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ORIGINAL ARTICLE

Nonseizure symptoms and broader seizure impacts in patients with Dravet syndrome and Lennox–Gastaut syndrome in clinical practice settings: Results from a multinational survey

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Abstract

Objective: To assess the burden of Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS), including managing seizure and nonseizure symptoms, on patients and caregivers.

Methods: Data were drawn from the Adelphi Real World DS and LGS Disease Specific Programme™, a cross-sectional survey in Asia (China, Japan), Europe (France, Germany, Italy, Spain, United Kingdom), and the United States of America between July 2022 and August 2023. Neurologists/pediatric neurologists reported demographics, clinical characteristics, and nonseizure symptoms for up to 10 consecutively consulting patients. Caregivers provided data on patient nonseizure symptoms, quality of life (QoL), satisfaction with treatment, and caregiver burden. Analyses were descriptive.

Results: Physicians ($n = 259$) reported data on 547 patients with DS and 811 with LGS. Caregivers ($n = 348$) provided data on 157 patients with DS and 191 with LGS. In the previous 6 months, 51% of patients with DS experienced ≥1 seizure-related injury and 61% experienced status epilepticus. For LGS, this was 50% and 43% of patients, respectively. Rates of moderate to very severe impairment in nonseizure symptoms were reported by physicians in learning/intellect (DS 69%; LGS 78%), verbal communication (DS 69%; LGS 71%), severity of developmental delay (DS 65%; LGS 68%), overall mental status (DS 57%; LGS 67%), and nonverbal communication (DS 61%; LGS 64%). Caregivers reported moderate to very severe impairment in learning/intellect (DS 53%; LGS 67%), severity of developmental delay (DS 52%; LGS 56%), verbal communication (DS 48%; LGS 48%), and nonverbal communication (DS 42%; LGS 45%). Caregivers reported nonseizure symptoms

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moderately to significantly impacted QoL for 56% of patients (DS 49%; LGS 61%); satisfaction with treatment rate was low for control over cognition/memory, verbal communication, and nonverbal communication impairment.

Significance: In this study, considerable burden in DS and LGS management and care was driven by nonseizure symptoms, suggesting a need for treatments that manage the broad spectrum of disease symptoms.

Plain Language Summary: We asked doctors and caregivers to tell us about the symptoms that patients with Dravet syndrome and Lennox–Gastaut syndrome have. We asked how the symptoms affect the lives of the patients as well as the caregivers. We found that seizures have a big impact on the health and well-being of patients and caregivers. We also found that other symptoms not caused by seizures have a big impact on patients and their caregivers.

KEYWORDS

caregiver, disease burden, Dravet syndrome, Lennox–Gastaut syndrome, nonseizure symptoms

1 | INTRODUCTION

Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) are rare developmental and epileptic encephalopathies that manifest in early childhood and are characterized by highly unpredictable and frequent treatment-resistant seizures.[1,2] In addition to multiple seizure types, DS and LGS are associated with a range of nonseizure symptoms, including developmental delay, intellectual disability, motor impairments, deficits in communication and sleep, and psychiatric and behavioral issues.[3–5] In both DS and LGS, nonseizure symptoms typically begin in infancy or childhood, and may worsen or become more detectable throughout childhood.[3,4] To date, management of DS has focused on seizure control and antiseizure medication adverse effects, with limited agreement on the optimal management of additional symptoms and comorbidities, such as intellectual disability and sleep problems.[6] For LGS, general management principles balance seizure control, adverse events, and patients' quality of life (QoL).[5] In addition to drug–drug interactions and adverse events, treatment with multiple antiseizure medications can adversely affect nonseizure symptoms, such as cognitive development and alertness.[7,8] Although the burden of seizure management in DS and LGS has been described,[1,2,5] and the frequency of nonseizure symptoms reported, it is also vital to understand the impact of these nonseizure symptoms on patients and their families.[3,4]

As most patients with DS or LGS require 24-h care, the impact on caregivers is substantial.[3] Indeed, anxiety, depression, and sleep problems are frequently reported by caregivers of patients with DS.[3,9] In a systematic literature review, high caregiver burden was identified in those caring for patients with LGS and was associated with physical problems (e.g., fatigue and sleep disturbances), social isolation, poor mental health, and financial difficulties.[4] Furthermore, guidance from the National Institute for Health and Care Excellence and Institute for Clinical and Economic Review recognizes the health effects and impact on caregivers as important factors when evaluating potential new therapies.[10,11]

There is a lack of comprehensive real-world data on the impact of nonseizure symptoms and broader seizure

Key points

- Real-world data are lacking on nonseizure symptom impacts on patients with Dravet (DS) and Lennox–Gastaut syndromes (LGS) and caregivers.
- Data were drawn from the Adelphi Real World DS and LGS Disease Specific Programme (DSP)™.
- Disease burden in DS and LGS was driven by both nonseizure symptoms and seizure outcomes.
- Physicians reported high severity rates for verbal and nonverbal communication, learning/intellect, and developmental delay.
- Nonseizure symptoms affected quality of life for more than half of the patients, according to their caregivers.

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impacts among patients with DS and LGS and their caregivers, both globally and in individual countries such as China and Japan.[4,12] We aimed to assess the real-world burden of DS and LGS, including the burden associated with managing seizure and nonseizure symptoms, both on the patients and their caregivers.

2 | MATERIALS AND METHODS

This noninterventional (observational) study was conducted in full accordance with the Guidelines for Good Pharmacoepidemiology Practice published by the International Society of Pharmacoepidemiology[13] and the laws and regulations of the countries in which the research was conducted. Local regulatory authority requirements were met before study commencement. Informed consent was collected from all enrolled caregivers. Data were collected in such a way that patients and physicians could not be identified directly.

2.1 | Study design

This was a retrospective analysis using data drawn from the Adelphi Real World DS and LGS Disease Specific Programme™,[14] a cross-sectional survey of physicians and their patients in Asia (China and Japan), Europe (France, Germany, Italy, Spain, and the United Kingdom), and the United States of America (USA) between July 2022 and August 2023. Disease Specific Programmes™ are large multinational surveys conducted in clinical practice that capture real-world disease management, disease burden impact, and associated treatment effects.[14–17] The study comprised patient record forms (PRFs) completed by physicians and a caregiver survey (Figure 1).

2.2 | Study population and data collection

Physicians were recruited by local fieldwork agencies, and a geographically representative sample was targeted. Neurologists and pediatric neurologists completed a PRF, a 30-min online cross-sectional survey, for up to 10 consecutively consulting patients with DS or LGS, regardless of their reason for the visit.

Caregivers of patients with DS or LGS were invited to complete a survey independently of the physician and immediately after consultation. Caregiver inclusion was defined by caregivers being present with the patients at the consultation that prompted inclusion in the DSP™. The caregiver survey was completed either via an online link or by pen and paper. As participation was voluntary, caregiver data were not available for every patient. As such, the DSP™ criteria did not require caregiver samples to be representative of the population in terms of race, ethnicity, income, social class, age, or any other demographics.

2.3 | Eligibility criteria

Eligible physicians were neurologists or pediatric neurologists involved in the treatment decisions and management of ≥1 patient with DS or LGS in a typical month. Patients were eligible for inclusion if they had a physician-confirmed diagnosis of DS or LGS and consulted with the physician during the data collection period. Patients not

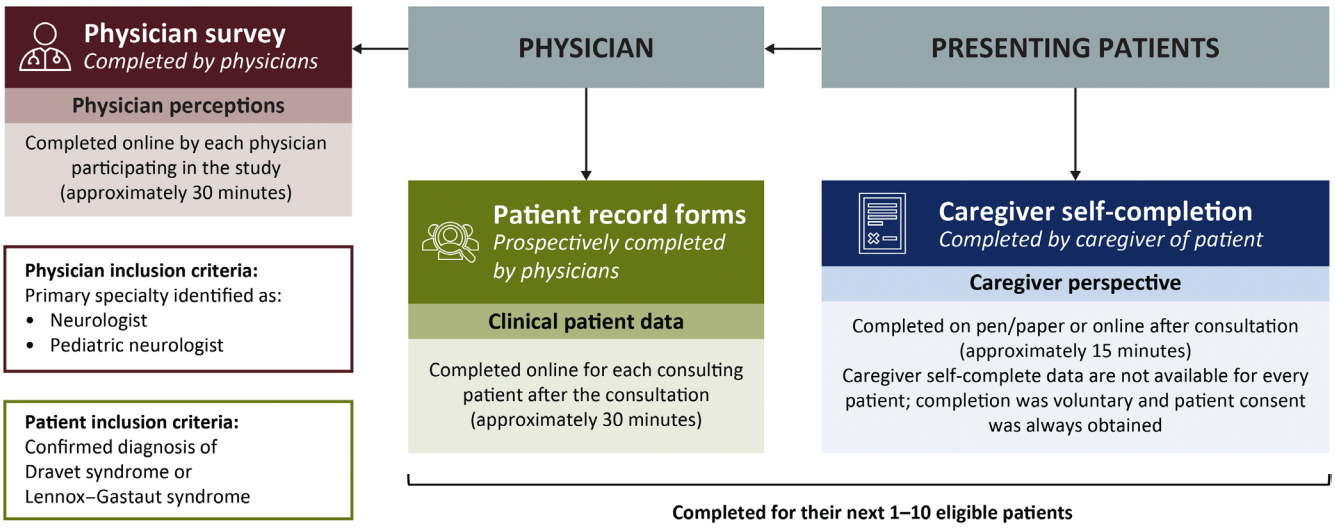

FIGURE 1 Study design.

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currently receiving treatment were excluded from this analysis. Caregivers were eligible if they were the main primary caregiver of a patient diagnosed with either DS or LGS whose information had been recorded on a PRF.

2.4 | Study measures and assessments

Outcomes collected on the PRFs included patients' demographics, patient journey (age at first seizure and age at diagnosis), seizures ever experienced, seizure-related injuries and status epilepticus in the 6 months prior to the survey date, other comorbid conditions, level of physical and mental impairment in the 4 weeks prior to the survey date, and patients' QoL. Nonseizure impairments included: verbal and nonverbal communication, mobility, overall physical, learning and intellectual, alertness, overall mental, developmental delay, and disruptive behavior. Severities of nonseizure impairments were recorded on a 5-point scale comprising "none," "mild," "moderate," "severe," and "very severe." Reports of "moderate," "severe," and "very severe" were grouped.

Caregiver-reported outcomes included caregivers' and patients' demographics, DS/LGS symptoms, and seizure characteristics (age of patients at first seizure and at diagnosis), their perspective on the patients' nonseizure symptoms, satisfaction with treatment in relation to reductions of nonseizure symptoms according to a prespecified list (communication, behavioral issues, sleep disturbance, etc.), and patients' QoL, as well as their own experiences of caring for a patient with DS or LGS. Satisfaction with treatment was rated using a 5-point scale, where 0 represents least satisfaction and 4 highest satisfaction. Caregiver-reported impact of nonseizure symptoms on the patients' QoL was assessed as "no impact," "slightly impacted," "moderately impacted," or "significantly impacted." Caregivers completed the Work Productivity and Activity Impairment Questionnaire (WPAI) to assess caregivers' loss of productivity due to caring responsibilities, including missed workdays and activity impairment.[18]

2.5 | Analyses

Analyses were descriptive in nature, with no formal hypothesis tested. Data were assessed for the total sample as well as by region (Asia, Europe, and the USA). For categorical measures, data included frequency and percentage of total study individuals observed in each category; for continuous and count variables, findings were presented as mean with standard deviation (SD) and median with interquartile range (IQR). Missing data were not imputed and therefore the base could vary between variables and is presented as appropriate.

3 | RESULTS

3.1 | Patients' demographics and clinical characteristics—Physician reported

Overall, 259 physicians participated in the study and provided data on 547 patients receiving treatment for DS and 811 receiving treatment for LGS (Table 1). Based on data from a separate physician survey, the physicians see a mean (SD) of 74.6 (93.5) patients with epilepsy in a typical month, including 5.0 (7.6) patients with DS and 6.6 (9.8) with LGS.

Patients' demographic and clinical characteristics reported by physicians are summarized in Table 1. The mean (SD) age of patients at the time of the survey was 9.2 (7.4) years for DS and 14.7 (11.1) years for LGS. Most patients were male. In Europe and the USA, most patients were White (both DS and LGS); in Asia, most patients were Han Chinese (both DS and LGS). Most patients experienced other comorbid conditions at the time of the survey, most commonly psychomotor/cognitive impairment, attention-deficit/hyperactivity disorder, and sleep disorder/insomnia. In DS, the most common seizure type ever experienced was myoclonic, and in LGS, it was tonic. At the time of data collection, stiripentol, cannabidiol, and fenfluramine were classified as orphan drugs specifically indicated for DS, and cannabidiol, rufinamide, and fenfluramine for LGS. The proportions of patients receiving these therapies are shown in Table 1.

3.2 | Caregivers' demographics—Caregiver reported

A total of 348 caregivers participated in the study and provided data on 157 patients receiving treatment for DS and 191 receiving treatment for LGS (Table 2). Most caregivers in Asia were from China (95%) and most in Europe were from Germany (72%). The mean ages of caregivers at the time of the survey, split by region, are given in Table 2; the majority were the patients' parent and female.

3.3 | Patients' seizure-related injuries and status epilepticus—Physician reported

Overall, 278 (51%) patients with DS and 407 (50%) patients with LGS experienced ≥1 seizure-related injury over the last 6 months. Further details relating to seizure injury and status epilepticus are shown in Table S1.

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TABLE 1 Demographic and clinical characteristics of the patients with DS or LGS (physician-reported data).

	DS				LGS			
	Total (*N* = 547)[a]	**Asia (*n* = 140)**	**Europe (*n* = 326)**	**USA (*n* = 81)**	**Total (*N* = 811)[a]**	**Asia (*n* = 196)**	**Europe (*n* = 448)**	**USA (*n* = 167)**
Mean (SD) age, years	9.2 (7.4)	5.6 (5.4)	10.3 (7.3)	11.1 (8.8)	14.7 (11.1)	8.9 (8.4)	16.1 (10.8)	17.9 (12.0)
Median (range)	6.0 (1–55)	4.0 (1–34)	9.0 (1–39)	10.0 (1–55)	13.0 (1–70)	6.0 (1–48)	16.0 (1–70)	16.0 (2–68)
Male, *n* (%)	322 (59)	81 (58)	198 (61)	43 (53)	530 (65)	129 (66)	293 (65)	108 (65)
Ethnicity, *n* (%)[b]	***n* = 505**	***n* = 140**	***n* = 284**	***n* = 81**	***n* = 732**	***n* = 196**	***n* = 369**	***n* = 167**
African American or Afro-Caribbean	15 (3)	0 (0)	4 (1)	11 (14)	36 (5)	0 (0)	8 (2)	28 (17)
Asian	13 (3)	0 (0)	8 (3)	5 (6)	12 (2)	0 (0)	8 (2)	4 (3)
Chinese	113 (22)	113 (81)	0 (0)	0 (0)	152 (21)	152 (78)	0 (0)	0 (0)
Hispanic/Latino	17 (3)	0 (0)	8 (3)	9 (11)	30 (4)	0 (0)	14 (4)	16 (10)
Japanese, Korean or Middle Eastern	32 (6)	27 (19)	4 (1)	1 (1)	50 (7)	45 (23)	3 (1)	2 (1)
Native American	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (1)
Other	1 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
White/Caucasian	318 (63)	0 (0)	263 (93)	55 (68)	459 (63)	0 (0)	341 (92)	118 (71)
Median (IQR) age at first seizure, years	0.8 (0.6–1.3)	0.8 (0.5–1.3)	0.8 (0.6–1.1)	1.0 (0.6–2.0)	3.0 (1.5–5.0)	2.5 (1.0–4.0)	4.0 (2.0–5.3)	2.5 (1.3–5.4)
Median (IQR) age at diagnosis, years	1.5 (0.8–3.0)	1.4 (0.8–2.5)	1.4 (0.7–3.0)	2.9 (1.3–4.8)	4.3 (2.5–6.6)	3.2 (1.9–4.7)	4.6 (2.8–6.5)	6.6 (3.2–11.0)
Top 5 seizure types ever experienced, *n* (%)								
Tonic	226 (41)	64 (46)	133 (41)	29 (36)	513 (63)	142 (72)	298 (67)	73 (44)
Generalized tonic–clonic	269 (49)	47 (34)	180 (55)	42 (52)	392 (48)	81 (41)	211 (47)	100 (60)
Atypical absence	193 (35)	61 (44)	110 (34)	22 (27)	454 (56)	117 (60)	279 (62)	58 (35)
Myoclonic	281 (51)	85 (61)	166 (51)	30 (37)	276 (34)	91 (46)	137 (31)	48 (29)
Atonic (drop attacks)	130 (24)	28 (20)	84 (26)	18 (22)	409 (50)	61 (31)	280 (63)	68 (41)
Any and top 5 other comorbid conditions at time of survey, *n* (%)[c]								
Any	363 (66)	88 (63)	222 (68)	53 (65)	567 (70)	136 (69)	309 (69)	122 (73)
Psychomotor/cognitive impairment	176 (48)	36 (41)	116 (52)	24 (45)	245 (43)	44 (32)	156 (50)	45 (37)
ADHD	154 (42)	44 (50)	91 (41)	19 (36)	204 (36)	60 (44)	113 (37)	31 (25)
Sleep disorder/insomnia	114 (31)	23 (26)	82 (37)	9 (17)	162 (29)	40 (29)	95 (31)	27 (22)
Autism	96 (26)	20 (23)	55 (25)	21 (40)	141 (25)	28 (21)	64 (21)	49 (40)
Anxiety	45 (12)	3 (3)	28 (13)	14 (26)	85 (15)	7 (5)	44 (14)	34 (28)

(Continues)

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TABLE 1 (Continued)

	DS				LGS			
	Total (*N* = 547)[a]	**Asia (*n* = 140)**	**Europe (*n* = 326)**	**USA (*n* = 81)**	**Total (*N* = 811)[a]**	**Asia (*n* = 196)**	**Europe (*n* = 448)**	**USA (*n* = 167)**
Any and top 5 physical impairments over the last 4 weeks, *n* (%)								
Any	394 (72)	105 (75)	243 (75)	46 (57)	589 (73)	150 (77)	330 (74)	109 (65)
Gait impairment in the absence of limb paralysis	220 (56)	47 (45)	149 (61)	24 (52)	311 (53)	64 (43)	202 (61)	45 (41)
Speaking difficulty (dysphasia)	217 (55)	72 (69)	131 (54)	14 (30)	299 (51)	94 (63)	163 (49)	42 (39)
Difficulty with maintaining visual focus	81 (21)	19 (18)	49 (20)	13 (28)	152 (26)	42 (28)	74 (22)	36 (33)
Swallowing difficulty	73 (19)	11 (10)	54 (22)	8 (17)	–	–	–	–
Speaking difficulty (aphasia)	67 (17)	16 (15)	44 (18)	7 (15)	135 (23)	32 (21)	65 (20)	38 (35)
Paralysis of both legs	–	–	–	–	89 (15)	21 (14)	40 (12)	28 (26)
Any and top 5 mental impairments over the last 4 weeks, *n* (%)								
Any	514 (94)	129 (92)	313 (96)	72 (89)	772 (95)	185 (94)	433 (97)	154 (92)
Cognition	338 (66)	101 (78)	201 (64)	36 (50)	577 (75)	142 (77)	345 (80)	90 (58)
Maintaining focus	310 (60)	83 (64)	190 (61)	37 (51)	470 (61)	129 (70)	273 (63)	68 (44)
Language/articulation	278 (54)	78 (60)	173 (55)	27 (38)	391 (51)	99 (54)	228 (53)	64 (42)
Memory	209 (41)	74 (57)	113 (36)	22 (31)	368 (48)	119 (64)	207 (48)	42 (27)
Performing >1 task at a time	198 (39)	45 (35)	132 (42)	21 (29)	–	–	–	–
Processing information	–	–	–	–	343 (44)	74 (40)	199 (46)	70 (45)
Proportion of patients receiving orphan drugs specifically indicated (ODSI) for DS or LGS	***n* = 230**	***n* = 23**	***n* = 173**	***n* = 34**	***n* = 274**	***n* = 10**	***n* = 196**	***n* = 68**
Stiripentol	145 (63)	18 (78)	117 (68)	10 (29)	–	–	–	–
Cannabidiol	73 (32)	3 (13)	51 (29)	19 (56)	121 (44)	0 (0)	74 (38)	47 (69)
Fenfluramine	38 (17)	2 (9)	27 (16)	9 (26)	21 (8)	0 (0)	17 (9)	4 (6)
Rufinamide	–	–	–	–	155 (57)	10 (100)	122 (62)	23 (34)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DS, Dravet syndrome; IQR, interquartile range; LGS, Lennox–Gastaut syndrome; SD, standard deviation; USA, United States of America.

[a]Number of patient report forms completed per country: China, *n* = 265; Japan, *n* = 71; France, *n* = 121; Germany, *n* = 157; Italy, *n* = 229; Spain, *n* = 191; United Kingdom, *n* = 76; USA, *n* = 248.

[b]Owing to data collection regulations, no data on patients' ethnicity were able to be collected from France.

[c]Data for individual comorbid conditions are reported as a percentage of the population with "Any" comorbid condition.

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TABLE 2 Caregiver-reported demographics.

	DS				LGS			
	Total (*N* = 157)[a]	**Asia (*n* = 103)**	**Europe (*n* = 39)**	**USA (*n* = 15)**	**Total (*N* = 191)[a]**	**Asia (*n* = 136)**	**Europe (*n* = 46)**	**USA (*n* = 9)**
Mean (SD) age of caregivers, years	37.7 (10.6)	35.7 (10.9)	41.9 (8.8)	40.3 (9.2)	40.4 (11.1)	39.7 (12.1)	43.4 (7.8)	36.0 (4.7)
Self-reported sex of caregivers, female, *n* (%)	131 (83)	87 (84)	30 (77)	14 (93)	149 (78)	100 (74)	41 (89)	8 (89)
Relationship to patient, *n* (%)[b]								
Parent	137 (87)	86 (83)	36 (92)	15 (100)	156 (82)	103 (76)	44 (98)	9 (100)
Grandparent	13 (8)	13 (13)	0 (0)	0 (0)	27 (14)	26 (19)	1 (2)	0 (0)
Other family member	7 (4)	4 (4)	3 (8)	0 (0)	7 (4)	7 (5)	0 (0)	0 (0)
Mean (SD) caregiver-reported patients' age, years	6.6 (5.3)	4.7 (3.9)	10.5 (6.3)	9.6 (4.4)	7.5 (5.8)	6.5 (5.3)	10.3 (6.5)	9.0 (3.4)
Caregiver-reported patients' sex, male, *n* (%)	94 (60)	58 (56)	28 (72)	8 (53)	128 (67)	90 (66)	36 (78)	2 (22)

Abbreviations: DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome; SD, standard deviation; USA, United States of America.

[a]Number of caregivers per country: China, *n* = 228; Japan, *n* = 11; France, *n* = 6; Germany, *n* = 61; Italy, *n* = 4; Spain, *n* = 14; United Kingdom, *n* = 0; USA, *n* = 24.

[b]Data missing for 1 caregiver of a patient with LGS in Europe.

3.4 | Severities of patients' nonseizure symptoms—Physician and caregiver reported

Overall, 72% of patients with DS had a physical impairment and 94% had a mental impairment at the time of the survey. A summary of the top 5 physical and mental impairments is shown in Table 1.

Physician-reported severities of nonseizure impairments in DS are summarized in Figure 2A, with learning/intellect, verbal communication, severity of developmental delay, nonverbal communication, and overall mental status reported as the most severely affected within this sample. Physician-reported "moderate" to "very severe" impairments are shown in Table S2.

The most common caregiver-reported nonseizure-related impairments rated as "moderate" to "very severe" were learning/intellect, severity of developmental delay, verbal communication, overall physical status, and nonverbal communication (Table S2).

Overall, 73% of patients with LGS had a physical impairment and 95% had a mental impairment at the time of the survey (Table 1).

The severities of physician-reported nonseizure impairments in LGS are summarized in Figure 2B. Physicians reported that learning/intellect, verbal communication, severity of developmental delay, overall mental status, and nonverbal communication were severely affected in patients with LGS. Physician-reported "moderate" to "very severe" impairments are shown in Table S3.

The most common caregiver-reported LGS nonseizure-related impairments rated as "moderate" to "very severe" were learning/intellect, severity of developmental delay, verbal communication, nonverbal communication, and alertness (Table S3).

3.5 | Patients' QoL—Caregiver and physician reported

A third of caregivers of patients with DS rated patients' QoL as "somewhat poor" to "very poor", with the impact of specific symptoms reported in Table S4. Overall, 102 of 156 (65%) caregivers reported daytime seizures as "moderately" to "significantly" impacting patients' QoL. In addition, 84 of 151 (56%) caregivers reported nighttime seizures as "moderately" to "significantly" impacting patients' QoL.

Overall, 49% of caregivers of patients with DS reported nonseizure symptoms as "moderately" to "significantly" impacting patients' QoL (Figure 3A). A "moderate" to "significant" impact on patients' QoL was reported for impaired cognition and memory (57%), verbal communication (56%), nonverbal communication (46%), appetite (35%), sleep (36%), mobility (49%), and behavior (35%).

Among caregivers of patients with LGS, 34% rated patients as having a "somewhat poor" to "very poor" QoL (Table S4). Overall, 136 of 191 (71%) caregivers reported daytime seizures as "moderately" to "significantly" impacting patients' QoL. Additionally, 121 of 188 (64%) caregivers reported nighttime seizures as "moderately" to "significantly" impacting patients' QoL.

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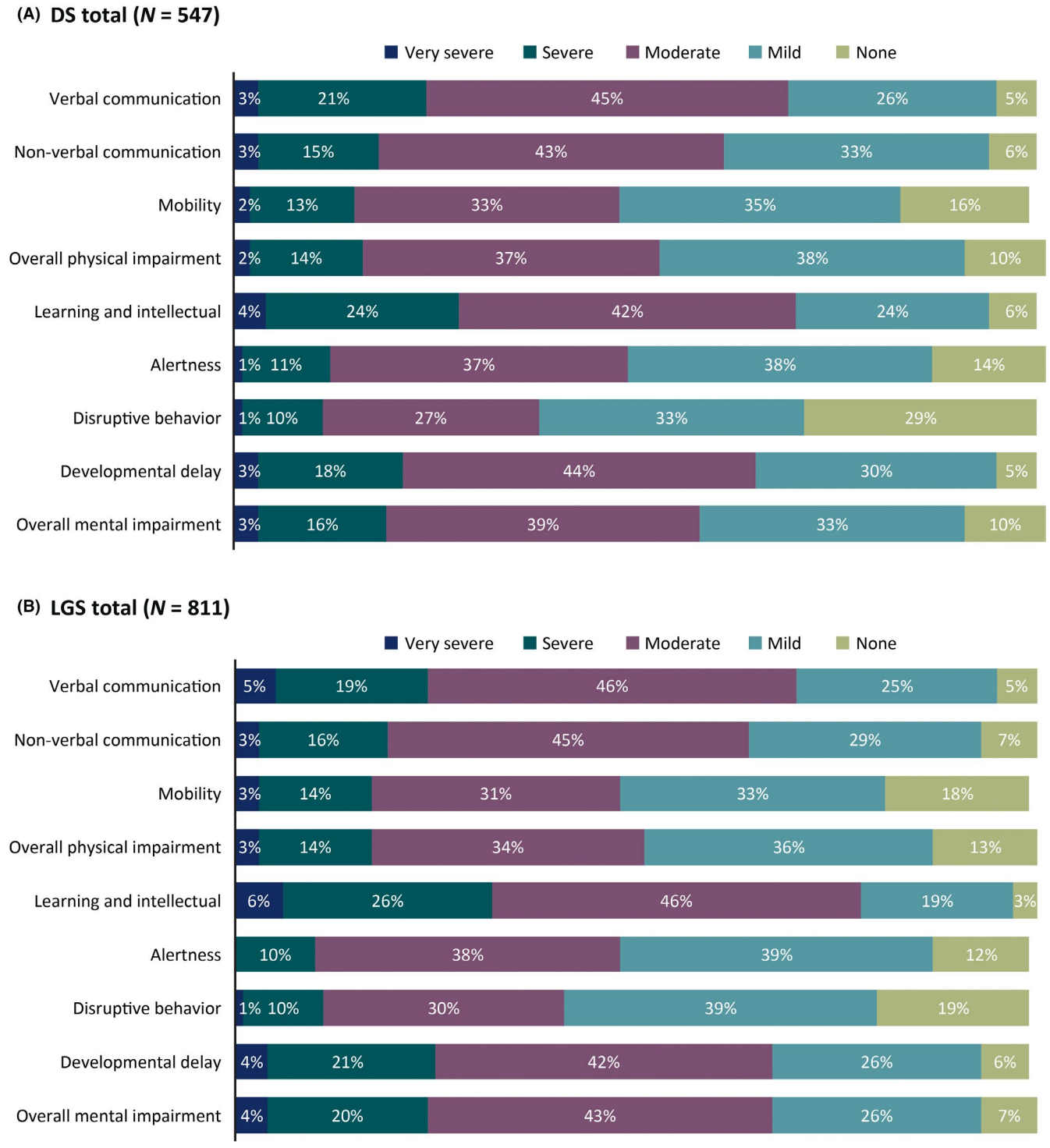

FIGURE 2 Severities of physician-reported nonseizure-related impairments in patients with (A) DS and (B) LGS. Verbal communication (e.g., speech, talking); nonverbal communication (e.g., facial expressions, gestures, eye contact); mobility (e.g., walking, gait); overall physical impairment (e.g., gross/fine motor skills); learning and intellect (e.g., reading, writing, learning disability); alertness (e.g., somnolence, lethargy, fatigue); disruptive behavior (e.g., aggression, violence); overall mental impairment (e.g., mental retardation, depression, anxiety); developmental delay (e.g., missing developmental milestones). DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome.

Overall, 61% of caregivers of patients with LGS reported nonseizure symptoms as "moderately" to "significantly" impacting patients' QoL (Figure 3B). A "moderate" to "significant" impact on patients' QoL for impaired cognition and memory (69%), verbal communication (63%), nonverbal communication (59%), issues with appetite (35%), sleep disturbance (49%), mobility (44%), and behavioral problems (48%).

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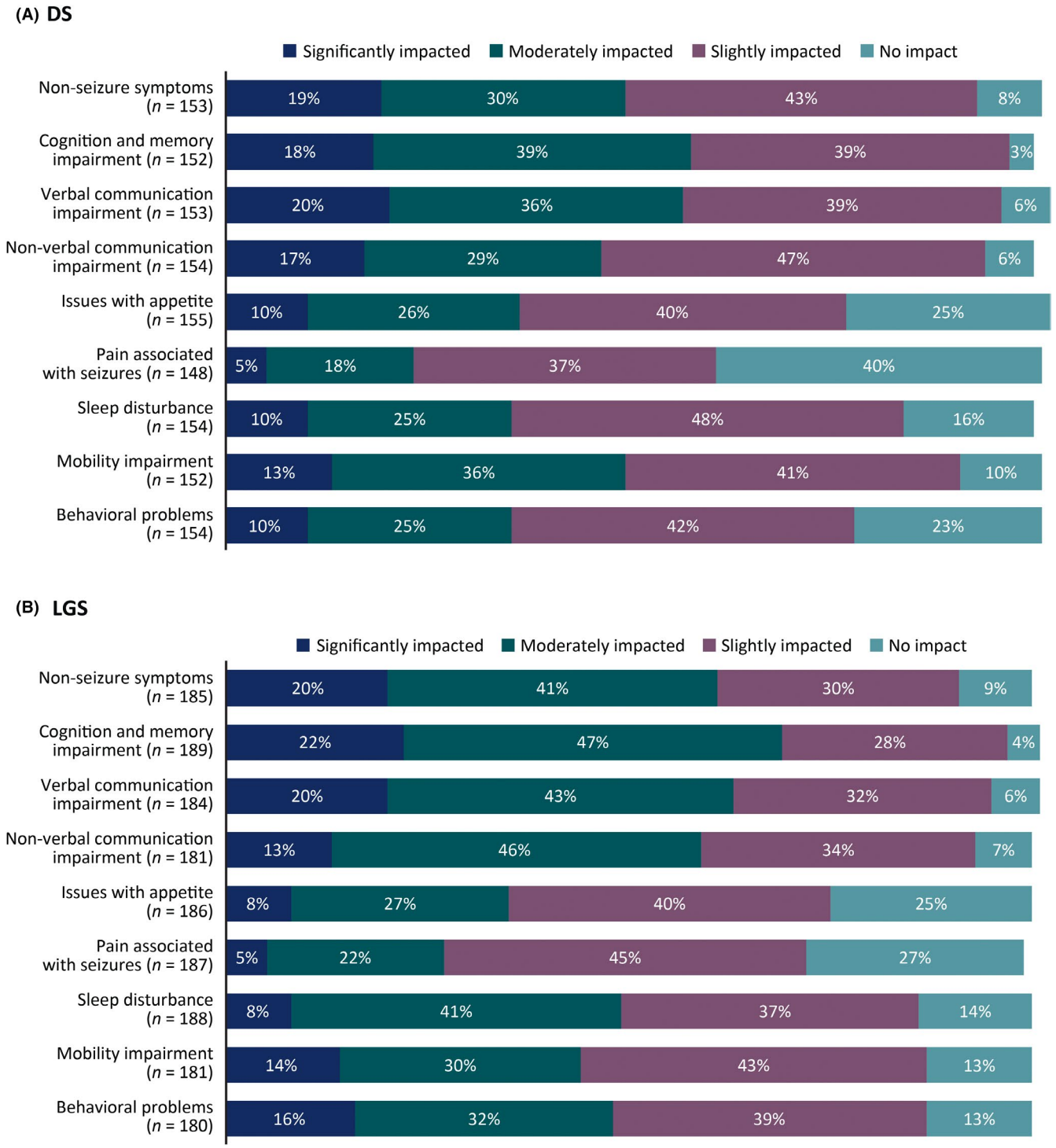

FIGURE 3 Caregiver-reported impact on patients' quality of life in patients with (A) DS and (B) LGS. DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome.

Data by region and physician-reported assessments of the patients' QoL are shown in Tables S4 and S5, respectively. Overall, physicians rated daytime seizures and mental impairment as having the greatest impact on patients' QoL, although nighttime seizures and mental impairment were rated as having a high impact on patients with DS and LGS, respectively, in Asia.

3.6 | Satisfaction with treatment in relation to reducing nonseizure symptoms—Caregiver reported

Satisfaction with treatment was reported in relation to reducing nonseizure symptoms (Figure 4, Table S6). Low satisfaction (rated 0–2) with DS and LGS treatment was

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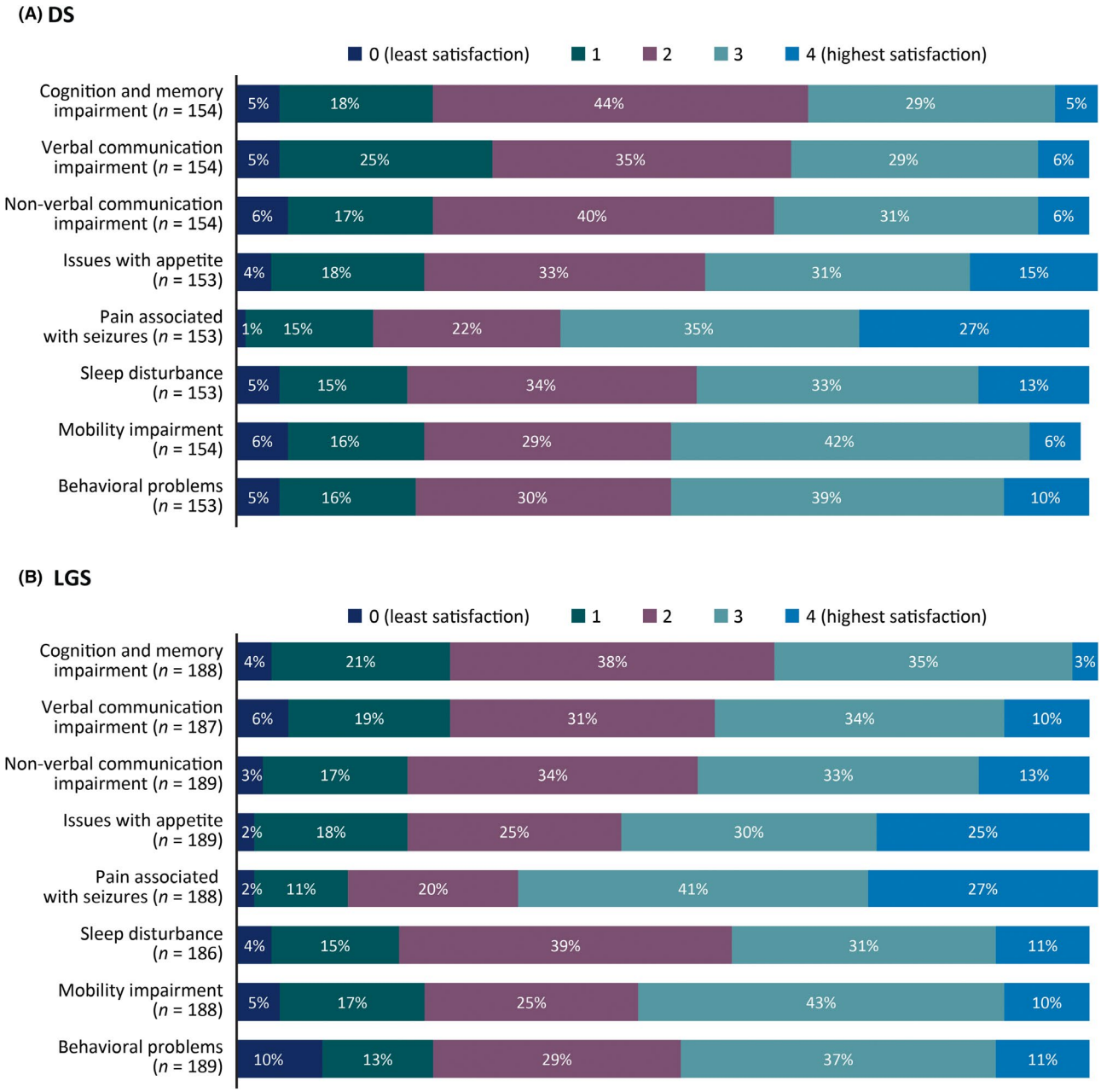

FIGURE 4 Caregivers' satisfaction with treatment in relation to reducing nonseizure symptoms for patients with (A) DS and (B) LGS. DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome.

reported by the largest proportion of caregivers for reducing cognition and memory impairment (Table S6).

3.7 | Caregivers' burden—Caregiver reported

3.7.1 | Work productivity and impact questionnaire

Twenty-nine percent (44/152) of caregivers of patients with DS reported being employed (Asia, 29/101 [29%]; Europe, 9/40 [22%]; USA, 6/11 [55%]). According to the WPAI, the mean (SD) percentage impairment while working was 37.7% (19.0; Asia, 36.9% [20.9]; Europe, 38.9% [12.7]; USA, 40.0% [20.0]) and the mean (SD) percentage of overall work impairment was 41.7% (21.4; Asia, 41.2% [23.6]; Europe, 43.1% [11.4]; USA, 42.5% [21.7]). The mean (SD) percentage of activity impairment was 59.3% (20.6; Asia, 58.5% [21.0]; Europe, 62.9% [20.4]; USA, 53.6% [16.3]).

Thirty-two percent (61/193) of caregivers of patients with LGS reported being employed (Asia, 40/136 [29%]; Europe, 12/44 [27%]; USA, 9/13 [69%]). The mean (SD)

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percentage impairment while working was 41.3% (20.0; Asia, 41.2% [22.6]; Europe, 45.0% [14.5]; USA, 36.7% [14.1]) and the mean (SD) percentage of overall work impairment was 44.8% (22.6; Asia, 46.0% [24.8]; Europe, 43.9% [14.9]; USA, 40.3% [20.4]). The mean (SD) percentage of activity impairment was 57.6% (19.8; Asia, 58.7% [20.4]; Europe, 55.2% [15.5]; USA, 53.8% [25.3]).

3.7.2 | Most difficult aspects of managing the patients' disease

The 5 most difficult aspects of managing DS were managing seizures, managing prolonged seizures (status epilepticus), inability to effectively communicate with the patients verbally, managing fever, and monitoring developmental milestones (Table S7).

Overall, 50% reported that caring for patients with DS in the last 4 weeks was "somewhat difficult" to "very difficult." In addition, 61% found it "somewhat difficult" to "very difficult" to find time for their own needs and interests; 21% reported that the patients' sleep disturbances "very often" or "always" disrupted their sleep, and 40% reported that caring for the patients "very often" or "always" impacted their other responsibilities (e.g., other family responsibilities or household chores; Table S7).

The five most difficult aspects of managing LGS were managing seizures, managing drop seizures (associated with falls), managing prolonged seizures (status epilepticus), monitoring developmental milestones, and managing aggression and other behavioral problems (Table S7).

In the LGS cohort, 44% reported that caring for the patients in the last 4 weeks was "somewhat difficult" to "very difficult". Overall, 52% found it "somewhat difficult" to "very difficult" to find time for their own needs and interests; 20% reported that the patients' sleep disturbances "very often" or "always" disrupted their sleep, and 31% reported that caring for the patients "very often" or "always" impacted their other responsibilities (Table S7). Data by region are shown in Table S7.

4 | DISCUSSION

This study provides data from a large and unique global resource, the Adelphi Real World DS and LGS DSP™, and includes data from China and Japan. Outcomes from this analysis showed that disease burden in DS and LGS is driven not only by seizure outcomes, but also by nonseizure symptoms. Overall, our data showed that physicians commonly reported nonseizure impairments, such as with cognition, difficulty maintaining focus, gait impairment, and speaking difficulty. Physicians and caregivers also reported that learning/intellect, verbal communication, developmental delay, and nonverbal communication were severely affected. Based on our descriptive data, patients with DS had a mean age of 9.2 years and those with LGS had a mean age of 14.7 years. This suggests that the patients are being assessed at different stages of their overall development. The younger mean age of patients with DS is also reflective of earlier onset of symptoms than for LGS and therefore diagnosis at a younger age.[1,2] Furthermore, although managing seizures was the most frequently reported difficulty for caregivers, 3 in 10 caregivers reported difficulty in monitoring the patients' developmental milestones. Although rates of nonseizure symptoms have been reported in the literature, understanding of physician-reported severity and its impact is lacking. Our data, including the caregivers' responses, provide a unique perspective on the burden associated with DS and LGS.

Seizure onset in infancy, high seizure frequency, and presentation with multiple seizure types all contribute to substantial care requirements, negative impacts on patients' QoL, and a significant humanistic burden for caregivers of patients with DS or LGS.[1,3,4,12,19–21] In this study, nonseizure symptoms impacted both patients' and caregivers' QoL. It has been reported that reductions in the severity and frequency of seizures might have benefits for impairments to cognition and neurodevelopment, but additional evidence is needed.[1] These responses from physicians and caregivers may highlight differences in the aspects of DS and LGS that each group considers to be the most important. Nonseizure symptoms, such as impairment to cognition and communication, have patient- and caregiver-relevant impacts and therefore are important to caregivers. These differences also reinforce the need to capture and consider different viewpoints to gain a holistic picture of care needs for patients with DS and LGS and when assessing potential new therapies.[22] To support this, recent initiatives have been undertaken to develop trial outcomes that capture changes that are important to patients with developmental and epileptic encephalopathies and their families,[23–26] and further characterize benefits for nonseizure outcomes.[27] Such measures could also be used to better characterize the clinical picture for an individual patient and establish appropriate treatment goals.[28]

With regard to patient outcomes, we observed that the percentage of patients experiencing status epilepticus in the last 6 months was 61% with DS and 43% with LGS. This finding may be reflective of the overall literature, as status epilepticus and sudden unexpected death in epilepsy were found to be reported more frequently in DS than LGS.[29] Prolonged seizure and status epilepticus have a high burden for patients and healthcare systems that

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increases with severity. Healthcare costs are mainly associated with the requirement for hospital management and length of stay.[12,30,31]

Physicians in Asia reported daytime and nighttime seizures as greatly impacting QoL in patients with DS, and mental impairment and daytime seizures as impacting QoL of patients with LGS. In Europe and the USA, daytime seizures were reported by the highest percentage of physicians as having the greatest impact on the QoL of patients with DS and LGS. In this sample, more caregivers in Europe than in Asia or the USA reported moderate to very severe levels of mobility and overall physical impairment in patients with DS and LGS, and moderate to very severe levels of disruptive behavior were reported by more caregivers of patients with LGS in Europe and the USA than in Asia. Finally, treatment satisfaction rates for control over nonseizure symptoms were notably low for caregivers located in the USA. It should be noted that most physicians and caregivers in Asia were from China, and potential geographical differences may be influenced by the availability of antiseizure medications licensed specifically for DS or LGS.

Caring for a patient with DS or LGS also places a burden on the caregiver, which in turn can have a detrimental effect on their health and well-being. There are also economic impacts associated with DS and LGS, not just directly through the costs of healthcare utilization, but also indirectly through caregivers' loss of productivity at work and the impact caring has on their health and health-related QoL.[3,4,9,12,19,20,22,32–40] In this analysis, fewer than a third of caregivers reported being employed.

Cross et al.[5] emphasized the need to involve patients/caregivers in LGS treatment decisions and to be led by QoL. Treatment goals should be agreed upon with the caregivers and, if possible, the patients before selecting a treatment plan. Indeed, it may be that assessments of QoL are more important in the long term than measurements of seizure outcome. Consequently, the future of treatment for DS and LGS should consider not only the number of seizures but also symptoms beyond seizure frequency reduction, such as reducing prolonged seizures and effects on cognition and behavior.[1]

4.1 | Limitations and strengths

This analysis has limitations due to its cross-sectional design and the method of physician and patient selection, as participating physicians may have been influenced by their willingness to complete the survey, and patients who consult more frequently are more likely to be included. Also, patients not currently receiving treatment were excluded from this analysis. Some data collected, such as severity of nonseizure impairments, used Likert scales without accompanying definitions. While not validated, Likert scales are very typically used to get the patient/caregiver perspective on outcomes that are not well defined in the literature. A limitation of pen and paper caregiver forms is survey completeness, as some questions may not have been answered, which affects the sample per question. The number of responses was low for some caregiver-reported data, and some questions in the WPAI are only relevant for employed adults; therefore, the overall indirect burden associated with caregiving may be underestimated. Furthermore, most of the caregiver data were from China. However, Disease Specific Programmes™ are large multinational surveys conducted in clinical practice that are able to capture current real-world disease management and disease burden impact from physicians, patients, and their caregivers.[14] Real-world studies play an important part in highlighting areas of concern that are not addressed in clinical trials, which represent a small proportion of the consulting population as a result of age restrictions and failure to meet stringent eligibility criteria. Furthermore, patients treated in the real-world setting may be less likely to be adherent to medication than those included in clinical trials. Potential bias in patient selection was mitigated by instructing physicians to provide data for a consecutive series of eligible patients. In addition, recall bias, a common limitation of surveys, was reduced by the data collection occurring at the time of the patients' appointment, and physicians had the possibility to extract the data from the medical records. It should be noted that as these analyses were descriptive, formal statistical comparisons between groups cannot be made; any comparisons are limited, therefore, to this study population. Despite some limitations, this analysis provides geographically representative insights from routine clinical practice in real-world settings. In addition, data collected by the Adelphi Real World DS and LGS DSP™ could be used for future research, such as investigating the disease burden associated with different age groups (adults and minors) and other age- or geographical-related differences in the impact of DS and LGS.

5 | CONCLUSION

Based on these data from real-world practice settings, considerable burden in DS and LGS management and care is driven by nonseizure symptoms, suggesting a need for treatments that manage the broad spectrum of disease symptoms. These findings suggest that in addition to

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seizure-related endpoints, clinical trials of potential new therapies should also reliably capture any impact on non-seizure symptoms.

AUTHOR CONTRIBUTIONS

Conceptualization: DS, VV, YT, SO, HC, SL, DD, AB, JSA. Methodology: DS, JSA. Data acquisition: DS, YT, SO, HC, SL, JSA. Data analysis or interpretation: all authors. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

DS and AB are employees of Takeda Development Center Americas, Inc., and stockholders in Takeda Pharmaceutical Company Limited. VV received honoraria and/or research funds from Angelini Pharma, Bial, Biocodex, Eisai, Jazz Pharmaceuticals, Neuraxpharm, Novartis, Nutricia, Takeda, UCB Pharma, and Xenon. DD receives research salary support from the Epilepsy Study Consortium for consulting activities, scientific advisory meetings, and investigator meetings for Beacon, Biohaven, Encoded, Grin, Jazz Pharmaceuticals, Longboard, Rapport, SK Life Sciences, Stoke, Takeda, and UCB. YT, SO, HC, and SL are employees of Adelphi Real World. JSA was an employee of Takeda Development Center Americas, Inc. at the time of the study, and stockholder in Takeda Pharmaceutical Company Limited. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

All data that support the findings of this study are the intellectual property of Adelphi Real World. All requests for access should be addressed directly to Jonathan DeCourcy at jonathan.decourcy@adelphigroup.com

ETHICS STATEMENT

This study was conducted in full accordance with the Guidelines for Good Pharmacoepidemiology Practice published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research was conducted. Local regulatory authority requirements were met before study commencement. The DSP™ methodology (protocol number AG9171) was reviewed and approved by the Pearl Institutional Review Board. Data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines and as such it did not require ethics committee approval. Each survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996.

PATIENT CONSENT STATEMENT

Informed consent was collected from all enrolled caregivers.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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