A targeted literature review to explore the patient, caregiver, and family member experience of Dravet syndrome and Lennox-Gastaut syndrome

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Background

- Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are rare, treatment-resistant, developmental and epileptic encephalopathies.
  - DS typically presents in the first year of life, with a prevalence of ~1.2–6.5 per 100,000 individuals.[1]
  - LGS manifests in early childhood (most commonly between ages 3 and 5 years), and has a prevalence of ~5.8–60.8 per 100,000 individuals.[1,2]
- Many people with DS and LGS experience cognitive, behavioural, social and mobility difficulties,[3,4] and often require a lifetime of care.
- Consequently, both DS and LGS can have a profound impact on the health-related quality of life (HRQoL) of patients as well as their caregivers and families.

Objectives

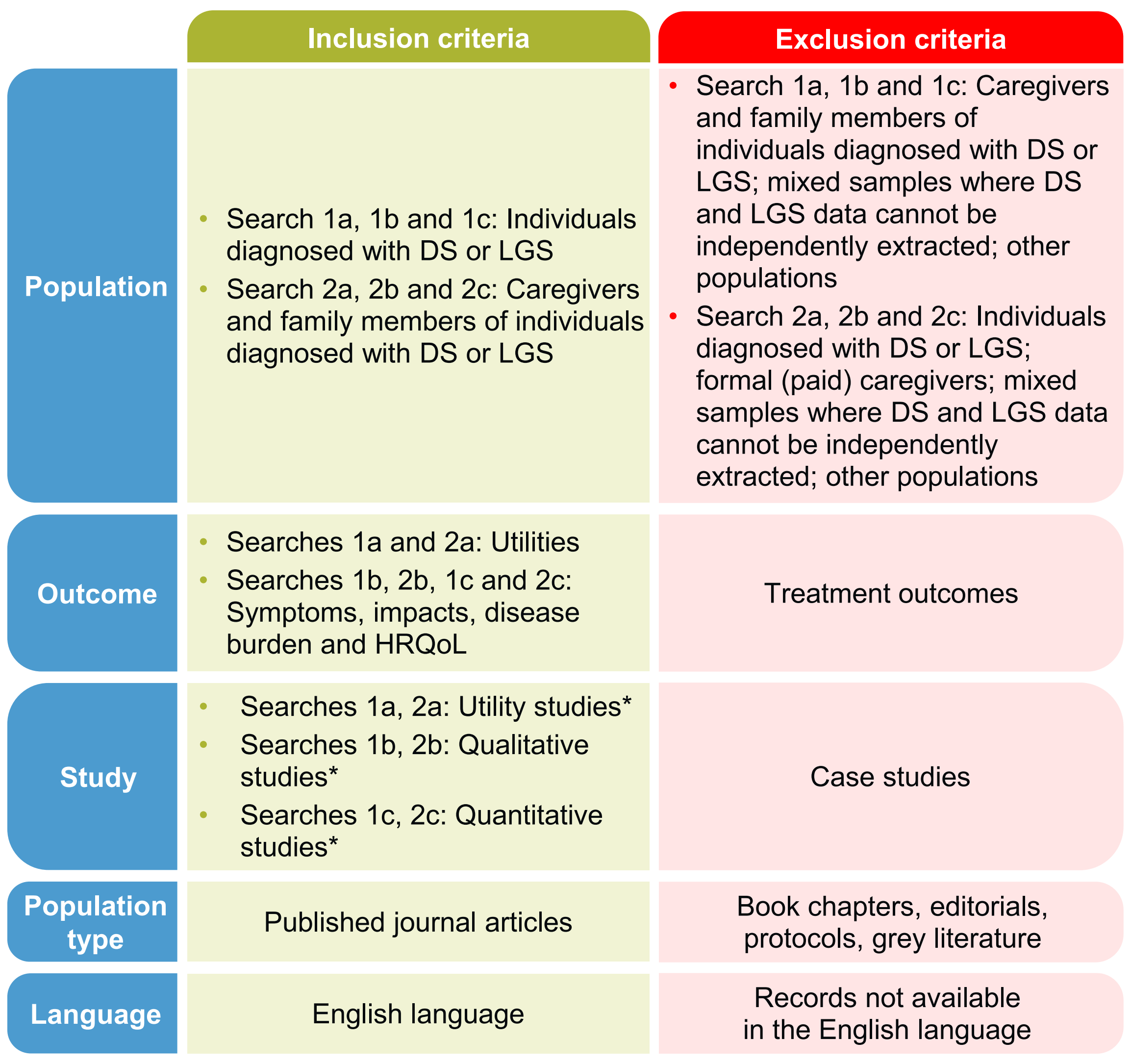
- To identify published health utility data and explore the symptoms and impacts of DS and LGS on patients and their caregivers/family members through a targeted literature review.

Methods

A series of literature searches were performed:

- Search 1 identified studies on the patient experience of DS and LGS; Search 2 identified studies on the caregiver and family member experience.
  - Pre-defined search strategies were performed in Embase and MEDLINE using the Ovid platform on 15 January 2024. No date restrictions were applied to the search.
  - Separate searches were conducted to identify utility (Search 1a and 2a), qualitative (Search 1b and 2b) and quantitative (Search 1c and 2c) studies exploring symptoms, impacts, disease burden and HRQoL data.
  - Studies were screened by 2 independent reviewers against pre-defined eligibility criteria (Figure 1).
- Search 3 identified testimonials on the DS and LGS patient, caregiver and family member experience.
  - This included testimonials from patient advocacy group websites and social media channels (Dravet Syndrome Foundation, Dravet Syndrome UK, Jumo Health, LGS Foundation).

Figure 1. Eligibility criteria



	Inclusion criteria	Exclusion criteria
Population	• Search 1a, 1b and 1c: Individuals diagnosed with DS or LGS • Search 2a, 2b and 2c: Caregivers and family members of individuals diagnosed with DS or LGS	• Search 1a, 1b and 1c: Caregivers and family members of individuals diagnosed with DS or LGS; mixed samples where DS and LGS data cannot be independently extracted; other populations • Search 2a, 2b and 2c: Individuals diagnosed with DS or LGS; formal (paid) caregivers; mixed samples where DS and LGS data cannot be independently extracted; other populations
Outcome	• Searches 1a and 2a: Utilities • Searches 1b, 2b, 1c and 2c: Symptoms, impacts, disease burden and HRQoL	Treatment outcomes
Study	• Searches 1a, 2a: Utility studies* • Searches 1b, 2b: Qualitative studies* • Searches 1c, 2c: Quantitative studies*	Case studies
Population type	Published journal articles	Book chapters, editorials, protocols, grey literature
Language	English language	Records not available in the English language

DS, Dravet syndrome; HRQoL, health-related quality of life; LGS, Lennox-Gastaut syndrome.
*Mixed-method studies and literature reviews were also included if identified.

Results

Patient utility

- A total of 6 studies reported utility data for patients with DS and LGS (Table 1).
- Utility values were lower with higher seizure frequency and fewer seizure-free days.
- Most studies used preference-based measures (eg, EQ-5D-5L, EQ-5D-3L, Health Utilities Index [HUI]-2/3).
  - Mean EQ-5D-5L: 0.33 to 0.72.
  - Overall HUI-2/3: 0.56/0.32.
- Vignette methods were utilised in 2 studies[5,8] to derive utilities for health states using the time trade-off (TTO) and/or visual analogue scale (VAS).
- Utility values ranged from 0.17 to 0.78 for patients with DS, and –0.28 to 0.83 for patients with LGS (Table 1).

Table 1. Overview of patient utilities

Publication	Utility method including valuation method/value set	DS utility values (mean, SD)	LGS utility values (mean, SD)
Primary research articles			
Auvin et al. (2021)[5,*,†]	Health state vignettes valued by patients and/or caregivers of patients with LGS/DS or other epilepsies using mean VAS scores converted to 0–1 utility scores	• Highest utility: 0.75‡ (0 convulsive seizures and 30 seizure-free days per month) • Lowest utility: 0.20‡ (32 convulsive seizures and 4 seizure-free days per month)	• Highest utility: 0.83‡ (0 drop seizures and 30 seizure-free days per month) • Lowest utility: 0.21‡ (130 drop seizures and 1 seizure-free day per month)
Gil-Nagel et al. (2023)[6]	Caregiver-reported HUI-2 and HUI-3 scored based on Spanish population norms[7]	• Overall multi-attribute score 0.56 (0.24) (HUI-2) and 0.32 (0.37) (HUI-3)	• N/A
Lagae et al. (2018)[3]	Caregiver proxy-repored EQ-5D-5L index values based on an unspecified UK value set	• Mean EQ-5D-5L: 0.42 (0.29) • Highest EQ-5D-5L: 0.46 (0.31) (pre-school participants); lowest: 0.33 (0.37) (infants <2 years)	• N/A
Lo et al. (2021)[8,§,‖]	Patient vignettes evaluated by UK general population using VAS and TTO methods	• Highest utility: 0.78 (0.24) (convulsive seizure freedom in the last month and >24 seizure-free days per month) • Lowest utility: 0.17 (0.57) (>25 convulsive seizures and ≤18 seizure-free days per month)	• Highest utility: 0.72 (0.42) (drop seizure freedom in the last month and >15 seizure-free days per month) • Lowest utility: –0.28 (0.67) (>110 drop seizures and ≤3 seizure-free days per month)
Conference abstracts/posters			
Teneishvili et al. (2020)[9]	Patient or caregiver proxy-reported EQ-5D-5L index values calculated with EQ-5D-5L Crosswalk Index Value Calculator, accounting for French population utility values[10]	• Highest EQ-5D-5L: 0.72‡ (0 or 1 seizure in the last month) • Lowest EQ-5D-5L: 0.36‡ (10 seizures in the last month)	• N/A
Pagano et al. (2019)[11] *Re-analysis of Lagae et al. (2018), UK cohort only*	Caregiver proxy-reported EQ-5D-5L index values based on an unspecified UK value set	• Mean EQ-5D-5L for UK cohort (children aged ≥2 years): 0.38 (0.27)	• N/A

DS, Dravet syndrome; HUI-2, Health Utilities Index – 2; HUI-3, Health Utilities Index – 3; LGS, Lennox-Gastaut syndrome; N/A, not applicable; TTO, time trade-off; VAS, visual analogue scale.

*Health states defined by seizure frequency (LGS, 0–130 drop seizures; DS, 0–32 convulsive seizures) and seizure-free days in the average month (LGS, 1–30; DS, 4–30). In total, 39 health states evaluated for LGS and 23 for DS. †Only UK utilities reported (see article for French data). ‡SD not reported. §Health states defined by seizure frequency (LGS, 0 to >110 drop seizures; DS, 0 to >25 convulsive seizures) and seizure-free days in the average month (LGS, >15 to ≤3; DS, >24 to ≤18). In total, 6 health states evaluated for LGS and 6 for DS. ‖Only UK utilities reported (see article for Swedish data).

Table 2. Overview of caregiver and family utilities

Publication	Utility method including valuation method/value set	DS utility values (mean, SD)	LGS utility values (mean, SD)
Auvin et al. (2021)[5,*,†]	Caregiver vignettes valued using mean VAS scores converted to 0–1 utility scores	• Highest utility: 0.74‡ (0 convulsive seizures and 30 seizure-free days per month) • Lowest utility: 0.49‡ (32 convulsive seizures and 18 seizure-free days per month)	• Highest utility: 0.78‡ (0 drop seizures and 30 seizure-free days per month) • Lowest utility: 0.38‡ (130 drop seizures and 3 seizure-free days per month)
Campbell et al. (2018)[12]	EQ-5D-5L index value computed and adjusted by US population–based preference weights[13]	• Mean EQ-5D-5L: 0.78 (0.17)	• N/A
Lo et al. (2021)[8,‡,§]	Caregiver vignettes evaluated by UK general population using VAS and TTO methods	• Highest utility: 0.87 (0.17) (convulsive seizure freedom in the last month and >24 seizure-free days per month) • Lowest utility: 0.47 (0.50) (>25 convulsive seizures and ≤18 seizure-free days per month)	• Highest utility: 0.79 (0.32) (drop seizure freedom in the last month and >15 seizure-free days per month) • Lowest utility: –0.10 (0.73) (>110 drop seizures and ≤3 seizure-free days per month)
Strzelczyk et al. (2019)[14]	EQ-5D-3L scored according to German value set derived using TTO methods[15]	• Mean EQ-5D-3L: 0.90 (0.18) (DS), compared to 0.90‖ for general population	• N/A
Strzelczyk et al. (2019)[16,¶] *Re-analysis of Strzelczyk et al. (2019)[14]*	EQ-5D-3L scored according to German value set derived using TTO methods[15]	• Mean EQ-5D-3L: 0.90 (0.18) (DS sample), 0.94 (0.10) (DRE sample), 0.96 (0.07) (SR sample), and 0.9 (general population)	• N/A

DRE, drug-resistant epilepsy; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; N/A, not applicable; SR, seizure remission; TTO, time trade-off; VAS, visual analogue scale.

*Health states defined by seizure frequency (LGS, 0–130 drop seizures; DS, 0–32 convulsive seizures) and seizure-free days in the average month (LGS, 3–30; DS, 18–30). In total, 3 health states evaluated. †Only UK utilities reported (see article for French data). ‡Health states defined by seizure frequency (LGS, 0 to >110 drop seizures; DS, 0 to >25 convulsive seizures) and seizure-free days in the average month (LGS, >15 to ≤3; DS, >24 to ≤18). In total, 6 health states evaluated for LGS and 6 for DS. §Only UK utilities reported (see article for Swedish data). ‖SD not reported. ¶Each patient with DS that participated in Strzelczyk et al. (2019)[14] matched based on age and sex with 1 patient with DRE and 1 patient in SR.

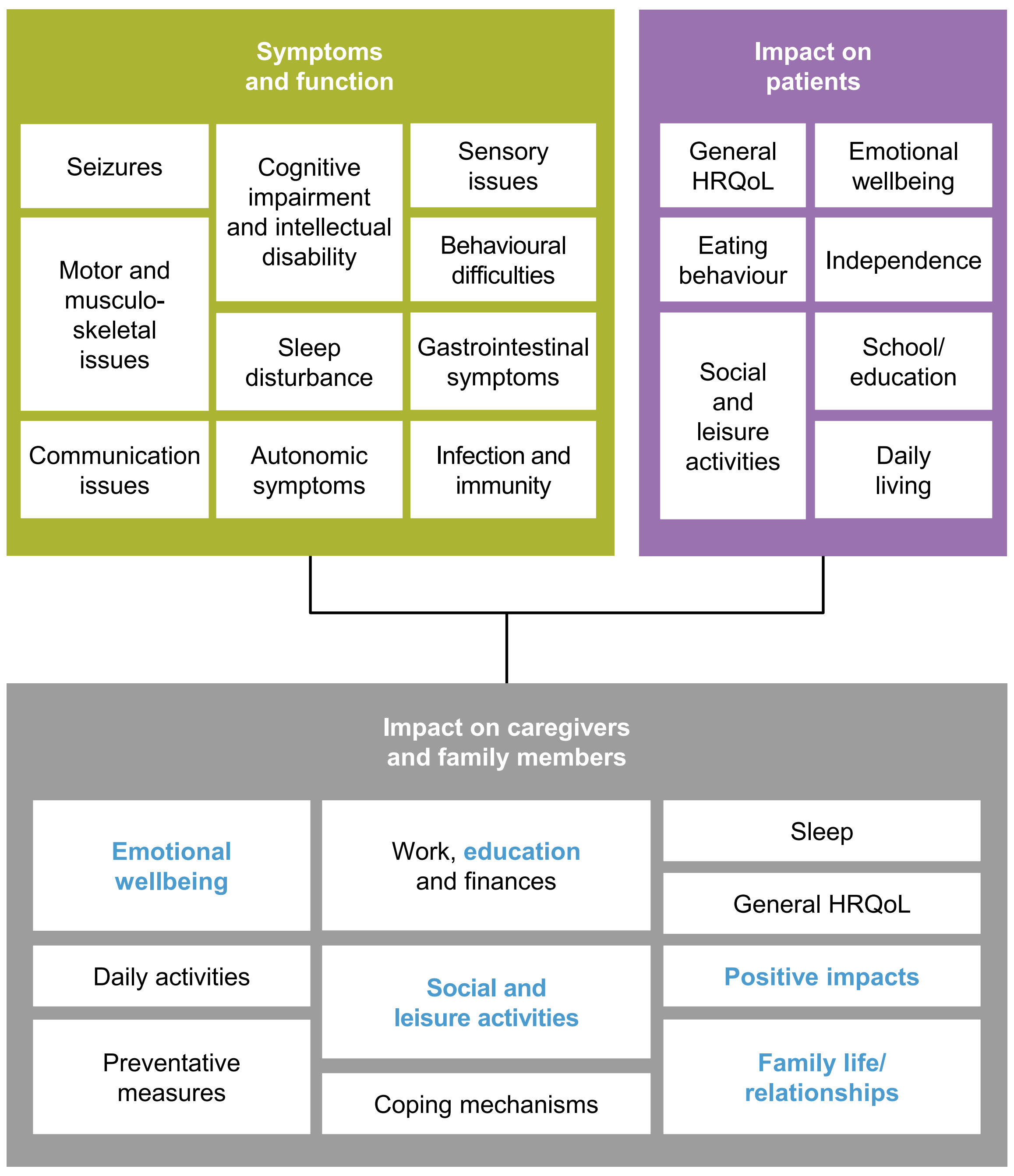
Caregiver utility

- A total of 5 studies reported utility data for caregivers of patients with DS and LGS (Table 2).
- Higher utility values were attributed to seizure freedom and more seizure-free days.
- Most studies used preference-based measures.
  - Mean EQ-5D: 0.78 to 0.90.
- Vignette methods were utilised in 2 studies[5,8] to derive utilities for health states associated with caring for a child with DS and LGS using the TTO and/or VAS.
  - Utility values ranged from 0.47 to 0.87 (DS) and –0.10 to 0.79 (LGS).

DS and LGS symptoms and impacts

- An overview of the key DS and LGS symptoms and impacts identified in the literature review are summarised in Figure 2.
- Fifteen studies reported qualitative (DS, n = 11; LGS, n = 2; DS and LGS, n = 2) and 38 studies quantitative data (DS, n = 33; LGS, n = 3; DS and LGS, n = 2) on patient symptoms and impacts.
  - Common symptoms (in addition to seizures) included behavioural disturbance, motor dysfunction, cognitive impairment, communication issues and sleep disturbance.
  - Common impacts included changes to eating behaviour, impacts to emotional and psychological wellbeing and social impacts.
- Twelve studies reported qualitative (DS, n = 9; LGS, n = 2; DS and LGS, n = 1) and 25 studies quantitative data (DS, n = 22; LGS, n = 2; DS and LGS, n = 1) on caregiver or family member impacts.
  - Common impacts included emotional or psychological wellbeing, work and finances, social life, family life and relationships.
- Impacts identified in the literature review aligned with testimonial accounts.
  - Patient testimonials focused predominantly on impacts to daily living and social/leisure activities.
  - Caregiver testimonials also described the positive impact of caring for/living with an individual with DS or LGS could have, such as how their child enriched their lives or made them feel blessed.

Figure 2. Key DS and LGS symptoms and impacts



Symptoms and function
- Seizures
- Cognitive impairment and intellectual disability
- Sensory issues
- Motor and musculo-skeletal issues
- Behavioural difficulties
- Sleep disturbance
- Gastrointestinal symptoms
- Communication issues
- Autonomic symptoms
- Infection and immunity

Impact on patients
- General HRQoL
- Emotional wellbeing
- Eating behaviour
- Independence
- Social and leisure activities
- School/ education
- Daily living

Impact on caregivers and family members
- **Emotional wellbeing**
- Work, **education** and finances
- Sleep
- General HRQoL
- Daily activities
- **Social and leisure activities**
- **Positive impacts**
- Preventative measures
- Coping mechanisms
- **Family life/ relationships**

HRQoL, health-related quality of life.
Blue text indicates the impact was also reported amongst siblings.

Conclusions

- Patient and caregiver utility scores were lower with increasing disease severity (ie, increasing seizure frequency and decreasing seizure-free days), indicating substantial HRQoL impacts of DS and LGS—particularly for those with high seizure burden.
- A wide variety of symptoms and impacts experienced by patients with DS and LGS were identified in the literature searches and testimonials, as well as impacts to caregivers and family members.
- The findings of this review highlight the significant burden of DS and LGS on patients', caregivers' and family members' quality of life.

Disclosures: GT, CL and EG are employees of Acaster Lloyd Consulting Ltd. DS, MD, FL and JSA are employees of Takeda Development Center Americas, Inc., and stockholders of Takeda Pharmaceutical Company Ltd. AB is an employee of Takeda UK Ltd.
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