

Burden of Illness in Developmental and Epileptic Encephalopathies Beyond Dravet Syndrome, Lennox-Gastaut Syndrome, and Tuberous Sclerosis Complex: A Systematic Literature Review

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Objective

- To evaluate the clinical and humanistic burden of developmental and epileptic encephalopathies (DEEs) beyond Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), and tuberous sclerosis complex (TSC), as reported in the published literature

Conclusions

- DEEs beyond LGS, DS, and TSC were associated with frequent, refractory seizures, and comorbidities including intellectual disability, developmental delay, motor impairment, and behavioural issues, indicating substantial clinical burden
- DEEs were associated with reduced quality of life and substantial caregiver burden, including emotional distress, anxiety, and reduced work capacity
- These findings provide an understanding of the collective burden associated with DEEs and support the need for treatments that address broader disease manifestations including seizure control, quality of life, nonseizure outcomes, and caregiver burden

References: 1. Raga S, et al. *Epileptic Disord.* 2021;23(1):40–52. 2. Palmer EE, et al. *Neurotherapeutics.* 2021;18(3):1432–1444. 3. Page MJ, et al. *BMJ.* 2021;372:n71. 4. Saldaris JM, et al. *Epilepsia.* 2024;65(10):3064–3075. 5. Gjerulfsson CE, et al. *Epilepsia.* 2025;66(4):1119–1128. 6. Cosu A, et al. *Epilepsy Behav.* 2023;142:109153. 7. Chipaux M, et al. *Epilepsia.* 2016; 57(5):757–769. 8. Dangles MT, et al. *Clin Neurophysiol.* 2021;132(6):1126–1137. 9. Frizzo BS, et al. *Epilepsia.* 2024;65(S1):48–49. 10. Demarest S, et al. *Epilepsy Behav.* 2023;142:109173. 11. Alado-Serrano A, et al. *medRxiv.* 2025;2025.01.12.24318239. 12. Dalby K, et al. *Neurology.* 2023;100(17 suppl 2):3167. 13. Muller A, et al. *Eur J Paediatr Neurol.* 2016; 20(1):147–151. 14. Berg AT, et al. *Epilepsia.* 2018;59(11):2096–2105. 15. Boets S, et al. *J Med Genet.* 2022;59(6):528–535. 16. Lo Barco T, et al. *Epilepsy Behav.* 2022;127:108500. 17. McKee JL, et al. *Genet Med.* 2025;101419. 18. Pisano T, et al. *Epilepsia.* 2015;56(5):685–691. 19. Casas-Alba D, et al. *Pediatr Neurol.* 2023;144:11–15. 20. Beck VC, et al. *J Pediatr.* 2021;237:41–9.e1. 21. Burgess R, et al. *Ann Neurol.* 2019;86(6):821–831. 22. Pellino G, et al. *Epilepsy Behav.* 2019;99:106465. 23. Downs J, et al. *Eur J Paediatr Neurol.* 2024;51:140–146. 24. Machado RA, et al. *Seizure.* 2025;127:115–126. 25. Berg AT, et al. *Epilepsy Behav.* 2020;111:107287. 26. Saldaris JM, et al. *J Clin Sleep Med.* 2024;20(12):1897–1903. 27. Salecio-Perez-Juana M, et al. *Front Pediatr.* 2023;11:1235377. 28. van Arnhem MM, et al. *Lancet Neurol.* 2024;23(2):147–156. 29. Downes M, et al. *Epilepsia.* 2015;56(11):1760–1766. 30. Berg AT, et al. *Epilepsia.* 2021;62(1):258–268. 31. Berg AT, et al. *Epilepsy Behav.* 2022;128:108586. 32. Leonard H, et al. *Epilepsy Res.* 2021;169:106521. 33. Lavery D, et al. *Value Health.* 2024;27(suppl 6):S308.

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Introduction

- Developmental and epileptic encephalopathies (DEEs) are a heterogeneous group of rare and severe neurodevelopmental disorders with early-onset seizures, developmental delays, and neurocognitive impairments^{1,2}
- These disorders typically manifest in infancy or early childhood, during critical periods of brain development, and are associated with substantial morbidity and lifelong functional impairments²
- Management of DEEs remains challenging due to the refractory nature of seizures and the progressive nature of cognitive and developmental deficits
- While the burden of Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), and tuberous sclerosis complex (TSC) is relatively well characterised, the overall burden of other DEEs remains less well described
- We reviewed published literature on the clinical and humanistic burden of DEEs beyond LGS, DS, and TSC

Methods

- A systematic literature review (SLR) was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines³ with searches conducted in MEDLINE, Embase, and MEDLINE In-Process (January 2015–April 2025), supplemented by five conference proceedings (2023–2025) and a bibliographic screening per predefined population, intervention, comparison, outcomes, and study design (PICOS) criteria (Table S1)
- For more details on methodology, see the **supplementary material** by scanning the poster QR code above

Results

Publications identified

- Among 2610 records identified by SLR, 58 studies were included for clinical burden and 13 studies for humanistic burden (Figure 1)

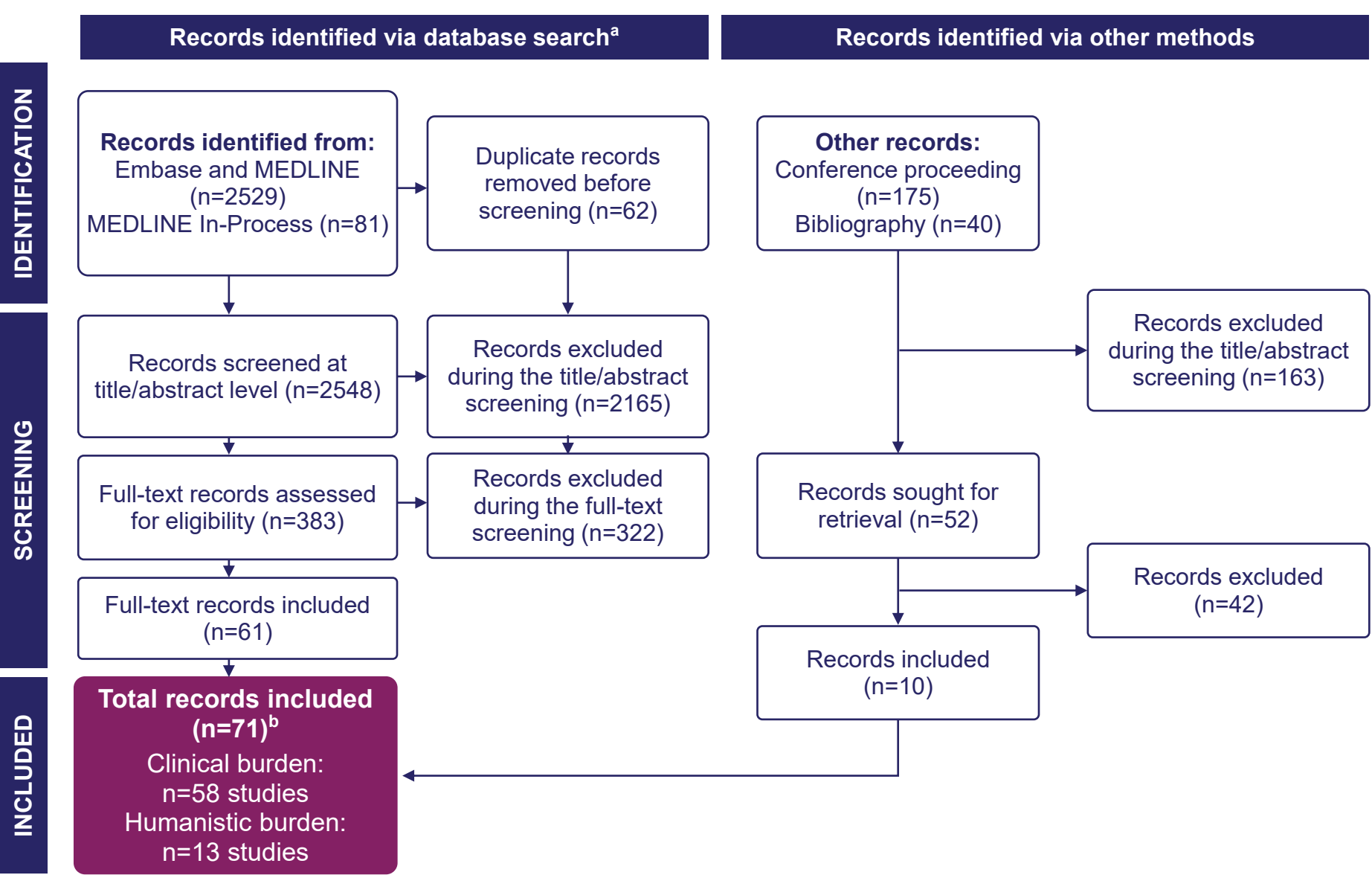
Clinical burden: study characteristics

- A total of 65 publications from 58 unique studies reported clinical burden, including 4 randomised controlled trials (RCTs), 5 non-randomised interventional studies, and 49 observational studies
 - Evidence was drawn from multinational collaborations as well as single-centre and multicentre studies across the US, Europe, and Japan
 - Participant age ranged from infancy to 45 years

Humanistic burden: study characteristics

- A total of 15 publications from 13 unique studies reported humanistic burden
 - Among the 13 unique studies, 2 were RCTs, 10 were observational studies, and 1 was a mixed-method design study
 - Participant age ranged from infancy (median age at onset: 1 month) to adolescence (mean age at assessment: 11.3 years), with some cohorts extending into adulthood (range: 0.3–40.7 years)

Figure 1. PRISMA diagram



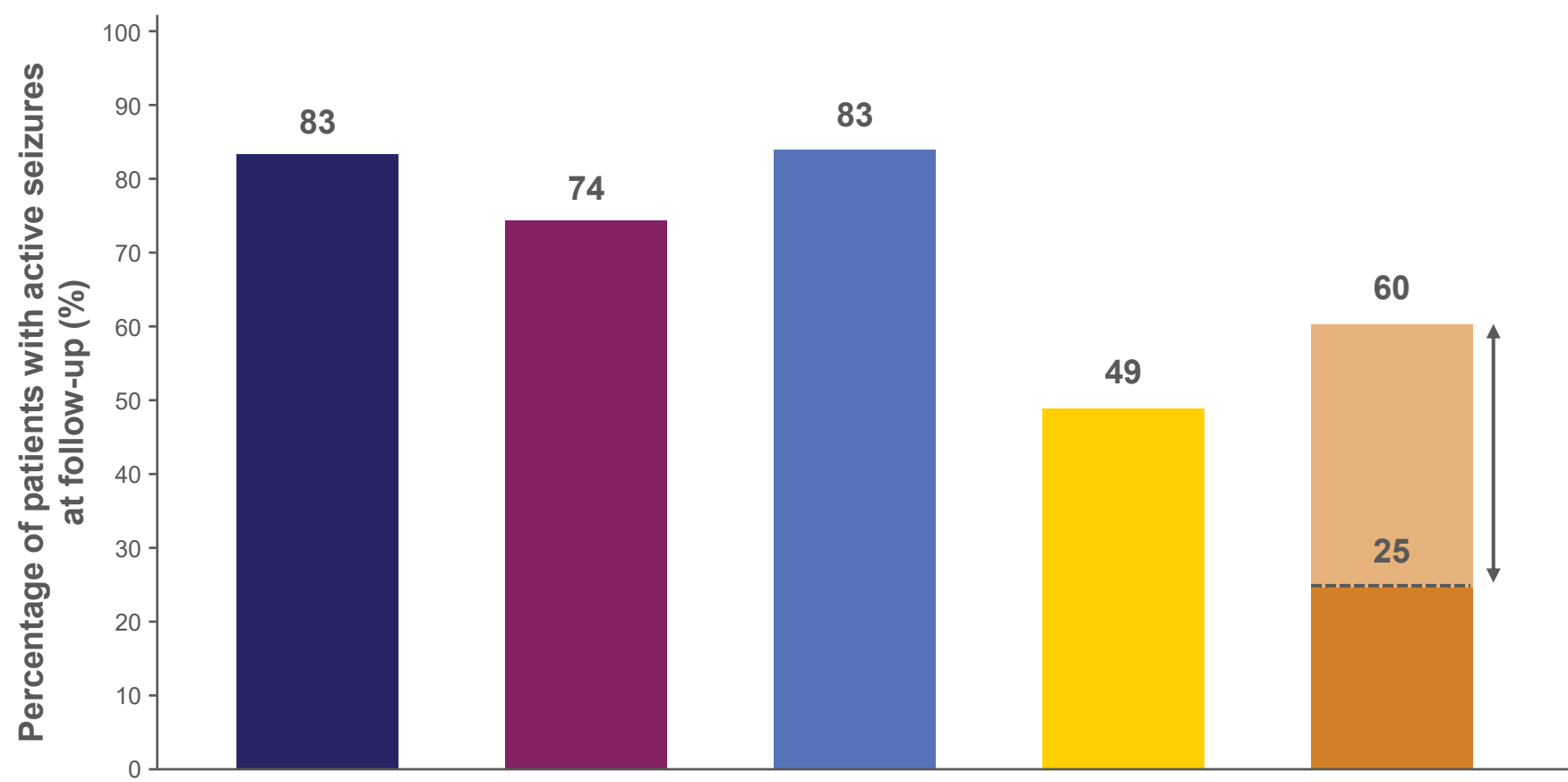
*Searches were performed on April 2, 2025. *Study counts are not mutually exclusive due to overlap of studies across clinical and humanistic reviews. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Clinical burden

Seizure burden Seizure burden was consistently high despite the commonly reported use of polypharmacy and broad-spectrum antiseizure medications

- CDKL5*-DEE was the most investigated (n=18 studies), followed by West syndrome and *KCNQ2*-DEE (n=8 studies each; Figure S1)
- Across five observational studies, seizure burden remained high and refractory across all DEE subtypes at follow-up (Figure 2)

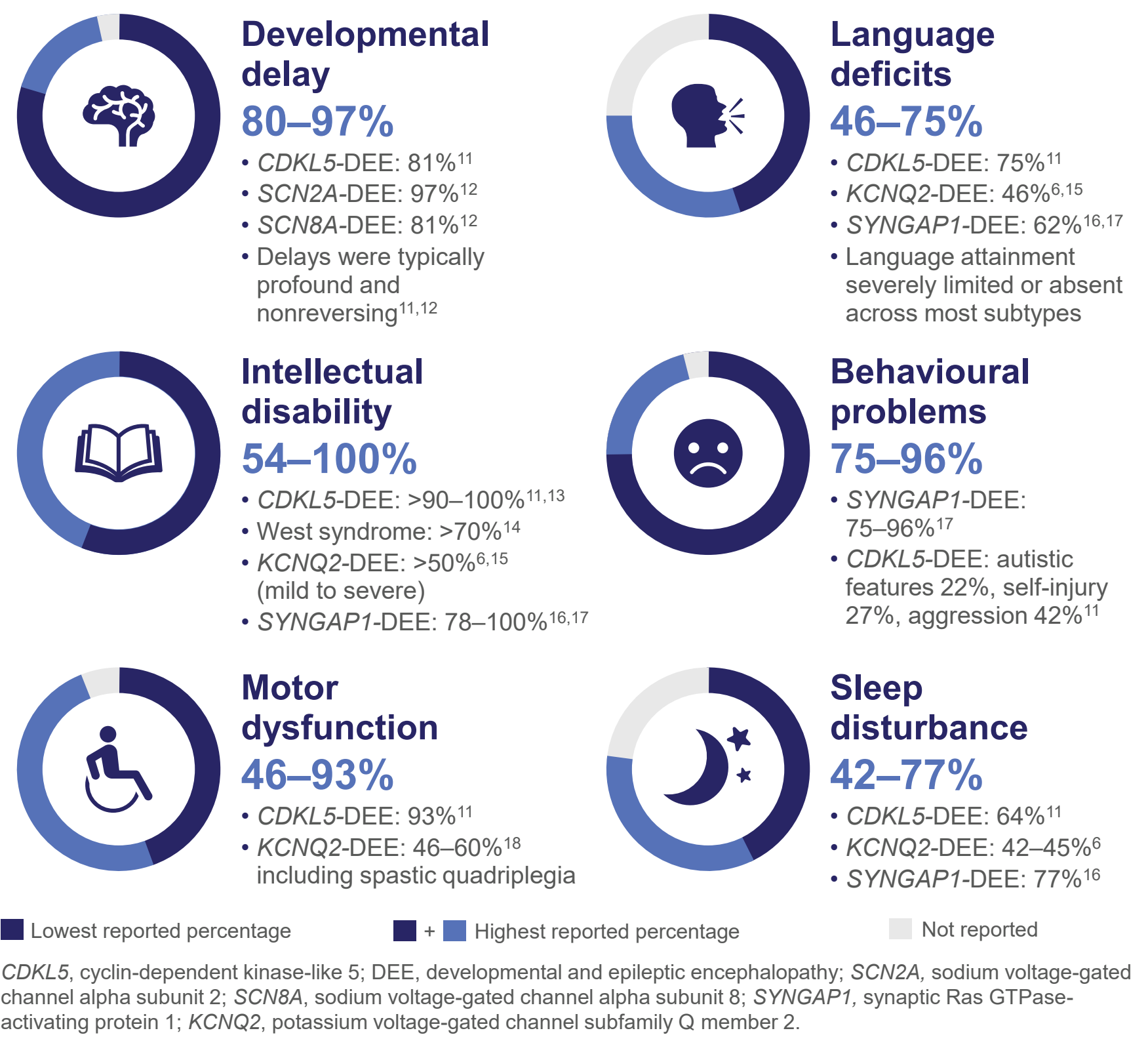
Figure 2. Percentage of patients with active seizures at follow-up by DEE subtype^{4–8}



Note: Follow-up timepoints differ by study. For West/CSWS, shaded bar and arrow represent the reported range across studies. *CDKL5*, cyclin-dependent kinase-like 5; *CSWS*, continuous spike waves during slow-wave sleep; DEE, developmental and epileptic encephalopathy; *KCNQ2*, potassium voltage-gated channel subfamily Q member 2; *SCN2A*, sodium voltage-gated channel alpha subunit 2; *SCN8A*, sodium voltage-gated channel alpha subunit 8; West, West syndrome.

Nonseizure burden Nonseizure comorbidities were near-universal and profoundly disabling, affecting development, cognition, motor function, language, and behaviour across all DEE subtypes (Figure 4)

Figure 4. Nonseizure burden of DEE

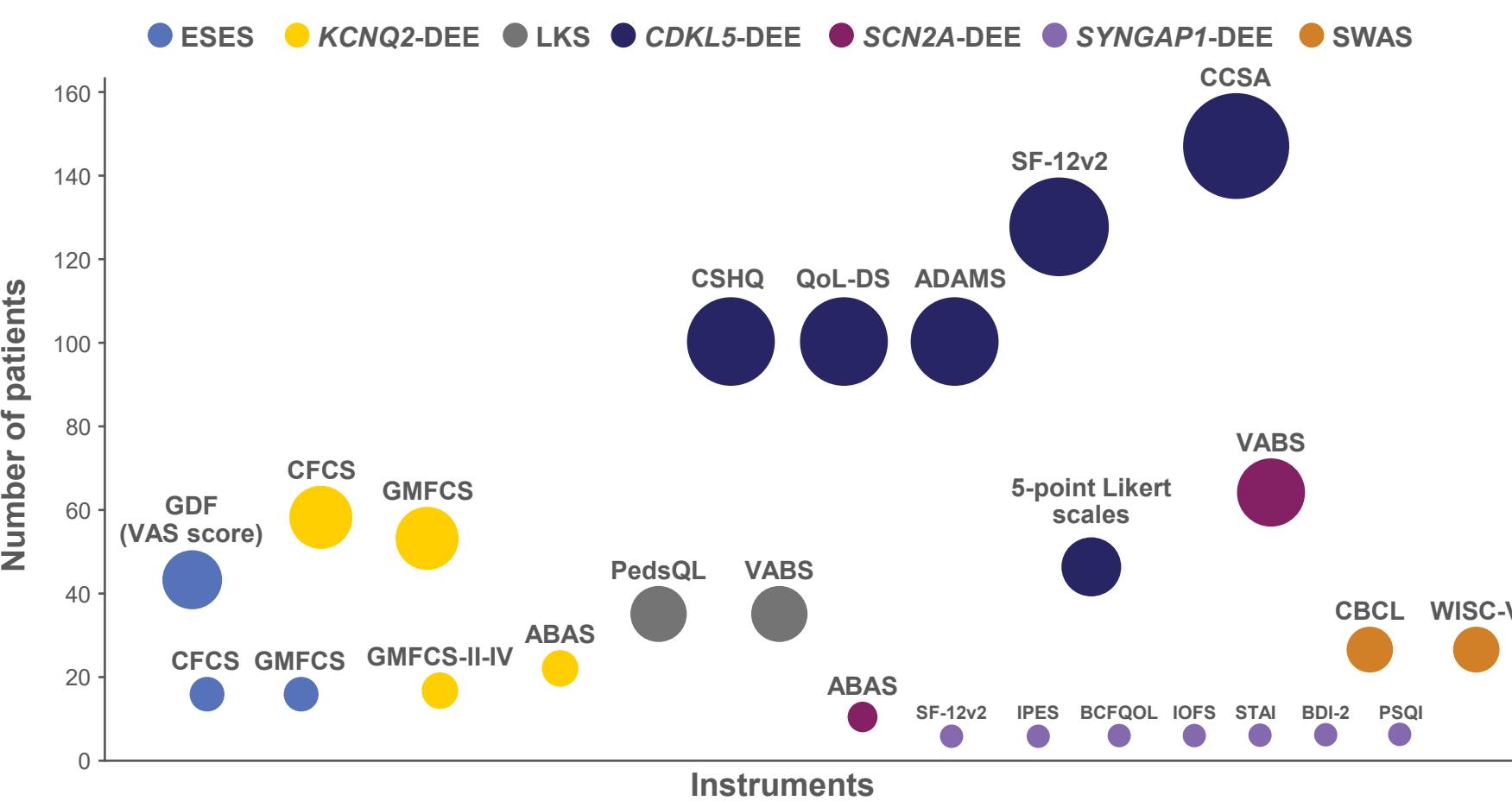


CDKL5, cyclin-dependent kinase-like 5; DEE, developmental and epileptic encephalopathy; *SCN2A*, sodium voltage-gated channel alpha subunit 2; *SCN8A*, sodium voltage-gated channel alpha subunit 8; *SYNGAP1*, synaptic Ras GTPase-activating protein 1; *KCNQ2*, potassium voltage-gated channel subfamily Q member 2.

Humanistic burden

- A wide range of instruments was used to assess humanistic and functional outcomes across DEE studies, and most focused on adaptive behaviour (VABS), quality of life (QoL; QoL-DS), mood (ADAMS), and sleep (CSHQ) (Figure 6); patients with *CDKL5*-DEE were most frequently evaluated
- A total of 13 studies consistently demonstrated significant impairments in adaptive functioning, QoL, behaviour, cognition, sleep, and caregiver well-being

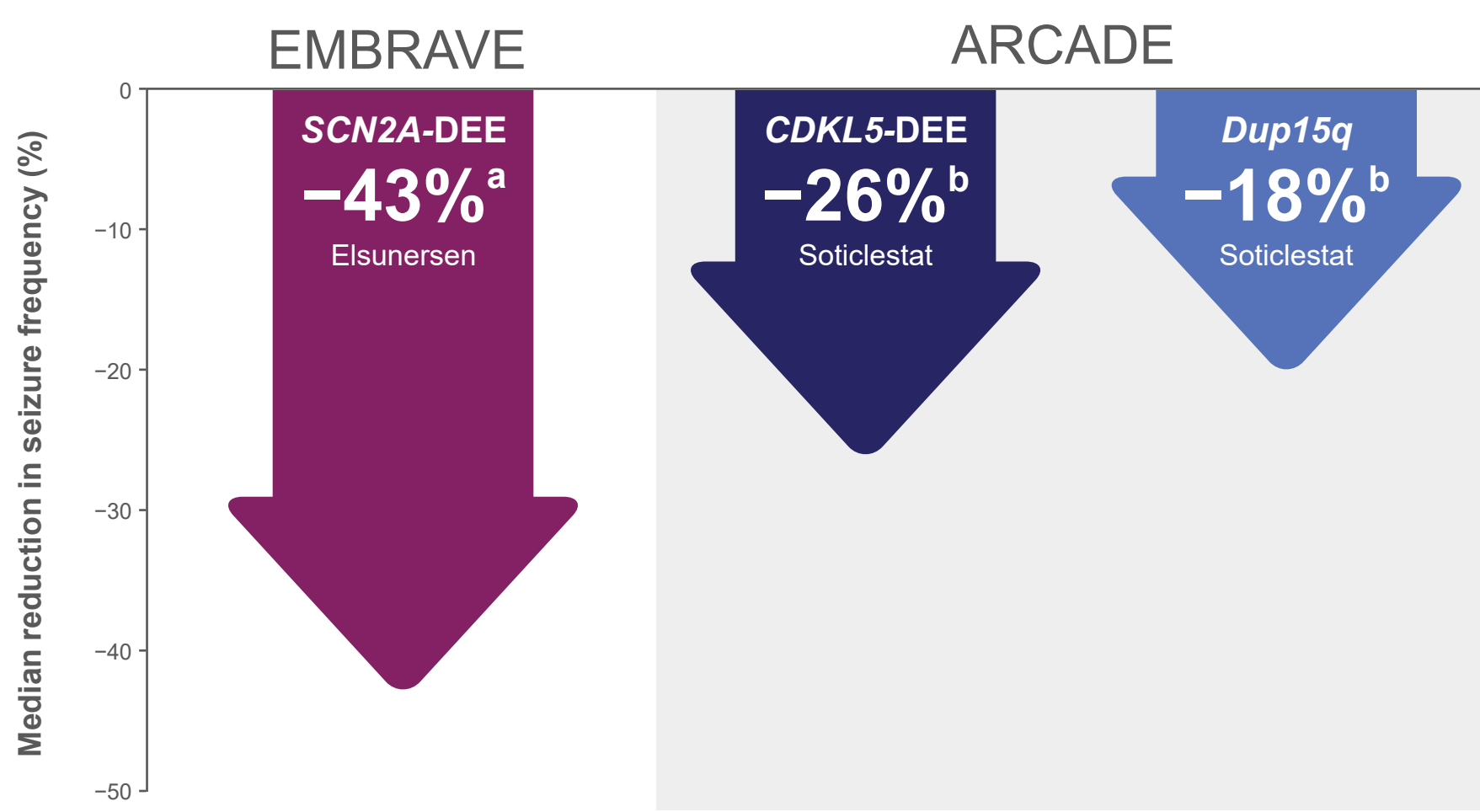
Figure 6. Instruments used to determine the humanistic burden in patients with DEE^{19, 23–33a}



*Each bubble represents an instrument used to assess humanistic and functional outcomes in people with a specific DEE represented by different colours; the y axis represents the number of patients assessed. Larger bubbles indicate a larger number of patients assessed with an instrument across studies. ABAS, Adaptive Behavior Assessment System; ADAMS, Anxiety, Depression, and Mood Scale; BCFQOL, Beach Center Family Quality of Life; BDI, Beck Depression Inventory; CBCL, Child Behavior Checklist; CCSA, *CDKL5* Clinical Severity Assessments; *CDKL5*, cyclin-dependent kinase-like 5; CFCS, Communication Function Classification System; CSHQ, Children's Sleep Habits Questionnaire; DEE, developmental and epileptic encephalopathy; ESES, electrical status epilepticus during slow-wave sleep; GDF, Global Daily Functioning; GMFCS, Gross Motor Functional Classification System; IQFS, Impact on Family Scale; IPES, Impact of Pediatric Epilepsy Scale; *KCNQ2*, potassium voltage-gated channel subfamily Q member 2; LKS, Landau-Kleffner syndrome; PedsQL, Pediatric Quality of Life Inventory; PSQI, Pittsburgh Sleep Quality Index; QoL, quality of life; QoL-DS, Quality of Life Inventory-Disability scale; *SCN2A*, sodium voltage-gated channel alpha subunit 2; SF-12v2, 12-Item Short Form Health Survey version 2.0; STAI, State-Trait Anxiety Inventory; SWAS, spike-and-wave activation in sleep; *SYNGAP1*, synaptic Ras GTPase-activating protein 1; VABS, Vineland Adaptive Behavior Scales; VAS, visual analogue scale; WISC-V, Wechsler Intelligence Scale for Children Fifth Edition.

- Two interventional studies reported reductions in seizure frequency following treatment (Figure 3), though seizure burden remained high across the included studies

Figure 3. Reductions in seizure frequency in patients with DEE subtypes across interventional studies^{9,10}



^aSeizure reduction after 13 weeks of treatment in EMBRAVE phase 1/2 trial.⁹ ^bSeizure reduction after 20 weeks of treatment in ARCADE phase 2 trial.¹⁰ *CDKL5*, cyclin-dependent kinase-like 5; DEE, developmental and epileptic encephalopathy; *Dup15q*, chromosome 15q11–q13 duplication; *SCN2A*, sodium voltage-gated channel alpha subunit 2.

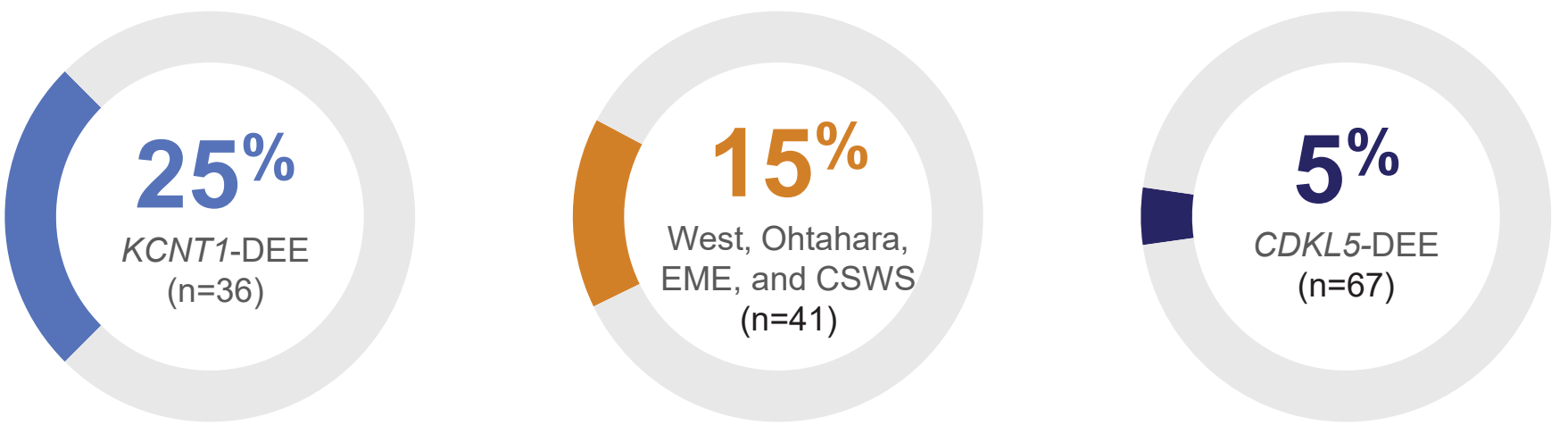
Treatment patterns Treatment patterns reflected widespread polypharmacy

- Studies reported that patients with DEEs were treated with multiple antiseizure medications (valproic acid, levetiracetam, phenobarbital, and clobazam), frequently used in combination with sodium channel blockers (eg, carbamazepine, phenytoin, lamotrigine) or adjunctive approaches (eg, ketogenic diet or steroids), reflecting the refractory nature of DEEs and the limited effectiveness of monotherapies^{8,11,13,19,20}

Mortality Mortality was rare in interventional studies but more frequent in real-world observational cohorts (Figure 5)

- The difference in mortality rates between interventional and observational studies may reflect the natural history of these severe disorders
- Because mortality rates were derived from small observational cohorts, estimates should be interpreted with caution and are not representative of population-level mortality rates

Figure 5. Mortality rates observed with various DEE subtypes in observational cohorts^{11,21,22}



CDKL5, cyclin-dependent kinase-like 5; *CSWS*, continuous spike waves during slow-wave sleep; DEE, developmental and epileptic encephalopathy; EME, early myoclonic encephalopathy; *KCNT1*, potassium sodium-activated channel subfamily T member 1; West, West syndrome.

Behavioural and functional burden Multidomain behavioural impairments and functional limitations were frequent across DEE subtypes (n=11 studies)

- One study reported social avoidance (Anxiety, Depression, and Mood Scale mean score: 6.8; maximum score: 21) and hyperactive behaviour (4.8; maximum score: 15) as common behaviours; another reported attention problems (Child Behavior Checklist mean percentile score: 86.5) and aggressive behaviour (68); higher scores indicate worse behavioural symptoms^{23,24}
- A further study reported that patients (N=214) experienced difficulty in walking (28%), feeding (40%), or communicating (73%).²⁵ In children with gross motor function levels II–IV, multiple adaptive subscales were moderately impaired¹⁹

Sleep disturbances Sleep disturbances were reported in two studies and contributed to the substantial disease burden of DEE

- The Sleep Disturbance Scale for Children showed difficulty in initiating sleep and excessive somnolence (mean score: 38.4 and 34.8, respectively [maximum score: 100]); higher scores indicate greater sleep disturbance²⁶
- Poor sleep quality was also reported in patients with *SYNGAP1*-DEE (Pittsburgh Sleep Quality Index mean score: 9; scores ≥5 indicate poor sleep quality)²⁷

Caregiver burden DEE imposed considerable psychological and economic strain on caregivers

- In one study caregivers (N=20) reported considerable psychological strain, including moderate depressive symptoms (30%), anxiety (State-Trait Anxiety Inventory–State median score: 26 [maximum score: 60; higher scores indicate greater anxiety]), and low satisfaction with family QoL²⁷
- A study in Italy (N=18) reported that 44% of caregivers gave up their jobs in order to assist the child with DEE⁶

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Supplementary Material

Methods

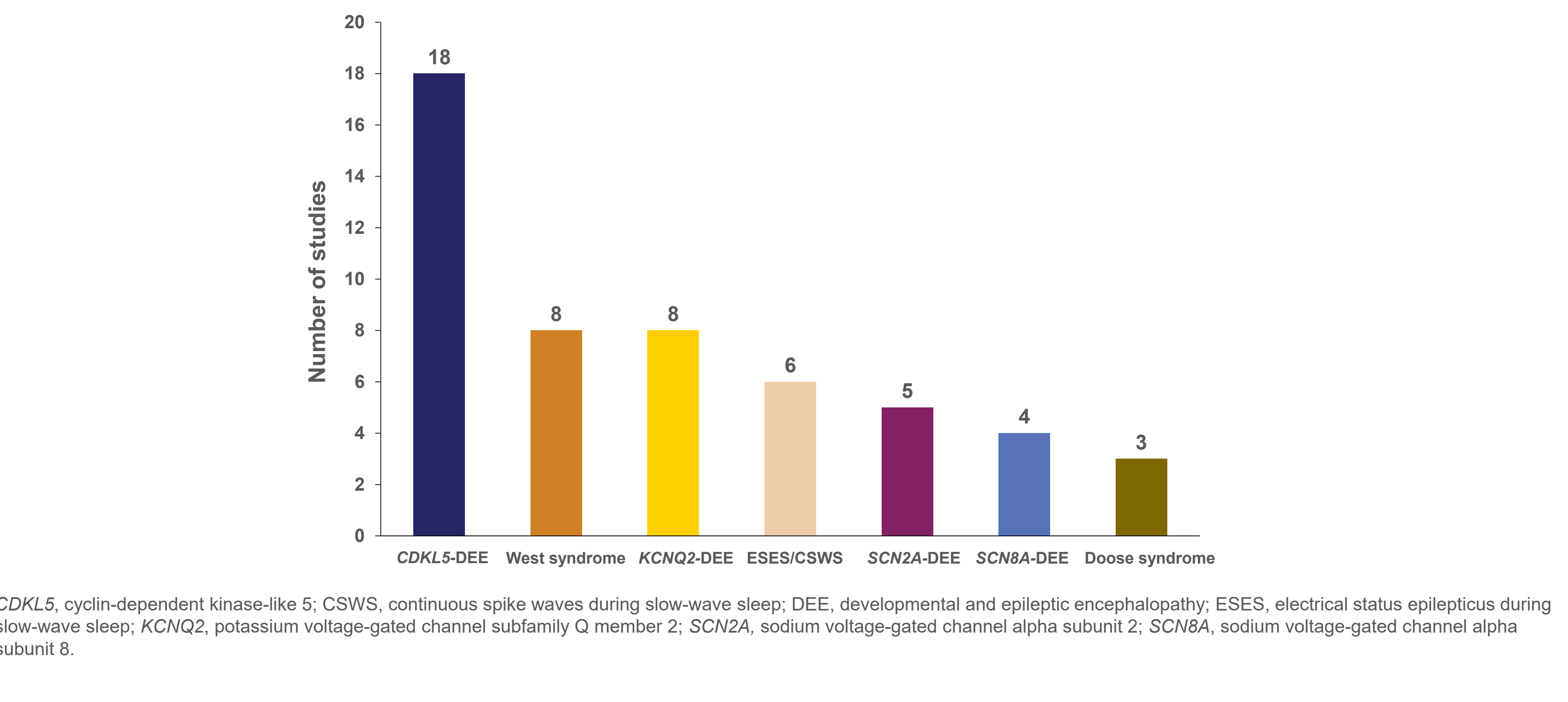
- A systematic literature review was conducted following PRISMA guidelines¹ with searches conducted in MEDLINE, Embase, and MEDLINE In-Process (January 2015–April 2025), supplemented by five conference proceedings (2023–2025) and a bibliographic screening using predefined population, intervention, comparison, outcomes, and study design (PICOS) criteria (**Table S1**)
- Articles of possible relevance were assessed independently by two reviewers. Any uncertainty regarding the inclusion was resolved by a third independent reviewer
- Data were extracted by one reviewer and quality checked against the source by another independent reviewer
- Seizure burden, complications, treatment patterns, and humanistic burden of developmental and epileptic encephalopathies other than Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex were qualitatively assessed and extracted

Table S1. PICOS criteria for review

Population	Patients with DEE ^a • Subgroups of interest: Specific DEE subtype, treatment received, age groups
Intervention/comparator	No restriction
Outcomes	Clinical burden • Mortality and/or morbidity (by DEE subtypes or subgroups and by non-Epidyolex® [EU]/Epidiolex® [US] treatments received); treatment patterns; prolonged seizures and/or status epilepticus; nonseizure symptoms including motor impairment, intellectual disability, speech/communication impairments, and developmental delay; efficacy outcomes including seizure frequency and CaGI-C/PGI-C; safety including TEAEs and SAEs, as defined by the publication/report; definitions and usage of endpoints in observational and RWE studies Humanistic burden • HRQoL measured by generic or disease-specific scales; societal burden; factors influencing HRQoL or social functioning; QoL burden on caregiver
Study design	• Clinical trials (RCTs and non-RCTs) • Observational/real-world studies • Cross-sectional studies • Published registry studies • Economic evaluations reporting HRQoL data
Country	US, UK, Japan, and EU4 only ^b
Limits	Full text: 2015–2025 Conference abstracts: 2023 onward

^aDEE subtypes of interest include Angelman syndrome, *Dup15q*, Landau-Kleffner syndrome, Ohtahara syndrome, West syndrome, myoclonic atonic epilepsy or early myoclonic encephalopathy (Doose syndrome), *CDKL5*, Fires, Aicardi, Ring14 or Ring20 syndrome, EE with spike-wave activation, *SCN1A* (excluding Dravet syndrome), *SCN2A*, *SCN8A*, *KCNQ2*, *KCNT1*, *PCDH19*, and *SYNGAP1*. ^bEU4, European Union countries comprising Germany, France, Italy, and Spain.
CDKL5, cyclin-dependent kinase-like 5; CaGI-C, Caregiver Global Impression of Change; DEE, developmental and epileptic encephalopathy; *Dup15q*, chromosome 15q11–q13 duplication; EE, epileptic encephalopathy; HRQoL, health-related quality of life; *KCNQ2*, potassium voltage-gated channel subfamily Q member 2; *KCNT1*, potassium sodium-activated channel subfamily T member 1; *PCDH19*, protocadherin 19; PGI-C, Participant Global Impression of Change; PICOS, population, intervention, comparison, outcomes, study design; QoL, quality of life; RCT, randomised controlled trial; RWE, real-world evidence; SAE, serious adverse event; *SCN1A* (excluding Dravet syndrome), *SCN2A*, and *SCN8A*, sodium channel gene variants; *SYNGAP1*, synaptic Ras GTPase-activating protein 1; TEAE, treatment-emergent adverse event.

Figure S1. Frequency of DEE types studied



Reference: 1. Page MJ, et al. *BMJ*. 2021;372:n71.

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Epidyolex® is approved in the EU for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam, in patients ≥2 years of age; it is additionally approved in the EU for the adjunctive treatment of seizures associated with tuberous sclerosis complex in patients ≥2 years of age.

Epidiolex® is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age.

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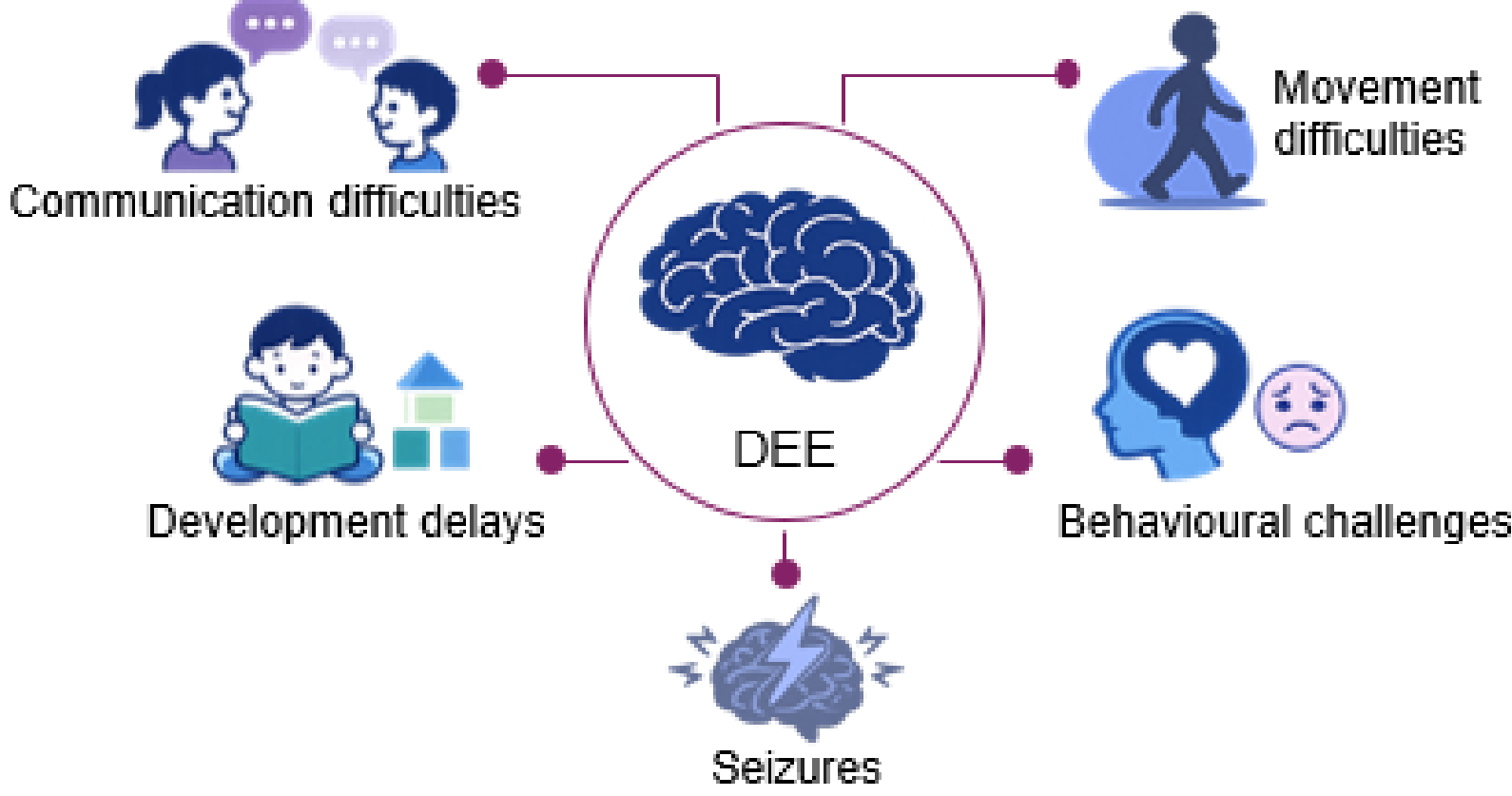
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What are developmental and epileptic encephalopathies (DEEs)?

- DEEs are a group of rare and severe brain disorders that usually begin **in infancy or early childhood**, when the brain is still developing
- People living with DEEs may often experience **seizures, delays in development, and difficulties with learning and thinking**^{1,2}
 - The effects of these conditions can be **long-lasting** and **may continue throughout life**
- DEEs can be difficult to manage because seizures often continue despite taking multiple medicines



Why was this study done?

- Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), and tuberous sclerosis complex (TSC) are DEEs that have been well studied
 - However, less is known about the burden of many other DEEs
- This study looked at what researchers have published to better understand the collective evidence about **how DEEs other than LGS, DS, and TSC affect patients and their caregivers**



How was the study conducted?

- Researchers searched databases of **published studies from 2015 to 2025** and **conference abstracts from 2023 to 2025**

Records identified:
N=2610

Studies included:
N=71

=

Health impacts of DEEs (n=58 studies)

- Seizures and their impact
- Health complications
- Treatments used to manage DEEs

4 randomised clinical trials

5 non-randomised clinical trials

49 observational studies

+

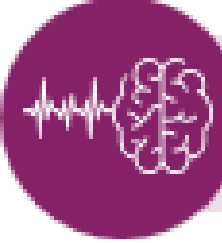
Daily life and well-being (n=13 studies)

- The impact of DEEs on patients' and caregivers' daily lives and well-being

2 randomised clinical trials

10 observational studies

1 mixed-method design study



What are the health impacts of DEEs in terms of seizures?

Seizure burden

Studies included seven DEE subtypes, with **CDKL5-DEE** being the most frequently studied

Across five observational studies, many participants continued to have active seizures despite treatment with multiple antiseizure medications

49–83% of patients had active seizures at follow-up across the different DEE subtypes shown below^{3–7}

83%

CDKL5-DEE

74%

SCN2A-DEE

83%

SCN8A-DEE

49%

KCNQ2-DEE

60%

West/CSWS

CSWS, continuous spike-and-wave during slow-wave sleep.

Italicised terms indicate gene names.

Two clinical trials reported fewer seizures after treatment, although many participants in these trials continued to experience seizures

18–43% reduction in seizure frequency was reported in three types of DEEs shown below^{8,9}

EMBRAVE study
Elsunersen

~43%
(SCN2A-DEE)

ARCADE study
Soticlestat

~26%
(CDKL5-DEE)

~18%
(Dup15q)

What are the health impacts of DEEs beyond seizures?

Non-seizure burden

Health conditions beyond seizures were common across DEE subtypes and affected development, thinking, movement, communication, and behaviour

Developmental delay^{10,11}

80–97%

Behavioural problems^{10,12}

75–96%

Intellectual disability^{5,10,12–16}

54–100%

Motor dysfunction^{10,17}

46–93%

Language deficits^{5,10,12,15,16}

46–75%

Sleep disturbance^{5,10,16}

42–77%

Lowest percentage reported

➡

Highest percentage reported

Not reported

Studies reported that many people with DEEs were **treated with more than one seizure medication** because a single treatment was often not enough^{7,10,13,18,19}

Mortality rates (%) observed with various DEE subtypes in observational studies^{10,20,21}

25%

KCNT1-related DEE

15%

West syndrome, Ohtahara, Early myoclonic encephalopathy, and continuous spike-wave during slow-wave sleep

5%

CDKL5-DEE

Deaths were reported more often in observational studies than in clinical trials

- These findings came from small studies and should be interpreted with caution

How do DEEs affect daily life and well-being?

Behaviour and daily functioning

Behavioural difficulties and challenges with daily activities were commonly reported across DEE subtypes^{18,22–24}

- Social avoidance
- Hyperactive behaviour
- Attention problems
- Aggressive behaviour
- Difficulty with walking/movement, feeding, or communicating

Sleep problems

Sleep problems were reported in several DEE subtypes and contributed to the overall burden of DEEs^{25,26}

- Difficulty falling asleep
- Poor sleep quality
- Excessive daytime sleepiness

Caregiver burden

DEEs can have a substantial psychological and economic impact on caregivers and their families^{5,26}

- Depression
- Anxiety
- Reduced quality of life
- **44%** of caregivers in one study stopped working to care for their child with DEE⁵

What do these results mean?

- People living with DEEs other than LGS, DS, and TSC often experience frequent seizures despite taking multiple treatments and have ongoing developmental difficulties and behavioural problems, which can have a substantial impact on their health
- DEEs also reduce quality of life and place a substantial burden on caregivers, including emotional distress, anxiety, and reduced ability to work
- These findings show that DEEs impact many aspects of a patient's life and also that of their families, and highlight the need for treatments that can improve seizure control while also addressing quality of life, other effects of DEEs and caregiver burden