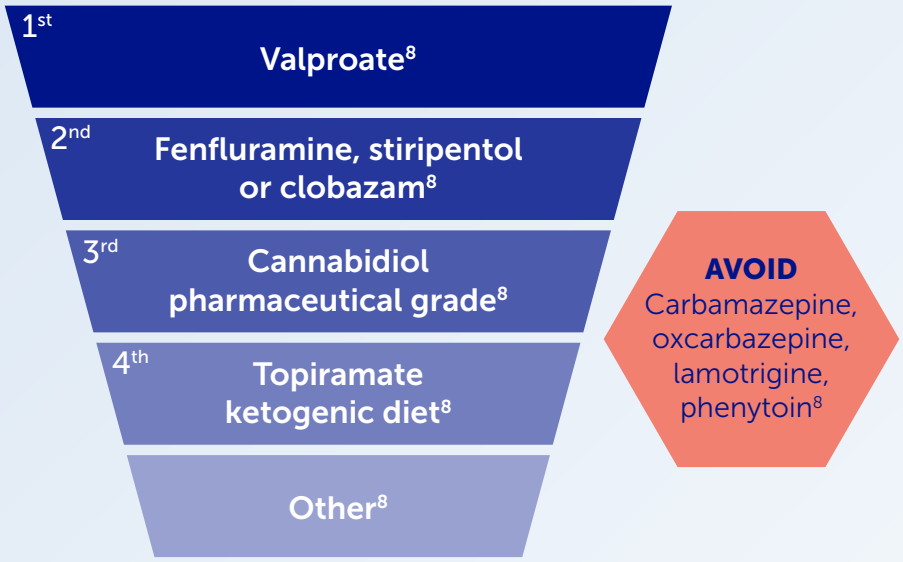
We do not have to wait for precision/genetic-based therapies, **we can act now** with:

- Early and accurate diagnosis
- Current antiseizure medications
- Repurposing of drugs
- Non-pharmacological therapies – surgery, ketogenic diet, neuromodulation etc.

How should treatment be prioritised in DEEs?

- Stéphane Auvin highlighted the importance of making treatment decisions based on **quality evidence from randomised controlled trials and real-world studies** to optimise the benefit–risk ratio for individual patients.

A therapeutic algorithm for the maintenance treatment of seizures in Dravet syndrome has been developed through international consensus[8]



Adapted from Wirrell EC, et al. Epilepsia. 2022;63(7):1761-77.

Please contact your local UCB representative to request clinical papers for fenfluramine.

A consensus paper addressing the management of Lennox-Gastaut syndrome is, currently, in development.

References: 1. Scheffer IE, et al. Epilepsia. 2017;58(4):512-21; **2.** Zuberi SM, et al. Epilepsia. 2022;63(6):1349-97; **3.** Palmer EE, et al. Neurotherapeutics. 2021;18(3):1432-44; **4.** Wirrell EC, et al. Epilepsia. 2022;63(6):1333-48; **5.** Specchio N, et al. Epilepsia. 2022;63(6):1398-442; **6.** Berkovic SF. Epilepsy Curr. 2015;15(4):192-6; **7.** de Lange IM, et al. Epilepsia. 2018;59(6):1154-65; **8.** Wirrell EC, et al. Epilepsia. 2022;63(7):1761-77.

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Please click the links or use the QR codes below to access Fintepla® ▼ (fenfluramine) product information.

EU API

Italian SmPC

Great Britain API

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Please see section 4.8 of the Summary of Product Characteristics for reporting details in your country.

In Italia Fintepla®, per l'indicazione terapeutica: "trattamento delle crisi epilettiche associate alla sindrome di Lennox-Gastaut come terapia aggiuntiva ad altri medicinali antiepilettici in pazienti di età pari o superiore ai 2 anni" non è dispensabile a carico del SSN.