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Original article

Burden-of-illness and cost-driving factors in Dravet syndrome patients and carers: A prospective, multicenter study from Germany

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ABSTRACT

Introduction: Dravet syndrome (DS) is a rare developmental and epileptic encephalopathy. This study estimated cost, cost-driving factors and quality of life (QoL) in patients with Dravet syndrome and their caregivers in a prospective, multicenter study in Germany.
Methods: A validated 3–12-month retrospective questionnaire and a prospective 3-month diary assessing clinical characteristics, QoL, and direct, indirect and out-of-pocket (OOP) costs were administered to caregivers of patients with DS throughout Germany.
Results: Caregivers of 93 patients (mean age 10.1 years, ±7.1, range 15 months–33.7 years) submitted questionnaires and 77 prospective diaries. The majority of patients (95%) experienced at least one seizure during the previous 12 months and 77% a status epilepticus (SE) at least once in their lives. Over 70% of patients had behavioural problems and delayed speech development and over 80% attention deficit symptoms and disturbance of motor skills and movement coordination. Patient QoL was lower than in the general population and 45% of caregivers had some form of depressive symptoms. Direct health care costs per three months were a mean of €6,043 ± €5,825 (median €4054, CI €4935-€7350) per patient. Inpatient costs formed the single most important cost category (28%, €1,702 ± €4,315), followed by care grade benefits (19%, €1,130 ± €805), anti-epileptic drug (AED) costs (15%, €892 ± €1,017) and ancillary treatments (9%, €559 ± €503). Total indirect costs were €4,399 ±€ 4,989 (median €0, CI €3466-€5551) in mothers and €391 ± €1,352 (median €0, CI €195-€841) in fathers. In univariate analysis seizure frequency, experience of SE, nursing care level and severe additional symptoms were found to be associated with total direct healthcare costs. Severe additional symptoms was the single independently significant explanatory factor in a multivariate analysis.
Conclusions: This study over a period up to 15 months revealed substantial direct and indirect healthcare costs of DS in Germany and highlights the relatively low patient and caregiver QoL compared with the general population.

1. Introduction

Dravet syndrome (DS) is a rare developmental and epileptic encephalopathy defined by refractory epilepsy and non-epileptic manifestations including impaired cognitive, motor and behavioural development.[1] Approximately 85% of patients clinically diagnosed with DS have a mutation in the *SCN1A* gene[2–4] which encodes a sodium channel involved in neuronal signaling. Although estimates vary, incidence is approximately 1 in 20,000 live births and prevalence 2 in 100,000.[2,4–6] In Europe, the number of affected individuals with DS has been estimated at between 11,345 and 13,721 in 2017.[7]

Seizures occur in the first year of life in an otherwise apparently normal infant and are characterised by initial prolonged, typically lateralised, febrile seizures.[8,9] Infants subsequently develop multiple seizure types including myoclonic, absence, focal and generalised tonic–clonic seizures.[10] Premature mortality in DS is high because of status epilepticus (SE), accidents, and sudden unexpected death in epilepsy.[11] In addition to ongoing, severe and intractable epilepsy, children have neurodevelopmental, behavioural and motor impairments.[1]

Providing care for a patient with severe epilepsy, intellectual disability and other comorbidities can have a wide-reaching socioeconomic impact on the family and the healthcare system. Recent studies report that caring for a child with DS is associated with significant humanistic burden and direct costs.[12] The direct medical cost of DS has been reported in a German retrospective pilot study of 13 patients over a 2 year period,[13] a European 3–12 month retrospective study[14] and a US 12 month retrospective study of 34 patients.[15] The latter also reported lost productivity and leisure time of caregivers, resulting in high indirect costs.

Studies exploring caregiver experience report an impact on relationships with friends, family and spouse, sleep problems, financial stress, work, and emotional stress. However, research to systematically identify the most important caregiver domains that are affected by caring for a child with DS has not been reported yet.[12]

The current study addresses knowledge gaps identified by Jensen et al. (2017) particularly in relation to the indirect costs of caring for a patient with DS.[12] It provides estimates of the direct and indirect costs of DS in Germany through a 15-month prospective and retrospective survey on socioeconomic impacts.

2. Methods

2.1. Patients and recruitment

The study was designed as a cross-sectional, prospective multicenter survey and enrolled patients with DS and their caregivers throughout Germany (Bielefeld, Dresden, Erlangen,

Frankfurt, Giessen, Hirschaid, Kiel, Kork, Münster, Tübingen, Vogtareuth) and through the German DS patient advocacy group (Dravet-Syndrom e.V., Markkleeberg, Germany).[16]

2.2. Survey methods

After receiving written informed consent from the patients' parents or legal guardians, all patients with DS and their caregivers were deemed eligible. The seizure and epilepsy syndrome classifications were adapted to the latest definitions of the ILAE.[17,18] The study had an ethics approval and was registered at the German Clinical Trials Register (DRKS00011894). The STROBE guidelines were followed.[19]

Carers of patients with DS were asked to complete a retrospective questionnaire relating to the previous 3 or 12 months and a prospective 12-week, page-per-week diary. The questionnaire, validated in earlier studies[20,21] and adapted for use in patients with DS, comprised 29 questions relating to disease characteristics (e.g. seizures, treatment patterns, additional symptoms) and health care resource use (e.g. healthcare visits, accidents, emergency care). Questions related to the previous 12 months for lower frequency, high recall events (e.g. emergency healthcare use) and to the previous three months for higher frequency, lower recall events (e.g. seizure frequency).

Three QoL instruments were included in the questionnaire. The QoL values of children and adolescents were assessed using the Kiddy-KINDL for children QoL aged 4–6 years, and the Kid-KINDL in those aged 7–17 years, both completed by proxy.[22] The Beck Depression Inventory (BDI) II depression scale[23] (summated scores of 14–19, 20–28, and 29–63 indicate symptoms of mild, moderate, and severe depression, respectively) and the EuroQol scale with 5 dimensions and 3 levels (EQ-5D-3L) and visual analogue scale (EQ-VAS)[24] were used as measures of caregiver QoL. Responses to the EQ-5D-3L were scored using the German value set derived using the time trade-off with reference points of death (0) and perfect health (1).[25] Respondents were also asked if patients had experienced any additional non seizure-related symptoms, and were asked to rate these by severity (no problem, minor problem, moderate problem, severe problem). The number of severe additional symptoms was the number of additional symptoms which were rated a 'severe problem' by respondents. This number was used in the univariate and multivariate analyses as an independent variable.

The prospective diary collected data on seizures, health service resource use, such as doctors' time, use of hospital beds, emergency services, medicines and other therapies, lost work time and OOP expenditure. The intention of the diary was to capture further data on events and costs and to validate the retrospective data.

Paper questionnaires were completed by carers in German between April 2017 and January 2018, and diaries in real time for three months after the period covered by the questionnaire (latest April 2018).

2.3. Costing methods

The aim of this study was to calculate the genuine costs due to DS rather than due to diseases unrelated to DS. Therefore, caregivers were asked in detail whether or not the medications, services and other resources used were particularly due to epilepsy and DS. Costs were evaluated by a bottom-up approach from the perspective of the statutory health insurer "Gesetzliche Krankenversicherung" (GKV) and society as a whole. The cost categories included in the analysis were direct health service costs, patients' and carers' OOP expenses, informal care costs and indirect costs. Costs were evaluated according to German recommendations for performing health economic evaluations.[26]

2.3.1. Direct health care costs

Direct health service costs (inpatient stays, outpatient visits, medicines [AEDs and emergency medication], medical aids, healthcare professional visits, emergency transportation, diagnostic studies and rehabilitation costs) were drawn from the literature and standard reference sources for Germany, and were estimated as previously described.[20,27] Drug costs were based on the Yellow List; an index of medicines and their average price in Germany.[28] Costs of inpatient and outpatient care, specialist care, therapies and diagnostic studies were standardised according to Bock et al.[29] and physician fee scales (Einheitlicher Bewertungsmaβstab).[30] Costs were inflated to 2017 using the consumer price index for Germany and expressed in annual terms in €2017.

2.3.2. Out-of-pocket expenses

OOP expenses (copayments) were reported by respondents. Where supply-side cost estimates were already calculated based off resource utilisation (ancillary treatments, medical aids, healthcare professionals and emergency transportation), OOP expenses were considered accounted for, and were therefore not added to total direct costs. Where supply-side utilisation estimates were not available (care and supervision, healing agents and diet), OOP expenses were added to total direct healthcare costs. OOP expenditures beyond the formal health care setting (alternative and occupational therapies, equipment costs, travel expenses, child care expenses for siblings and home teaching expenses) were also reported.

2.3.3. Care grade (informal care) costs

Average care grade allowances (insurance payments determined by patient care grade level I, II or III on the Pflegebedürftigkeit scale [a categorisation of need for care, on the basis of which care allowances are paid]),[31] were calculated under the assumption that nursing services are provided by family members.[32] Care grade costs are interpreted here as a proxy for informal care costs.

2.3.4. Indirect costs

Productivity losses due to DS (days off, quitting work, early retirement, reduction in working hours) were calculated using the human capital approach for caregivers below the age of 66. The mean gross wage of €40,661 in 2017[33] was assumed for calculating the productivity cost of a caregiver quitting their job. For days taken off work to care for a child with DS, annual gross wages were €111.40 per calendar day (€13.93 per hour) and daily income multiplied by days off. Income for caregivers working part time was assumed to be 60% of the wage in full

time employment. This approach is consistent with that adopted by Strzelczyk et al. (2012).[21]

2.3.5. *Patient characteristics and disease burden*

The relationship between patient characteristics and DS-related costs was investigated in multivariate regression. Total health care costs were regressed on a set of clinical variables selected following univariate analysis and evidence from previous cost-of-illness studies in epilepsy.

2.3.6. *Grouping of questionnaire items*

Some questionnaire items were collated into groups when presenting results as follows:

'ancillary costs': physiotherapy, speech therapy, occupational therapy, accupuncture, hippotherapy, other ancillary costs; 'healthcare professionals': neurologists, GPs, orthopaedic surgeons, child psychiatrists, alternative medicine practitioners, homeopathy, dietitians, other specialists; 'diagnostic studies': EEG, Blood tests, CT scans, X-rays, other diagnostic studies.

2.4. *Statistical analysis*

Statistical analysis was conducted with IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Variables of interest were summarised using the mean, median and standard deviation (SD). For cost data, confidence intervals were calculated using the bootstrap-corrected and accelerated method in Stata considering the fact that most cost variables are highly skewed.[34]

The significance of differences in proportions and differences in medians was tested with Pearson χ^2 and Kruskall Wallis H tests, respectively. In univariate analysis on cost drivers, the Kruskall Wallis test was used to assess the significance of individual explanatory variables. In univariate analysis, a Bonferroni correction was applied for multiple testing. Multivariate analysis was conducted with ordinary least squares regression. A $p = 0.05$ significance level was used in all statistical analysis.

3. Results

3.1. *Demographic and clinical characteristics*

Ninety-three carers completed the questionnaire. Seventy-five of these and a further two subjects not in the questionnaire sample completed the prospective diary. Demographic characteristics are described in Table 1. The mean patient age was 10.1 years (SD 7.1, median 8.7) and the vast majority (75%) had experienced one seizure or more over the course of a month. Seventy seven percent of patients had experienced SE at least once in their lives. Only 4% (n = 4) were reported to be seizure free for more than a year. Amongst those patients the mean age was 14.8 (SD 9.1, median 11.9, range 7–27). Retrospective and prospective sections of the survey were comparable regarding seizure frequency and distribution among age groups (Appendix Tables 1 and 2).

Table 1 – Demographic characteristics of survey population (questionnaire respondents, n = 93).

	n (% of full cohort)	Mean (SD)	Median	Range
Patient characteristics				
Age (y)		10.1 (7.1)	8.7	15 m–33.7 y
Male	49 (53)			
Age of adult patients (y)		23.7 (4.4)	22.2	
Age of seizure-free patients (y)		14.8 (9.1)	9.1	7–27
Age of first seizure (m)		5.9 m (3.7 m)	5	0–26
Duration between initial seizure and diagnosis (m)[1]		44.7 (66.5)	14.0	
Duration between initial seizure and first therapy (m)		4.8 (13.1)	2.0	
Patients in mainstream school[2]	24 (26)			
Patients in special school or a sheltered workplace	61 (66)			
Patients that are working	1 (1)			
Patients in a range of other environments (for example nursery, vocational facility and day care centre)	6 (6)			
Caregiver characteristics				
Age of Mother (y) (n = 93)		42.1 (7.6)	41.5	
Age of Father (y) (n = 93)		45.2 (7.7)	45.0	
Mothers in work (full or part time)	52 (56)			
Fathers in work (full or part time)	76 (82)			
Patients in dual-parent households	78 (84)			
Clinical characteristics				
SCN1A mutation	89 (96)			
Patients who had experienced a seizure in the last year	88 (95)			
Number of SE in the last 12 months (of those who had experienced a SE)		5.0 (5.1)	3.0	1–19
Patients who experienced a DS-related injury in the last year	36 (39)			

Abbreviations: DS, Dravet syndrome; m, month; SE, status epilepticus; y, year.
[1] Time to diagnosis was much longer in older age groups, particularly patients ≥ 12 years.
[2] Forty-four percent (24/54) of patients aged 5–17 years were in mainstream school.

3.1.1. *Comorbidities*

Patients suffered from a range of comorbidities, the impact of which ranged from minor to severe. Behavioural problems and delayed speech development were reported by carers for over 70% of patients while attention deficit symptoms and disturbance of motor skills and movement coordination were experienced by over 80% (Fig. 1). The majority of impairments were rated by at least half of caregivers as moderate or severe problems (disturbance of motor skills and movement coordination, delayed speech development, attention deficit symptoms, behavioural problems, muscular hypotension and cognitive disorders as 69%, 64%, 56%, 54%, 54% and 51% respectively).

3.1.2. *Quality of life*

Patients aged 4–6 years had a mean score of 65.0 on the Kiddy-KINDL (SD 11.1, median 64.6, range 39.6–82.3, Fig. 3A). Patients aged 7–17 had a mean score of 54.4 on the Kid-KINDL scale (SD 14.2, median 55.2, range 27.1–80.2, Table 2 and Fig. 3B). The mean scores compare with scores of 81.9 and 77.0 for the general population of children and adolescents, respectively.[35] In those aged three years or younger and those aged above 18, QoL was not assessed.

Forty-five percent of carers scored >13 points on the BDI-II, indicating symptoms of mild (22%, n = 20), moderate (15%, n = 14) or severe (9%, n = 8) clinical depression (Fig. 3C). Carers scored a mean 0.9 (SD 0.18, median 0.9, range 0.3–1) on the EQ-5D-3L and 71.3 (SD 18.0, range 19–100) on the EQ-VAS, which did not differ from the general German population (0.9 and 77.3, respectively) (Table 2 and Fig. 3D).[25] Caregivers reported higher levels of problems in the anxiety/depression component of the EQ-5D-3L with 38.2% reporting some problems compared to 4.3% of German population norms.[25]

3.2. *Health care resource use*

3.2.1. *Medicines and supplements*

The patients were taking a mean number of 2.5 AEDs (SD 1.1, median 3, range 0–6), with 54% of patients using three or more AEDs and 17% four or more. The five most commonly prescribed drugs were valproate (66% of patients, n = 61), bromide (44%, n = 41), clobazam (41%, n = 38), stiripentol (35%, n = 31) and topiramate (24%, n = 22). The most common AED regimen was a combination therapy of valproate, stiripentol and clobazam used by 16% of patients (n = 15/93). Two thirds of patients had used emergency medication in the last three months. In addition to drug treatment, 16% of patients (n = 15) reported adopting a specific diet in the past three months. Eleven percent (n = 10) used a ketogenic or modified Atkins diet. Retrospective and prospective sections of the survey were broadly comparable regarding AED use.

3.2.2. *Hospital admissions and other cost drivers*

The questionnaire showed that 52% (n = 48) of patients were admitted as an inpatient at least once in the last 12 months (46% annualised based on the diary), 47% (n = 44) called the emergency service at least once in the previous year (58% annualised based on the diary), and 22% (n = 20) required intensive care over the same time period. Among the 44 patients for whom the emergency services had been called in the last 12 months due to DS, the mean number of calls was 4.2 (SD 4.9, median 2.5, range 1–30). The 48 hospitalised patients experienced a mean of 4.3 hospitalisations (SD 5.3, median 3, range 1–35). Responses from 47 patients gave a mean of 25.6 days' stay (SD 39.6, median 11, range 1–200) as inpatients over the previous 12 months due to DS. A mean of 5.5 days' intensive care (SD 5.9, median 3.5, range 1–23), was required for the 20 patients admitted to intensive care units in the last three months.

The diary recorded neurologist visits, planned outpatient and inpatient visits, and physiotherapy and speech therapy utilisation. Just under half of the sample made at least one neurologist visit over the three month period; a similar percentage made use of speech therapy and over 50% of patients used physiotherapy (Appendix Table 3). The latter two services are noteworthy because they are indicative of impairments other than seizures.

3.3. *Health care costs*

Total direct health care costs summed to €6043 per three months (SD €5825, median €4054, range €148– €30,447, CI

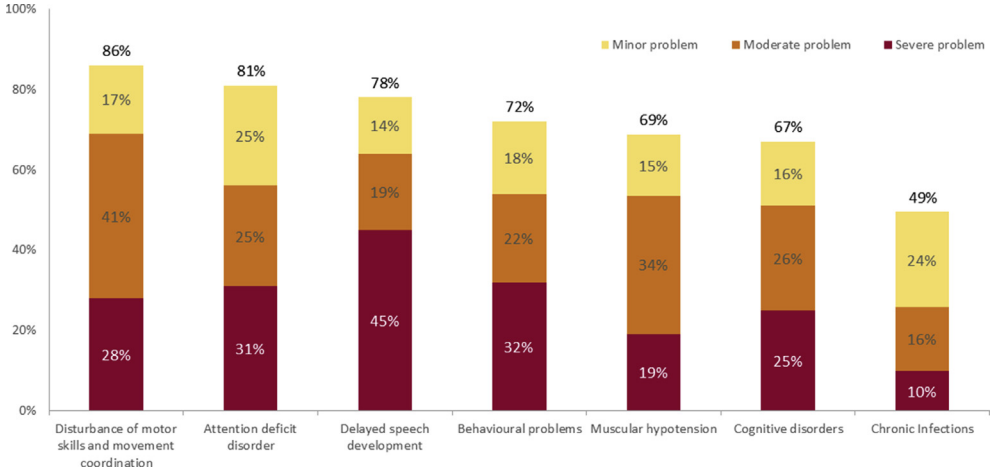

Fig. 1 – Patient comorbidities and their impact reported by carers in the past 3 months (source: questionnaire, n = 93).

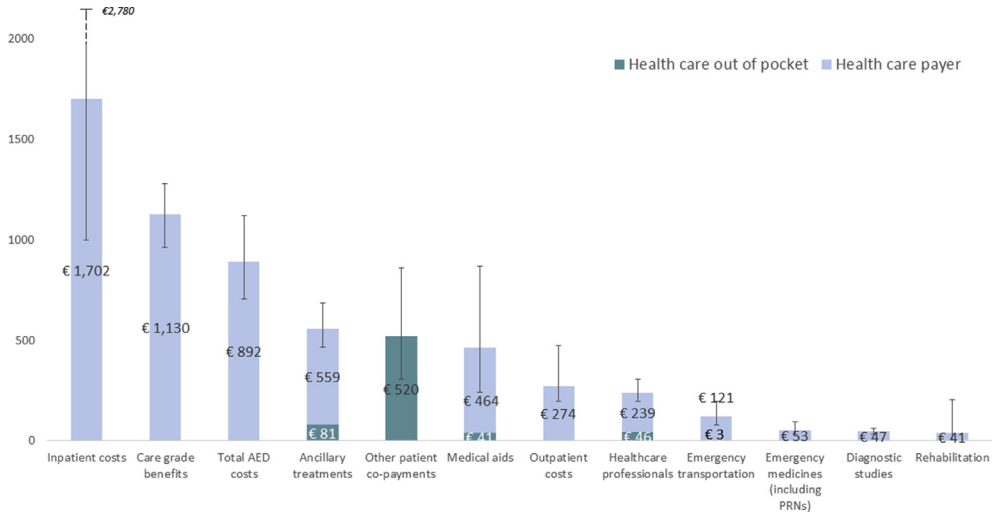

Fig. 2 – Breakdown of total health care cost per patient over 3 months (source: questionnaire, n = 93). Error bars indicate the confidence interval for the mean total of each cost category. The upper limit of the inpatient cost (€2,780) is off the chart and indicated by a dashed error bar.

A

Kiddy-KINDL

Category	Mean (n=37)	SD	Norm values[1]
1 Physical wellbeing	62.0	21.2	80.2
2 Emotional wellbeing	74.3	14.8	83.0
3 Self-esteem	61.0	17.3	73.6
4 Family	74.8	14.8	80.7
5 Friends	48.0	21.0	79.7
6 School	69.8	15.4	83.8
Total (subscales 1-6)	65.0	11.1	80.0
7 Additional questions	62.9	11.4	
8 Disease	76.0	13.8	

B

Kid-KINDL

Category	Mean (n=18)	SD	Norm values[1]
1 Physical wellbeing	44.8	19.3	80.5
2 Emotional wellbeing	53.1	22.3	82.3
3 Self-esteem	51.7	22.6	70.8
4 Family	72.2	14.7	79.8
5 Friends	38.5	18.0	78.5
6 School	66.0	15.5	82.6
Total (subscales 1-6)	54.4	14.2	79.0
7 Disease	68.1	21.2	

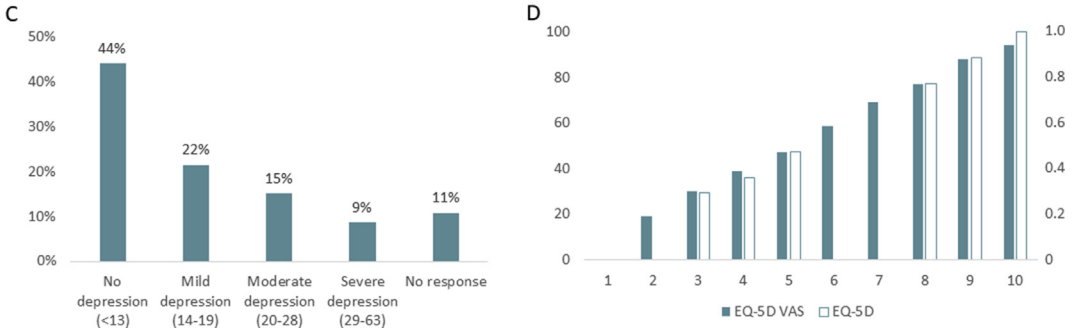

Fig. 3 – Patient and caregiver quality of life (QoL) scores. A. Kiddy-KINDL scores for 4–6 year old and B. Kid-KINDL scores for 7–17 year old patients, both completed in proxy. QoL was not assessed in patients ≤3 years and >18 years C. Caregiver Beck Depression Inventory (BDI) II depression scale scores. Summated scores of 14–19, 20–28, and 29–63 indicate symptoms of mild, moderate, and severe depressive symptoms, respectively C. Bars show the mean responses to the EuroQol scale with 5 dimensions and 3 levels (EQ-5D-3L) instrument scored using the value set and to the visual analogue scale (VAS), by decile of score (≤0.1 to >0.9 on the value set (right y-axis) and ≤10 to >90 on the VAS (left axis). [1]U. Ravens-Sieberer et al. (2000).[35]

Table 2 – Quality of life measurements of patients (aged 4–17 years) and caregivers.

	Mean (SD)	Median	Range	Mean German population norm (SD)	t-statistics
KINDL					
Kiddy-KINDL (ages 4–6y) (n = 37)	65.0 (11.1)	64.6	39.6–82.3	81.9 (9.1)	10.5
Kid-KINDL (ages 7–17y) (n = 18)	54.4 (14.2)	55.2	27.1–80.2	77.0 (10.0)	9.0
EQ-5D					
EQ-5D-3L (caregivers)	0.9 (0.18)	0.9	0.3–1	0.9	
EQ-VAS (caregivers)	71.3 (18)	73.0	19–100	77.3	

T-tests between the two groups found scores significantly lower amongst the 7–17 age group at $p < 0.05$. Abbreviations: EQ-5D-3L, EuroQol scale with 5 dimensions and 3 levels; EQ-VAS, visual analogue scale; SD, standard deviation; y, years.

€4935-€7350) per patient (Fig. 2, Table 3). This equates to a mean approaching €25,000 (median €17,000) on an annual basis. Inpatient costs formed the single most important category of direct health care costs, accounting for €1,702 per patient over three months (SD €4315, median €0, range €0– €20,736, CI €1,000-€2,780; 28% of total direct health care costs). Amongst those 24 patients who had reported an inpatient visit in the last 3 months, the median cost for inpatient visits was €2,804. These were followed by care grade benefits at a mean of €1,130 (SD €805, median €1374, range €0– €2184, €963-€1,281; 19%), total AED costs with a mean of €892 (SD €1017, median €532, range €0– €4779, CI €708-€1,120; 15%) and ancillary treatments with a mean cost of €559 (SD €503, median €451, range €0–€2152, CI €465-€687; 9%).

Mean OOP costs were estimated at €1151 per patient over three months, or €4,604 over 12 months, including a broader set of items than purely health care costs (equipment expenditure, child care expenses for the DS child, child care expenses for siblings, travel expenses for appointments and home teaching expenses) (Fig. 2).

3.4. *Care needs and care grade (informal care) costs*

Seventy eight percent of patients were categorised as requiring care levels I to III on the Pflegebedürftigkeit scale (24% level I ['significant need for care'], 27% level II ['heavy need for care'] and 27% level III ['most difficult to care for']). Eleven percent of patients did not meet the level I–III criteria but were nevertheless in need of care according to their caregivers.

Table 3 – Total costs associated with Dravet syndrome for a 3-month period (in 2017 Euro) (source: questionnaire and diary *).

Cost components (n = 93 unless noted)	Mean cost	SD	Min	Median	Max	95% CI[1]	Annual costs[2]
Direct health care costs							
Total including care grade allowances							
Informal care approach	6,043	5,825	148	4,054	30,447	4,935–7,350	24,171
Outpatient nursing approach	7,468	6,180	148	6,004	32,505	6,351–8,833	29,872
Total excluding care grade allowances	4,913	5,661	148	2,795	29,073	3,950–6,311	19,653
Inpatient costs	1,702	4,315	0	0	20,736	1,000–2,780	6,810
Care grade allowances							
Informal care[3]	1,130	805	0	1,374	2,184	963–1,281	4,518
Outpatient nursing services	2,555	1,852	0	3,432	4,836	2,176–2,907	10,219
Total AED costs	892	1,017	0	532	4,779	708–1120	3,569
Ancillary treatments	559	503	0	451	2,152	465–687	2,235
Other patient co-payments	520	1,329	0	50	8,360	308–861	2,081
Medical aids	464	1,365	0	0	7,000	243–869	1,854
Outpatient costs	274	589	0	0	4,455	196–475	1,097
Healthcare professionals	239	253	0	179	1,709	199–306	956
Emergency transportation	121	288	0	0	1,324	78–196	484
Emergency medicines[4]	53	138	0	10	893	34–96	213
Diagnostic studies	47	66	0	33	360	36–63	188
Rehabilitation	41	398	0	0	3,841	0–207	165
Non-health care OOP costs[5]							
Total non-health care OOP costs (n = 77)	624	2,402	0	80	20,350	310–1,811	2,494
Productivity costs							
Total	4,790	5,325	0	2,841	21,327	3,868–5,953	19,159
Total maternal indirect costs	4,399	4,989	0	2,339	20,191	3,466–5,551	17,594
Quit work (n = 29)	3,170	4,734	0	0	10,165	2,186–4,044	12,679
Reduced working hours (n = 27)[6]	732	1,522	0	0	10,030	491–1,188	2,930
Missed days (n = 37)	496	1,594	0	0	10,026	266–976	1,986
Total paternal indirect costs	391	1,352	0	0	10,165	195–841	1,565
Reduced working hours (n = 6)[6]	155	635	0	0	3,343	63–352	618
Missed days (n = 25)	127	374	0	0	3,008	74–254	509
Quit work (n = 1)	109	1,054	0	0	10,165	0–328	437
Total costs							
Informal care approach	11,456	10,382	443	8,927	71,127	9,727–14,026	45,825
Outpatient nursing service approach	12,881	10,753	443	10,287	73,185	11,024–15,358	51,525

Abbreviation: OOP, out-of-pocket; SD, standard deviation; AED, anti-epileptic drug; *All cost items were drawn from the questionnaire (93 respondents) apart from non-health care OOP costs which were drawn from the diary (77 respondents).

[1] 95% CI = 95% confidence interval using the bootstrap-corrected and accelerated method.

[2] Estimation based on the mean costs in three months multiplied by four.

[3] Care grade benefits.

[4] Includes pro re natas (PRN).

[5] Non-health care OOP costs (drawn from the diary, n = 77) consist of equipment expenditure, travel expenses for appointments, child care expenses for DS child, child care expenses for siblings, home teaching expenses.

[6] Assuming part time workers produce/paid 60% of full-time workers.

Where nursing care provided for all patients by an outpatient nursing service, the three month mean cost of care grade benefits would amount to €2,555 (SD €1852, median €3432, range €0– €4836, CI €2,176-€2,907), or €10,219 annually compared with the €1,130 or €4,518 annually assuming a grade allowance for informal care by family members (see care grade cost item in health care costs, Table 3). Only 12% of patients were not in need of care. Eighty-nine percent had a severely disabled pass.

3.5. *Indirect (productivity) costs*

Lost work time was recorded separately for mothers and fathers. Twenty-nine of ninety-three mothers (31%, compared with 1% of fathers) reported that they quit work, 27 reduced their working hours (29%, compared with 6% of fathers) and 37 missed days from work during the last three months due to DS (40%, compared with 27% of fathers). Mean productivity costs over three months were estimated at €3,170 (SD €4,734, median €0, range €0– €10,165) associated with mothers quitting work, compared with €109 (SD €1,054, median €0, range €0– €10,165) for fathers; €732 (SD €1,522, median €0, range €0– €10,030) associated with mothers' reduced working hours, compared with €155 (SD €635, median €0, range €0– €3,343) for fathers; and €496 (SD €1,594, median €0, range €0– €10,026) associated with mothers' lost work days, compared with €127 (SD €374, median €0, range €0–€3,008) for fathers. These gave total mean maternal costs for lost work of almost €4,399 over three months or €17,594 annually. For fathers, the figure amounted to €391 over three months, or €1,565 annually (Table 3).

3.6. *Total costs*

In order to avoid double counting when estimating total costs, items that appeared in the total health care cost calculations were removed from OOP expenses. Non-health care OOP payments are made up of: equipment expenditure, child care expenses for the DS child and siblings, travel expenses for appointments and home teaching expenses. These OOP expenses were based on diary responses. When summing these together with questionnaire-based costs, it was assumed that the full questionnaire sample had the same average expenditure as the smaller diary sample. Care grade costs (treated as a proxy for informal care costs) are treated as a separate entity. Summing these components together with productivity costs gives a total mean annual cost per DS patient of €45,824 or €51,525 depending on the approach to care grade benefits (Table 3).

3.7. *Cost drivers*

We investigated the relationship between health care costs, total indirect costs and a number of demographic and clinical patient characteristics. Applying a Bonferroni correction for eight comparisons, giving a threshold p value of 0.00625. At this threshold, all variables were significantly associated with total direct health care costs with the exception of age, BDI-II category, level of disability and whether patients had experienced any accidents/injuries in the last 12 months due to DS (Table 4). On the other hand, no variable was significantly associated with productivity costs at the $p < 0.00625$ threshold, although seizure frequency and level of disability were significant at the $p = 0.05$ threshold. In multivariate regression, only one variable emerged as significant in both models, namely the number of severe additional symptoms (symptoms rated by severity by respondents [no problem, minor problem, moderate problem, severe problem]), emphasizing the importance of disease characteristics in addition to the experience of seizures (Table 5).

4. Discussion

This prospective, detailed cost study based on a large sample of patients within a single health care system contributes important new information about the costs associated with DS in Europe. Two previous studies have reported cost estimates for patients with DS in Europe.[13,14] However, the German pilot study had a small sample ($n = 13$) and while the European cost study by Lagae et al. (2019) is generalisable to the European context, data was not reported at the same granularity as in this country-level study. Nevertheless, the most closely comparable evaluation of resource use and carer burden in DS is the European cost study by Lagae et al.[14] The two samples were comparable in terms of demographic characteristics (age and gender), carer support (more than one adult in the household), seizure frequency and type and range of comorbidities.

Patient QoL (4–17 age group) based on the age-adjusted and well-established KINDL instrument was diminished compared with normative data,[35] thereby confirming observations from other studies.[32,36] This study broadens the evidence base of epilepsy-specific instruments and a generic tool (PedsQL)[36] used by Brunklaus et al. (2011) as well as adding more detailed QoL data compared with the generic preference-based instrument (EQ-5D) used by Lagae et al. (2018).[32]

This is the first study to explore the impact of DS on caregivers using a mental health instrument (BDI-II) to measure depressive symptoms. The high frequency (45%) of caregivers with some level of depressive symptoms has also been reported for caregivers of children with intractable epilepsy and epilepsy in general.[37,38] Notably, DS caregiver EQ-5D-3L and EQ-VAS scores were similar to population norms, suggesting that a purely health-related QoL instrument such as the EQ-5D-3L may not sufficiently reveal the true impacts of DS on caregivers. Indeed, as concluded in a recent review of literature on the humanistic and economic burden of DS on caregivers and families by Jensen et al. (2017) the important caregiver domains that are impacted by caring for a child with epilepsy in general, or DS in particular, are largely unknown.[12]

A particular contribution of this study is the collection of data on nursing requirements measured by care grade allowances which were one of the most important components of direct care costs, reinforcing the importance of non seizure-related as well as seizure-related costs found in the Lagae et al., 2019 study.[14]

Generally, the results of this study indicate that the management of DS is considerably more resource intensive than is

Table 4 – Univariate analysis – association of variables with health care cost.

Variable	Number of patients (n = 93)	Total direct health care costs (€)	SD	p-value[1]	Total indirect costs (€)	SD	p-value[1]
Age				0.94			0.37
<2 y	5	6,144	7,073		8,260	8,439	
2–5 y	28	7,275	7,172		3,483	4,179	
6–11 y	28	5,446	5,817		4,749	5,244	
12–17 y	19	4,979	3,105		4,179	4,773	
Adult	13	6,190	5,563		7,249	6,494	
Seizure frequency				**0.003***			**0.04****
At least 1/d	21	8,581	8,135		6,173	6,261	
At least 1/wk	20	7,002	4,253		6,500	5,268	
At least 1/6 m	29	5,477	5,385		3,027	3,959	
At least 1/6 m	15	4,218	4,656		5,498	6,045	
At least 1/6 y	3	1,245	923		156	168	
No seizures for >1y	4	2,733	1,884		3,022	4,848	
Did not respond	1	4,967	0		3,009	–	
Level of disability				**0.02****			**0.03****
None	10	6,095	8,555		5,371	4,459	
<50%	0	0	0		–	–	
50–75%	10	3,837	5,352		2,641	6,283	
>75%	73	6,338	5,465		5,005	5,299	
Has the patient ever experienced an SE?				**0.002***			0.11
Yes	72	6,580	5,890		4,721	5,262	
No	16	3,367	4,713		3,406	4,210	
I do not know	5	6,874	6,834		10,204	7,060	
Nursing care level				**0.0001***			0.18
None	11	2,234	1,638		3,490	4,493	
No care, but in need of care	10	4,742	8,069		3,569	4,809	
Care level I	22	5,975	5,560		3,170	4,827	
Care level II	25	6,308	6,122		4,948	5,361	
Care level III	25	8,034	5,334		7,117	5,746	
The number of severe additional symptoms[2]				**0.002***			0.07
0	24	3,219	2,174		2,444	3,728	
1	20	5,861	7,013		5,531	5,901	
2	17	5,664	3,899		4,266	4,325	
3	15	6,915	5,481		3,833	3,743	
4	9	8,780	8,633		9,314	6,497	
5	5	10,920	5,641		8,265	8,853	
6	2	5,295	477		5,417	6,715	
7	1	23,299	0		10,165	–	
BDI-II				**0.02****			0.11
No depression	41	3,885	2,981		3,537	4,533	
Mild depression	20	7,345	5,742		5,786	5,135	
Moderate depression	14	9,088	9,170		6,649	6,770	
Severe depression	8	6,747	6,978		4,397	4,857	
No response	10	7,459	6,031		5,701	6,531	
Have you experienced any accidents/injuries due to Dravet syndrome in the last 12 months?				0.97			0.59
Yes	57	6,064	5,780		5,017	5,070	
No	36	6,010	5,979		4,429	5,761	

*$p < 0.00625$, **$p < 0.05$.

Abbreviations: BDI-II, Beck Depression Inventory-II; d, day; m, month; SD, standard deviation; SE, status epilepticus; wk, week; y, year.

[1] Kruskal–Wallis H test.

[2] Number of additional symptoms rated by caregivers as problematic (from a total of 8 additional symptoms: chronic infections, muscular hypotension, muscular spasticity, behavioural problems, attention deficit symptoms, delayed speech development, cognitive disorders, disturbance of motor skills and movement coordination).

the case with other epilepsy patients. Total annual direct health care costs are put at just under €20,000 (median €12,000) in this study excluding care grade allowances. The components of this figure are broadly comparable with the cost categories itemised by Strzelczyk et al. (2012) in a sample of general adult epilepsy patients and by Riechmann et al. (2015) in children and

Table 5 – Multivariate regression analysis of cost-driving factors.

Explanatory variable	Coefficient	Standard Error	t	P > t	95% CI[1]	
Dependent variable: Total health care costs						
Age in months	−14.01	8.12	−1.73	0.089	−30.22	2.19
Seizure frequency	−936.10	520.36	−1.80	0.076	−1974.45	102.26
Level of disability	−3.77	28.27	−0.13	0.894	−60.17	52.63
Ever experienced SE	−918.99	1817.87	−0.51	0.615	−4546.50	2708.51
Nursing care level	34.52	731.76	0.05	0.963	−1425.69	1494.73
No. of severe additional symptoms[2]	991.81	486.41	2.04	0.045	21.19	1962.42
BDI-II	82.14	71.64	1.15	0.256	−60.82	225.09
Any accidents/injuries in last 12 months	−673.38	1281.72	−0.53	0.601	−3231.01	1884.26
Constant	9007.12	4494.62	2.00	0.049	38.25	17975.99
Dependent variable: Total productivity costs						
Age in months	6.869082	7.047375	0.97	0.333	−7.19374	20.9319
Seizure frequency	−688.1079	451.4873	−1.52	0.132	−1589.04	212.8209
Level of disability	−43.64513	24.52418	−1.78	0.08	−92.5824	5.292119
Ever experienced SE	−1048.427	1577.276	−0.66	0.508	−4195.83	2098.978
Nursing care level	384.2082	634.913	0.61	0.547	−882.741	1651.157
No. of severe additional symptoms[2]	900.7471	422.034	2.13	**0.036***	58.59134	1742.903
BDI-II	7.492026	62.15841	0.12	0.904	−116.543	131.5272
Any accidents/injuries in last 12 months	−1471.478	1112.085	−1.32	0.19	−3690.61	747.6535
Constant	9045.569	3899.753	2.32	0.023	1263.733	16827.4

Variance Inflation Factors (VIFs) for independent variables were all found to be VIF<2.5.

* $p < 0.05$.

Abbreviations: BDI-II, Beck Depression Inventory-II; SE, status epilepticus; t, t statistic for significance of the coefficient.

[1] 95% CI = 95% confidence interval using the bootstrap-corrected and accelerated method.

[2] Number of additional symptoms rated by caregivers as problematic (from a total of 8 additional symptoms: chronic infections, muscular hypotension, muscular spasticity, behavioural problems, attention deficit disorder symptoms, delayed speech development, cognitive disorders, disturbance of motor skills and movement coordination).

adolescents with epilepsy in whom annual total direct per patient costs were estimated at €2,406 (2008 prices) for adults and at €6,476 (2011 prices) for children and adolescents.[20,21] The addition of care grade allowances, interpreted here as a proxy for informal care costs (a conservative cost estimate compared with providing the same care through an outpatient nursing service) brings the total direct per patient health care costs up to more than €24,000 annually.

Wider societal impacts were assessed by the indirect costs for caregivers of patients with DS (approximately €4,800 (median €2,800) over a three month period). This compares with the €1,300 reported by Riechmann et al. among caregivers of children and adolescents with epilepsy in Germany,[20] indicating a high strain on caregivers' working life.

In Germany, reimbursement for healthcare costs come from a combination of public and private sources. Patients have a large degree of choice over what health services they utilise. Under the statutory system, small copayments for doctor's appointments and hospital visits exist but are capped by law.[39,40] OOP expenses for ancillary treatments such as alternative medicine are less likely to be covered under the statutory system.

The number of severe additional symptoms was the single variable significantly associated with DS-related costs in the regression analysis. This is worthy of note in light of the study by Riechmann et al. who found that symptomatic etiology (corresponds most closely to structural etiology according to the latest ILAE definition) of epilepsy in contrast to idiopathic etiology (in addition to younger age and polytherapy) was an independent cost driver among children and adolescents with epilepsy and their caregivers and reinforces the importance of non seizure-related morbidity in patients with DS.[20] Interestingly, univariate analysis of categorical variables find a wider range of cost-drivers to be statistically significant. However, the univariate results find no variable statistically significant when a Bonferroni correction is applied, which may mean these results were amplified by false positives. The results of the multivariate analysis shows that when these independent variables are controlled for by other patient characteristics they are no longer found to be statistically significant. An alternative explanation could be that the Krusal–Wallis test is more sensitive to age and BDI scores when categorised or more sensitive to the small sample size. Further analysis in larger samples is welcome to better explore this phenomenon.

4.1. *Limitations*

Limitations of the questionnaire used in this study might be a recall bias regarding the 3–12 month-old events, which might result in incomplete (although only high-recall events were queried for up to 1 year) and underestimated costs. Furthermore, while the sample consisted of patients recruited from multiple clinics across Germany and through the patient advocacy group, it is unknown whether the sample is representative of DS patients in Germany, given the difficulty in estimating patient numbers for rare diseases.[7] In addition, interpretation of the analysis of cost drivers should take account of the sample size (n = 93) compared with other evidence on cost drivers in epilepsy (Riechmann et al.; n = 489),[20]

which may account for the identification of only a single significant independent predictor (of those variables tested). However, the significance of severe additional symptoms in the current study suggests some common ground with the earlier study which found a symptomatic etiology of epilepsy to be a significant cost driver. In addition, skewness found in cost calculations should be noted, as there is disparity between mean and median costs. The strength of the study is its large sample size of 93 patients and caregivers given the rarity of DS, furthermore we applied a prospective approach using a detailed diary that matched well with the questionnaire.

5. Conclusions

Expenditures in patients with DS are high and driven by the severity of comorbidities. Efforts should focus on therapeutic interventions in epilepsy as well as comorbidities, and on improved caregiver support.

Ethical publication statement

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.

Conflicts of interest

AS reports personal fees and grants from Desitin Arzneimittel, Eisai, GW Pharma, LivaNova, Medtronic, Sage Therapeutics, UCB Pharma and Zogenix. TB reports fees from Bial, Biocodex, Eisai, Desitin Arzneimittel, GW Pharmaceuticals, Nutricia, Shire, UCB Pharma, Viropharma, and Zogenix. AW-K reports personal fees from Desitin Arzneimittel, Dr. Schär, Novartis, Nutricia, Vitaflo, UCB Pharma. GK reports personal fees from UCB Pharma, Desitin Arzneimittel, Zogenix, LivaNova, Eisai, GW Pharma, Bial, Dibropharma, Novartis, Biogen, Actelion. RT reports personal fees and grants from Novartis, Desitin Arzneimittel, UCB Pharma and Pfizer. DM, JC and CP are employed by Wickenstones Ltd and received support from Zogenix International Limited to complete this study. KMK reports personal fees from UCB pharma, Novartis Pharma AG, Eisai and GW pharmaceuticals. FR reports personal fees from Eisai, UCB Pharma, Desitin Arzneimittel, Novartis, GW Pharma, Medtronic, Cerbomed and Shire, grants from the European Union, Deutsche Forschungsgemeinschaft, the federal state Hessen through the LOEWE programme, and the Detlev-Wrobel-Fonds for Epilepsy Research. SSB reports personal fees from UCB, Desitin Arzneimittel, Novartis, Zogenix, LivaNova, and Eisai. None of the other authors reported any related conflicts of interest. This study was sponsored by Zogenix International Limited.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.02.014.

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