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Caregiver impact and health service use in high and low severity Dravet syndrome: A multinational cohort study

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ABSTRACT

Purpose: To estimate costs associated with the current management of Dravet syndrome (DS), explore psychosocial aspects of the disease in caregivers and siblings, and identify patient characteristics associated with higher costs in a large, predominantly European survey cohort of patients and their caregivers conducted in 2016.
Methods: Health and social care resource use, productivity and quality of life (QoL) data were summarised. Costs for European five (EU5) countries (France, Germany, Italy, Spain and UK) were calculated and patients with high and low current seizure burden compared. Direct healthcare costs and out-of-pocket costs were calculated using literature reported health service costs and participant reported costs, respectively.
Results: Direct annual costs of management of non-seizure-related symptoms ($7929) contributed to approximately 50% of all costs (including medication). Excluding medication, non-seizure-related costs dominated costs of care. Cost for patients with high seizure burden were higher for seizure-related healthcare use and physiotherapy, but lower for other therapies. Most (80%) caregivers reported an influence on their career choices and 28% of those in work had missed over three working days in the past four weeks for emergency or routine needs of their child. Caregivers had little free time, relied on family members for support and respite, and experienced emotional stress and uncertainty about their child's future healthcare needs.
Conclusion: Families caring for a DS patient manage considerable social and financial impacts. Total direct costs of DS patients (excluding drugs) are driven by non-seizure-related healthcare use and high seizure burden is associated with higher healthcare costs.

1. Introduction

Dravet syndrome (DS) is a rare and complex developmental encephalopathy characterised by refractory epilepsy, motor and cognitive impairments, and behavioural disorders (such as attention/hyperactivity symptoms, autistic traits, conduct problems and problems with peer relationships) [1–3]. Families of children with DS report significant health and social burden, however, few studies have assessed the magnitude of this impact [4].

DS typically presents in the first year of life with febrile and afebrile, generalised clonic or hemiclonic epileptic seizures. After the first year of age, further seizure types appear, including myoclonic, focal and atypical absences, which are frequently prolonged and refractory to antiepileptic drug treatment [1,5]. The long-term outcome of DS is unfavourable, with developmental and cognitive slowing, behavioural disorders and mobility problems appearing during childhood alongside ongoing epilepsy [6,7]. Episodes of status epilepticus are common and the mortality risk is high [8–10].

The impact of DS on families has not been widely studied. A recent international survey reported that caregivers of patients with DS contend with a wide range of other effects of the disease, with speech/communication, impacts on siblings and cognitive impairment ranking as their top concern. [11] Nearly two-thirds of caregivers were reported as having suffered from depression [11].

The cost of refractory epilepsy, including that of DS has been reported in several studies. A recent systematic review of the direct costs of epilepsy in the US [12] and another study of the direct and indirect costs of epilepsy in general in Germany [13] found notably higher direct costs for patients with uncontrolled or more refractory epilepsy and for patients with comorbidities; both of which are features of DS [3,14–16]. A study of 13 paediatric DS patients from a single clinic in Germany comparing direct costs before and after treatment with

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conventional anticonvulsants vs. a new treatment option stiripentol (with clobazam) found that caring for a child with DS has significant direct financial costs, although these may be variable [17]. A survey of 34 caregivers of DS patients treated at Children's Hospital Colorado in the US reported substantial healthcare utilisation, financial burden, and time commitment [18].

The DS caregiver survey (DISCUSS) was a large multinational online survey conducted in 2016 with the objective of furthering the understanding of the clinical, economic and humanistic burden of DS [14]. The survey cohort consisted of 584 caregivers of paediatric (83%) and adult (17%) patients with DS of which over 90% reside in Europe. The vast majority of patients had experienced at least one seizure in the last three months and nearly all (91%) patients older than five years reported at least one and on average three non-epilepsy related conditions, such as a motor impairment, speech impairment or behavioural difficulties. Patient quality of life (QoL) was very low (a mean European Quality of Life-5 Dimensions 5-level scale [EQ-5D-5 L] index value of 0.42 in patients older than two years compared to a normative index value of 0.88). Analysis of patients at the two extremes of DS severity revealed that those with a high current seizure frequency suffered from more comorbidities, reported more emergency treatments, and have a lower QoL compared to patients with a low current seizure frequency.

In this paper, we report the mean annual direct costs per patient for seizure-related and non-seizure-related healthcare and caregiver out-of-pocket costs for the DISCUSS EU5 cohort. Furthermore, we compare the healthcare costs of EU5 patients with the highest and lowest current seizure burden. Financial support and out-of-pocket costs for the full DISCUSS cohort are reported, as is the impact of DS on caregiver work and social life.

2. Methods

2.1. Study design

The Dravet syndrome caregiver survey (DISCUSS) has been previously described [14]. DISCUSS was an anonymous online survey conducted in 2016 that measured caregiver household (demographic information), quality of life (including EQ-5D-5L [19]; family, career, leisure, childcare), disease severity (diagnosis journey, epilepsy management, comorbidities), support (social and financial support [no payment, full payment or co-pay, i.e. payment of contribution charged by the insurance], out-of-pocket expenses, healthcare system use) and treatment (current and past anti-epileptic drugs [AEDs], non-AED treatments, and therapy for comorbidities). Only fully completed surveys (apart from one question about the cost of non-pharmacological treatments) were accepted for submission. Gate questions ensured negative responses were not probed further.

2.2. Data processing

The following assumptions were made. Where currency was not stated, the currency of the participant's given country was assumed. The annual numbers of emergency admissions and ambulance calls were estimated by replacing standard answers as follows: 0 calls = 0, 1–5 calls = 3; 6–10 calls = 8; 11–20 calls = 15; > 20 calls = 20. The annual frequency of therapy visits was estimated by replacing standard answers (for frequency per month) as follows: less than once a mth = 6; once a mth = 12, twice a month = 24; 3 times a month = 36; 4 times a month = 48; 5–8 times a month = 84; more than 8 times a month = 96 times a year. Patient age of < 1 was estimated as 0.8 years. The annual cost of special school attendance in the UK was assumed to be that of an individual holding a Statement of Special Educational Needs (£13,036, approximately $16,165). [20]

2.3. Descriptive analysis

Data are reported as total counts, frequency of responses and summary statistics (mean and standard deviation) of the full, country or EU5 cohorts. Age groups were described as infant (< 2 years) preschool (2–5 years), middle childhood (6–11 years), adolescent (12–17 years) and adult (18 years and older).

2.4. Cost assessment

Healthcare costs were calculated using participant reported data and health service reported costs at 2016 values (Additional file 1). Personal (out-of-pocket) costs were taken as reported by survey participants. All costs were calculated in US dollars (USD, exchange rate 9/11/2016 [21]). Annual total cost of the top four AEDs currently taken by patients (valproate, clobazam, stiripentol and topiramate) was estimated assuming a mean patient weight of 30.9 kg (the mean weight of the 64 patient [3–18 y] cohort of the French and Italian STICLO trials [22,23]) and doses of stiripentol 50 mg/kg/day for stiripentol, clobazam 0.5 mg/kg/day for clobazam, valproate 30 mg/kg/day for valproate and 2.0 mg/kg/day for topiramate [22,24].

2.5. Comparison of high vs low seizure burden

Patient seizure burden was defined using a composite score for total seizure frequency (composite seizure frequency [CSF] score) [14]. Parents were asked how often (0, 1–12, 13–30, 31–60, 61–150, or > 150 times) their child had experienced a seizure type (tonic–clonic, myoclonic, partial/focal, absence, atonic/drop attack, and unidentified seizure) in the past three months. Based on survey answers, each patient received a score for the frequency of each seizure type (maximum 10 [> 150 in past 3mo], minimum 0 [none in past 3mo]) after which the seizure frequency scores of each type were combined into a CSF score (maximum 39 [the highest score recorded], minimum 0 [the lowest score recorded]; only countable seizures and seizures with a motor component were used for this score). Patients in the highest and lowest seizure burden category had CSF scores of 14–39 and 0–2, respectively.

2.6. Statistics

Differences in means were compared using a two-sample Student's *t*-test assuming unequal variance. P values less than 0.05 were considered statistically significant.

3. Results

3.1. Direct healthcare costs

The annual direct per patient cost for DS in the EU5 was $15,885 ($9783 excluding AEDs), comprising $7957 for seizure-related symptoms ($1854 excluding AEDs) and $7929 for non-seizure-related symptoms. Drivers of total direct cost are AEDs (38%) and non-seizure-related therapies (50%). Excluding AEDs, non-seizure-related costs contribute to 81% of direct costs. A similar pattern was observed across all EU5 countries (Fig. 1A and Table 1).

3.2. Epilepsy-related healthcare resource use

Fewer than 10% of patients in the DISCUSS cohort reported no seizures in the previous three months. Half required at least one emergency admission and 46% at least one ambulance call in the past twelve months. Patients took on average of three AEDs, and visited an epilepsy specialist on average four times in the previous year. [14]

The epilepsy-related direct costs in the EU5 countries were calculated for emergency visits (annual mean cost per patient $587),

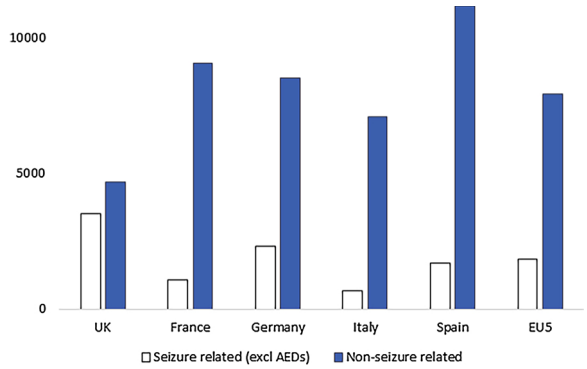

Fig. 1. Mean annual direct healthcare system costs per patient (US dollars) for seizure-related (empty bars) and non-seizure-related (filled bars) healthcare resource use in the European 5 (EU5). See Table 1 for a breakdown of costs per country. Abbreviation: AEDs,anti-epileptic drugs.

Table 1
Annual mean per patient cost (USD) for EU5 countries (n = 344).

Cost Variable	UK	France	Germany	Italy	Spain	EU5
Seizure-related symptoms						
Emergency visits	783	176	1060	262	714	587
Ambulance calls	1343	736	1036	284	492	774
Epilepsy specialist visits	1410	182	215	155	504	493
Valproic acid	232	185	187	198	45	175
Clobazam	57	30	95	56	64	60
Stiripentol	8284	4726	6613	4340	5203	5831
Topiramate	4	24	52	53	49	36
Total drug costs	8577	4965	6947	4647	5360	6103
Total with drugs	12,112	6060	9258	5348	7071	7957
Total without drugs	3535	1094	2311	701	1711	1854
Non-seizure-related symptoms						
Physiotherapy	1678	3995	4921	3048	3337	3358
Speech therapy	1765	3279	2767	2091	5420	2932
Therapy for learning difficulties (apart from specialist schooling)	466	836	366	841	1231	732
Therapy for autism/ autistic-like symptoms	480	650	228	121	408	365
Therapy for ADHD	102	53	38	158	454	152
Behavioural therapy	192	272	209	851	325	390
All therapies	4681	9084	8529	7110	11,175	7929

Abbreviations: EU5, European 5 (France, Germany, Italy, Spain and UK); USD, US dollars.

ambulance calls ($774), epilepsy specialist visits ($493) and for drugs valproic acid ($175), clobazam ($60), stiripentol ($5831) and topiramate ($36), totalling $7957 (Table 1). AEDs are the driver of epilepsy-related cost, accounting for 77% of direct epilepsy-related costs. Excluding AEDs, emergency visits, ambulance calls and epilepsy specialist visits each contributed 10% or less to direct epilepsy-related costs (10%, 7% and 6%, respectively).

3.3. Non-epilepsy related healthcare resource use

Nearly all (99.6%) patients five years or older in the DISCUSS cohort experienced at least one or more motor, speech, learning, or behavioural impairment [14]. In patients older than five years, 66% had therapy for a motor impairment, 68% for a speech impairment (excluding those that do not talk at all), 29% for learning difficulties (apart from specialist schooling), 26% for autism, 15% for attention deficit hyperactivity disorder (ADHD) and 25% for behavioural challenges (other than ADHD or autism) (Fig. 2). The uptake of therapies was variable across countries, ranging from 50% (UK, Spain)–80% (Poland) for motor impairments, 32% (Netherlands)–86% (Poland) for speech impairments, 9% (Netherlands)–50% (Spain) for learning impairments, 7% (Netherlands)–50% (France, Poland) for autism, 4% (Italy)–30% (Germany) for ADHD and 7% (Netherlands)–46% (Spain) for behavioural difficulties (Additional file 2).

The non-seizure-related annual per patient costs in the EU5 countries were calculated for physiotherapy ($3358), speech therapy ($2932), therapy for learning difficulties (apart from specialist schooling) ($732), therapy for autism ($365), ADHD ($152) and behavioural impairments ($390), totalling $7929 per patient. Physiotherapy and speech therapy are the drivers of non-seizure-related costs, accounting for 79% of non-seizure-related costs (Table 1).

3.4. High versus low seizure burden

Patients in the DISCUSS cohort displayed a wide range of seizure severity and those with the highest seizure frequency suffered from more comorbidities and more frequently reported one or more emergency admission or ambulance call [14]. This translated into higher healthcare resource use for epilepsy-related symptoms in the highest seizure subgroup, in which the mean annual number of epilepsy specialist visits (6.0 ± 5.4), emergency admissions (3.6 ± 5.4), ambulance calls (3.3 ± 5.0) and physiotherapy visits (36.1 ± 39.7) was significantly higher than in the lowest seizure frequency group (2.7 ± 3.2 [$P < 0.001$]; 2.0 ± 4.1 [$P < 0.001$]; 1.2 ± 2.3 [$P < 0.05$]; 18.6 ± 31.9 [$P < 0.001$] respectively) (Additional file 3). The use of therapy for non-seizure-related symptoms other than physiotherapy did not differ significantly between the low and high seizure frequency groups.

To illustrate resource use in terms of monetary cost for the EU5 countries, low and high seizure burden costs were compared using average unit costs for each cost category to remove the variation caused by differential costs for healthcare in each country. Annual per patient costs for all seizure-related categories were significantly higher for patients in the highest than lowest seizure burden group ($863 ± 1290 vs. $391 ± 876 [$P < 0.05$] for emergency admissions, $1140 ± 1609 vs. $389 ± 790 [$P < 0.005$] for ambulance calls and $824 ± 817 vs. $337 ± 333 [$P < 0.001$] for epilepsy specialist visits, respectively). For non-seizure-related symptoms, the costs for physiotherapy was also significantly higher in the high seizure frequency group ($1963 ± 2197 vs. $894 ± 1619 [$P < 0.005$]). For all other non-seizure-related symptoms, there was a trend (but no statistically significant difference) toward the low seizure burden group incurring higher costs for speech therapy, therapy for learning difficulties (apart from specialist schooling) and therapies for autism, ADHD and behavioural issues (Additional file 3, Fig. 3).

3.5. Out-of-pocket expenses

3.5.1. Reimbursement

Caregivers were asked whether they received financial support for physician fees, antiepileptic drugs, therapies for comorbidities, expenses arising from emergency visits and home adaptations related to the care of their child with DS. The majority of caregivers reported receiving full reimbursement for fees (i.e. patient co-pay was 0%) for epilepsy specialists (80%), epilepsy medication (59%) and therapies (therapy for motor impairment [68%], speech impairment [74%], learning impairment (apart from specialist schooling) [52%], autism [57%], ADHD [74%], and behavioural difficulties [48%]) (Additional file 4). However, co-pay requirements varied widely across countries, with the number of patients requiring some level of co-pay (partial or full) ranging from 1% (UK)– 42% (Poland) for epilepsy specialist fees, 0% (France, UK)– 100% (Poland) for antiepileptic medicine, 0% (Netherlands)– 62% (Spain) for motor impairments, 0% (Netherlands, UK)– 47% (Poland) for speech impairments, 10% (UK)– 72% (Spain) for learning impairments, 0% (Germany, Netherlands, Poland, UK)– 100% (Spain) for autism, 0% (France, Netherlands, UK)– 67% (Germany) for ADHD and 0% (UK, France, Netherlands)–83% (Spain) for behavioural

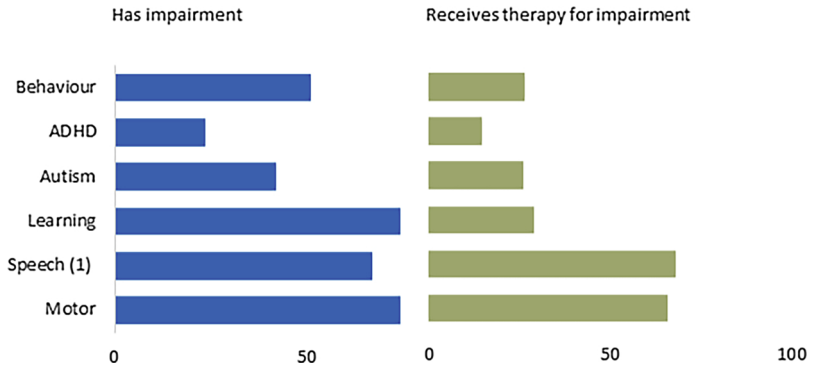

Fig. 2. Percentage of patients older than 5 years (n = 409) in the full DISCUSS cohort with an impairment that receive therapy. (1) Excludes patients that do not talk at all. Abbreviation: ADHD, attention deficit hyperactivity disorder.

difficulties (Additional file 4).

3.5.2. Personal costs

While the majority of caregivers reported receiving either full (i.e. patient co-pay was 0%) or partial support for fees for epilepsy specialists, epilepsy medication and therapies, support varied across countries (Additional file 4) and those who were not reimbursed faced a range of fees depending on the patient's requirements (Table 2). For example, families paying for therapies faced median annual costs between $1213–3303 per therapy. Also, families that relied on childcare faced a median annual cost of $3371 for their child with DS and $1538 for siblings.

3.6. Family impact and social support

3.6.1. Caregiver productivity

Most (80%) caregivers reported that caring for a child with DS had influenced their career choices. Over a third (34%) of caregivers were unemployed, many (81%) citing the reason for their unemployment as giving up their job because of their caregiver responsibilities. Of those in employment (61%), many (65%) reported taking time off work in the past four weeks to care for the needs of their son or daughter (such as emergency care or a routine visit to the doctor). Over a quarter (28%) had missed over three working days in the past four weeks. Support from the employers was variable. Of those in full or part-time employment, 30% reported never, 34% always and 30% sometimes having time taken off work being subtracted from their salary/income, holiday or sick leave. This varied across countries. For example, 57% caregivers in Poland vs. 15–21% in Germany and the Netherlands reported time taken off work never being subtracted (Table 3).

3.6.2. Personal impact, support and leisure

Nearly all caregivers (91%) indicated that caring for a child with DS makes daily activities, family relationships (70%) and social life (80%) difficult. Most (77%) caregivers reported having less than one hour per day to themselves, for example for relaxing or for social activities. This was true across all age groups, dropping only slightly for adult patients. When asked about their childcare arrangements (apart from school and therapy sessions), most (64%) caregivers received help from their partner, other family members or relatives (46%), a smaller number from caregivers provided by social services (19%) or privately sourced (21%). This varied across countries. For example, 70% of caregivers in the Netherlands reported using childcare provided by social services (vs. < 25% in all other countries). Most (65%) reported travelling on holiday, although there was a marked difference across age groups with only half or fewer in the younger but 70% and over in the older groups reporting travelling on holiday (Table 3).

3.6.3. Adult patient support

Very few adult patients (36%) reported benefiting from interventions such as supported employment (14%), further education and training (15%), supported housing (18%) or other services to support independent living (21%) (Table 3). The type of support and proportion of adult patients receiving support varied across countries. Countries providing the most support for employment were Germany (33%), the Netherlands (33%) and the UK (25%); for further education, the UK (42%) and Poland (25%); for housing, the Netherlands (45%), the UK (25%) and France (25%); for other support for adults, the UK (43%) and Spain (40%).

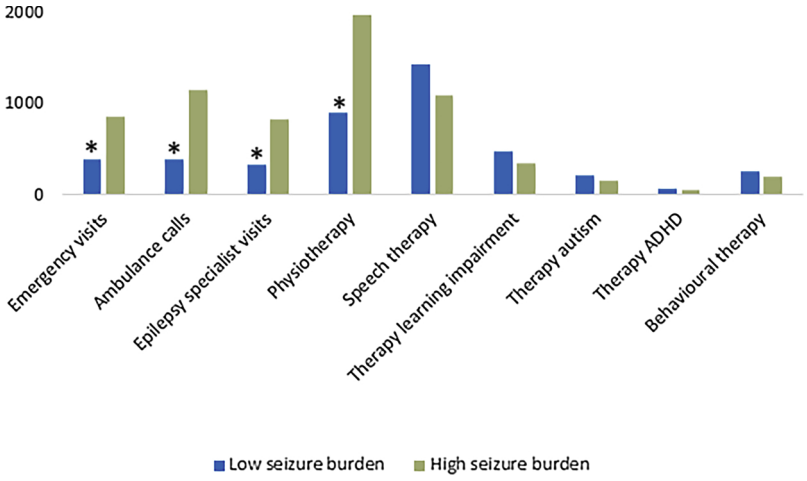

Fig. 3. Mean annual healthcare system costs (US dollars, based on averaged European five [EU5] costs) per patient in the EU5 in the low vs. high seizure burden group. The highest and lowest seizure frequency groups contain patients with composite seizure frequency (CSF) scores 14–39 and 0–2, respectively. Asterisks indicate a statistically significant difference ($p < 0.05$) in mean cost between the high and low seizure burden groups. Abbreviation: ADHD, attention deficit hyperactivity disorder.

Table 2
Out-of-pocket costs (full DISCUSS cohort, n = 584).

Cost category		Median cost in USD (range) [number of patients who reported paying in part or full]
Treatment fees	Epilepsy specialist	270 (3 – 5940) [n = 95](1)
	Therapy for motor impairment	3231 (90–33,033) [n = 85] (1)
	Speech therapy	2424 (76–28,800) [n = 63] (1)
	Therapy for learning difficulties (apart from specialist schooling)	3303 (61–66,067) [n = 64] (1)
	Therapy for autism/autistic-like symptoms	2697 (404–21,573) [n = 21] (1)
	Therapy for ADHD	1213 (480–12,741) [n = 5] (1)
	Therapy for behavioural problems	2063 (202–72,000) [n = 32] (1)
Caregiver fees	For child with Dravet syndrome	3371 (135–40,449) [n = 154] (1)
	For siblings	1538 (0–26,967) [n = 51] (1)
Adaptive motor equipment (including orthopaedic footwear)		169 (0–199,422) [n = 264] (2)
Non-epilepsy drugs and alternative treatments		308 (0–11,200) [n = 318] (1)
Epilepsy medicine		461 (25–18,000) [n = 223] (1)

(1) Annual cost. (2) Total cost. Abbreviation: ADHD, attention deficit hyperactivity disorder.

3.6.4. Siblings

Over two thirds of patients with DS had siblings living in the same household. Nearly half (46%) reported siblings missing leisure opportunities in the past four weeks so that the caregiver could take care of their sibling with DS. School attendance appeared less affected, with only few missing school in the past four weeks (Table 3).

4. Discussion

Increasingly, DS is being viewed as a developmental encephalopathy with epilepsy rather than primarily an epilepsy syndrome [2] and the DISCUSS survey confirmed in a large multinational study, that patients struggle with a wide range of symptoms in addition to treatment refractory seizures [14]. In this study, the emerging picture is not only of substantial costs due to intractable seizures – only 10% of the DISCUSS cohort did not experience seizures in the past three months [14] - but of much higher costs due to the non-seizure manifestations of Dravet symptoms. Indeed, non-seizure-related costs contribute to 81% of direct costs (excluding AEDs). As a comparison, in a general paediatric population with epilepsy, costs for ancillary treatments have been reported at 9.1% of total direct costs [13].

An estimation of the cost of education for DS patients was beyond the scope of this study given the different education systems in Europe, but we expect these also to be higher than seizure-related costs, given that 98% of DS patients in the DISCUSS cohort were reported to have learning difficulties. As a comparison, a UK study of school-aged children with epilepsy (all types) reported a cognitive impairment in 55% of children and an annual education cost of £7701 (about $9549) per child. [20] In the UK cohort of DISCUSS, 94% of the 32 school-aged children (6–17 years old) attended a special school, equating to an annual cost of £12,269 (about $15,214) per school-aged patient. This is higher than that reported by Hunter et al. (2015) and supported by the observation that a higher proportion of DS patients in the DISCUSS have learning difficulties.

The annual direct costs for epilepsy-related symptoms in the DISCUSS EU5 cohort (on average $1854 per patient; not including AEDs) are higher than the mean non-AED annual direct costs of €1222 (approximately $1331) for the baseline period (using traditional anticonvulsants) reported in the Germany study by Strzelczyk et al. [17] The difference possibly reflects the different unit costs for resources across the DISCUSS countries. When including AEDs, annual epilepsy-related healthcare utilisation costs of the DISCUSS EU5 cohort are $7957, lower than the total annual direct cost of €11,901 (approximately $12,972) reported for DS patients on adjunctive care with stiripentol and clobazam in Germany [17]. This is most likely due to the higher cost of stiripentol (compared to traditional anticonvulsants), which was used by only 47% of the DISCUSS cohort. Our estimation of direct costs for seizure-related symptoms are much lower than the $27,000 reported by Whittington et al. (2018) for patients treated in Children's Hospital Colorado in the US, possibly due to different health care systems, unit costs and factors not measured in the DISCUSS survey such as in-home visits, and air ambulance [18].

In the DISCUSS cohort, healthcare resource use for seizure-related symptoms was significantly higher in the highest than the lowest seizure burden subgroup. Similarly, in the Germany study, patients with more controlled seizures incurred lower non-AED costs. [17] Both studies support previous reports of higher costs for patients with more uncontrolled epilepsy [12,13].

A comparison of the impact on healthcare resource use between the high seizure and low seizure burden patients showed that for the group with a high seizure burden, epilepsy-related healthcare resource use (emergency admissions, ambulance calls and epilepsy specialist visits) and physiotherapy was significantly higher. Apart from physiotherapy, there was no clear difference in therapy use between the two groups possibly reflecting the choice of therapy by caregivers, and variation of uptake across countries, possibly due to different availabilities of therapists, reimbursement structures and cost. Of note is that while many patients were reported having additional symptoms, uptake of therapy was only high for motor and speech impairments (68% and 70% in the full cohort excluding the infant age group), and less than a third for therapy for learning impairment, autism, ADHD and behavioural issues (other than autism and ADHD). Whether low uptake of the other therapies is due to availability, cost or other factors such prioritisation by caregivers remains to be determined.

This study shows that the impact of caring for a child with DS on parent's ability to work and socialise is high. Parents report having very little time completely to themselves. While this may be expected for parents of young children, this is generally not common for parents of adolescents and adults and highlights the life-long caring responsibilities for parents and the larger family. Indeed, the recent study by Whittington et al. (2018) reports lost productivity and leisure time of caregivers of patients of DS, resulting in high indirect costs and financial burden. [18] Long term studies on patients with DS show that very few individuals live independently [25], and this survey found that relatively few adult patients with DS receive help for independent living. The emotional impact on parents in the DISCUSS cohort is similar to those reported by families caring for a child with DS, other rare diseases and childhood epilepsies in general [3,11,26–28]. Future research to systematically identify the most important caregiver domains that are impacted by caring for a child with DS would be useful to obtain a quantitative measure to enable comparison to other groups of carers and the public and understand the true impact of DS on caregivers' lives [4].

For the most part, caregivers received childcare support from social services their partners and other family members. Caregivers paying for childcare out of their own pocket faced a median annual cost of $3371. Other caregivers received childcare support from social services. This varied across countries for example with 70% of caregivers in the

Table 3
Impact of Dravet syndrome on the family (full DISCUSS cohort, n = 584).

Career		% Total responses
Employment status[1]	I am unemployed	34.4
	I am employed part time	26.4
	I am employed full time	25
	I am self-employed	9.6
Reason for unemployment[2,3]	I am unemployed because I do not need to work	5.2
	I am unemployed because I can't find a job	7.5
	I gave up my job because of my caregiver responsibilities	81
	Full-time carer	2.9
Students and retirees[1]	Student	4
	Retiree	5.7
Impact on career choices[4]	Yes	79.6
	No	14.9
	I don't know	4.8
	I'd prefer not to answer	0.7
Missed work in past 4 w?[5, 3]	Yes	65
Quantity missed work in past 4 w[3, 6]	< 3h	8.8
	4–7h	20.9
	1d	21.4
	2d	20.9
	≥ 3d	27.9
Subtraction of time taken off work from salary/income, holiday or sick leave[3, 6, 7]	Yes, sometimes	30.1
	Yes, always	34.1
	No, never	30.1
Personal impact, support and leisure		
Personal impact	Caring for a son/daughter with Dravet syndrome makes daily activities difficult	90.8
	Caring for a son/daughter with Dravet syndrome has made family relationships difficult	69.9
	Caring for a son/daughter with Dravet syndrome has made my social life difficult	80
	Find it difficult to communicate to others about having a son/daughter with Dravet syndrome	29.3
Worry[8]	Whether son/daughter's medical treatments are working	71.2
	Side effects of son/daughter's medications/medical treatments	82.5
	How others will react to my son/daughter's condition	36.3
	How illness is affecting other family members	46.4
	Son/daughter's future	95.7
	Having more children	21.9
	Emotional impact on other children in family	50
	Prefer not to answer	0.2
	None of the above	0.5
Time to yourself[9]	0-5 h (Less than 1 h/day)	76.5
	6-50h	15.9
	> 50h	0.3
	Don't know	6.3
Childcare[10]	Me	83.9
	Caregivers provided by social services	18.5
	Other family members or relatives (such as grandparents or cousins)	46.1
	Caregivers (privately sourced)	20.9
	My partner	64.2
	My friends	11.6
	Hospice	0.3
Travel on holiday?[11]	Yes	64.9
Holiday plans[12]	It doesn't affect our plans	9.2
	Unable to travel by plane	25.3
	Mostly short holidays, like going away for weekends	20.6
	Choose places that have points of emergency care	58.3
	Choose places according to the climate	42
	We travel less during our holidays because of the work and stress involved	37.2
	Other:	17.9
Reasons for not travelling on holiday[13]	Don't want to leave points of emergency	50.7
	Patient's mobility problems	16.1
	Patient's uncontrolled seizures	50.2
	Patient's behavioural problems	32.2
	Do not have the money to travel	34.1
	Other	10.2
Siblings living in same household		67.5
Siblings missed school in past 4 weeks[14, 15]		10.9
	Not applicable because siblings not in school	13.5
Siblings missed leisure opportunities in past 4 weeks[14, 16]		46.2
Care for siblings[14, 17]	Family and friends [18]	66.5
	Paid for help out of own pocket	8.1

(*continued on next page*)

Table 3 (*continued*)

Career		% Total responses
	Family, friends and paid help	8.1
	Other	6.3
	Siblings old enough to look after themselves	10.9
Adult patients		% responses in adult age group
Adult patient support[19]	Employment (supported)	14.0
	Further education and training	15.0
	Housing (supported)	18.0
	Other services to support independent living	21.0
	None of the above	54.0

(1) Total number of observations includes standard and free text answers to question 23 (Q23). (2) Expressed as percentage of population indicating unemployment in a standard answer to Q23. (3) Excludes population indicating a free text answer to Q23. (4) Response to Q28. (5) Expressed as percentage of population indicating part or full time work or self-employment in a standard answer to Q23. (6) Expressed as percentage of population in part or full time work or self-employment having missed work in the past 4 weeks to care for the needs of their child. (7) Response to Q25. Country-specific answers: 26% in the UK, 34% in France, 55% in Spain, 37% in Italy, 21% in Germany, 15% in the Netherlands and 57% caregivers in Poland reported time taken off work never being subtracted from salary/income, holiday or sick leave. (8) Response to Q49. (9) Response to Q37. Age group responses for "0-5 h (Less than 1 h/day)" were: I, 82.4%; PS, 86.5%; MC 79.2%; A, 72.9%; Adult, 59%; (10) Response to Q34. Country-specific answers: 24% in the UK, 14% in France, 2% in Spain, 22% in Italy, 12% in Germany, 67% in the Netherlands and 2% caregivers in Poland reported using caregivers provided by social services. (11) Response to Q38. Age group responses for "yes" were: I, 44.1%; PS, 50.4%; MC 70.3%; A, 75.7%; Adult, 70%; (12) Response to Q39. Percentage of the population that travel on holiday (Q38). (13) Response to Q40. Percentage of population that do no travel on holiday (Q38). (14) Percentage of population that have siblings living in their household. (15) Response to Q30. (16) Response to Q31. (17) Response to Q32. (18) Partner, older siblings, parents or other relatives. (19) Country-specific answers: 25%, 44%, 25%, 44% and 19% adult patients in the UK (n = 16); 0%, 0%, 23%, 23% and 62% in France (n = 13); 0%, 10%, 0%, 40% and 50% in Spain (n = 10); 5%, 19%, 5%, 44% and 76% in Italy (n = 21); 33%, 11%, 11%, 22% and 33% in Germany (n = 9); 33%, 0%, 47%, 0% and 47% in the Netherlands (n = 15) and 0%, 25%, 0%, 0% and 25% in Poland (n = 4) were reported receiving employment support, further education, housing, other support and none of the above, respectively. For survey questions please refer to Lagae, L. et al. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol. 2018;60:63–72. Abbreviations: I, Infant (< 2 years); PS, Pre-school (2–5 years); MC, Middle childhood (6–11 years); A, Adolescent (12–17 years); Adult, Adult (18 years and older). Because of rounding, conditional and free text answers, percentages might not add up to 100.

Netherlands using childcare support from social services (compared to 1.8% in Spain or 2.4% in Poland), suggesting that if such services were available in other countries, more caregivers would make use of them.

Most caregivers reported being fully or partially reimbursed for AEDs, epilepsy specialist visits, and therapies for motor, speech, learning and behaviour, however this did vary substantially across countries. For the most part, patients in the UK, Germany, France and the Netherlands were fully reimbursed for treatments and therapies (the numbers of patients having therapy for autism and ADHD were too low to make any conclusions about reimbursement), whereas many patients in Italy, Spain and Poland paid either partially or fully for treatment or medicine. Uptake of therapy also varied across countries, but did not appear to be related to whether a therapy was reimbursed or not. For example, in patients with a speech impairment (excluding those that do not talk at all), 81% in Spain vs. 32% in the Netherlands have speech therapy and 42% of patients in Spain pay partial or full fees whereas patients in the Netherlands do not pay for speech therapy. However, other factors may play a role, such as patient age or severity of the disease, which were not explored because of low sample size.

4.1. Limitations

Several assumptions were made in this study in extrapolating costs from the survey cohort. Drug costs were based on average dosages; annual therapy visits and childcare usage were estimated from reported monthly usage and visits, respectively; the number of emergency admissions and ambulance calls was averaged from ranges. The derived figures can therefore be considered approximations only.

The advantage of a multinational survey was that it captured a large number of patients with a rare disease. However, differences in healthcare, education and socioeconomic structures of the countries mean that certain aspects of the data can only be conveyed as rough estimations at cohort level. For example, the impact of parenthood on employment varies with gender as well as country, and these factors need to be considered in addition to the impact of having a child with DS. [29]

This study was not population based and participants might therefore not be representative of the overall caregiver population, possibly representing more engaged and informed caregivers with access to expert care. [14]

5. Conclusion

Patients with DS require extensive healthcare support not only for the treatment of epilepsy, but also for non-epilepsy symptoms, for which total annual direct costs are four times higher than epilepsy costs. Patients with the highest current seizure frequency use more healthcare resources (both seizure and non-seizure-related), indicating not only the need to find improved treatment for both seizures and the neurodevelopmental aspects of DS but also the importance of social and healthcare systems to take the long term and all-encompassing impact of DS on patients and their families into account.

Declarations

Ethics approval and consent to participate

DISCUSS was an initiative of the Dravet Syndrome European Federation (DSEF), who granted permission to analyse the anonymised data. Participants of the online survey read a front page description of the study explaining the anonymous storage of their data according to current European data protection regulations.

Availability of data and materials

The data that support the findings of this study are available from the DSEF but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Aggregate data are however available from the authors upon reasonable request and with permission of the DSEF.

Competing interests

LL received consultancy fees and is on advisory boards of Zogenix, UCB, Novartis, Shire, LivaNova, GW Pharma and Takeda. EG and AB

are employed by Wickenstones Ltd and received support from Zogenix International Limited to complete this study.

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Authors' contributions

All authors were involved in the design of the study. AB analysed the data and drafted the first and further versions of the manuscript. All authors reviewed and revised the manuscript and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2018.12.018.

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