


Caregiver burden associated with caring for individuals with tuberous sclerosis complex-associated seizures: A descriptive, non-interventional survey in Sweden

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ABSTRACT

Tuberous sclerosis complex (TSC)-associated seizures result in a significant burden for caregivers. To quantify time spent and describe activities undertaken by caregivers of individuals with TSC-associated seizures in Sweden, primary caregivers participated in a cross-sectional, non-interventional online survey. Questions comprised patient/caregiver characteristics, care provision, time, and activities associated with generalized seizures or non-seizure-related care. Twenty-three primary caregivers participated; 96 % parents, 100 % female. Median number of caregivers per individual was three. In the last month, median (interquartile range [IQR]) hours for caregiving per week was 52.0 (25.7–100.0; $n = 21$); median (IQR) hours for non-seizure-related care was 46.7 (20.0–93.3; $n = 21$) and for generalized seizure-related care was 4.7 (1.7–15.8; $n = 12$). Beyond the last month, hours/week of generalized seizure-related care varied from 1.9 (0–8.8) to 14.0 (0.5–77.0). Professional/paid carers contributed 99.2 (73.5–127.5) hours/week of care. Non-seizure-related care activities included assisting with routine medical care ($n = 22$, 96 %) and daily activities ($n = 22$, 96 %). Activities relating to generalized seizures included assessing the need for ($n = 16$, 84 %) and giving ($n = 17$, 89 %) rescue medication, providing physical support ($n = 16$, 84 %), and clearing the individual's environment during generalized seizures ($n = 13$, 68 %). During generalized seizure recovery, activities included taking the individual to bed ($n = 18$, 95 %), emotional support ($n = 14$, 74 %), and managing behavioral issues ($n = 14$, 74 %). In Sweden, despite contributions of paid caregivers, individuals with TSC-associated seizures require substantial time from unpaid primary caregivers, including seizure- and non-seizure-related care. Generalized seizures have a considerable impact on time spent caregiving and the care activities undertaken.

1. Introduction

Tuberous sclerosis complex (TSC) is a rare, multisystem genetic disorder with an estimated worldwide incidence of 10–16.67 per 100,000 live births [1]. TSC is primarily caused by mutations in the *TSC1* and *TSC2* genes and is characterized by the development of benign tumors in multiple organ systems, such as the heart, skin, and brain [2,3]. These multiorgan benign tumors can cause a variety of symptoms throughout an individual's lifetime, from mild to severe organ manifestations, neurological impairments, and death [1–3].

The neurological manifestations of TSC include epilepsy and TSC-associated neuropsychiatric disorders (TAND), such as autism

spectrum disorder, attention deficit hyperactivity disorder, anxiety, and depression [2–6]. Seizures are highly prevalent among individuals with TSC, with ~80–90 % of individuals diagnosed with epilepsy – typically before the age of 3 years [1,7]. TSC-associated seizures typically manifest as focal seizures and infantile spasms in the first year of life, although individuals with TSC can experience other seizure types, such as tonic, atonic, or tonic-clonic seizures [1,8,9]. The early onset of epilepsy in individuals with TSC is associated with drug-resistant seizures and higher risk of TAND / neurodevelopmental deficits [9,10]; further, this places these patients at higher risk of sudden unexpected death in epilepsy (SUDEP) compared with individuals with later-onset seizures [11].

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Owing to the multifaceted, developmental nature of the clinical manifestations of TSC, the burden of illness varies broadly both between individuals and throughout each individual's lifetime [2–4]. In particular, it has been shown that individuals experiencing TSC-associated seizures and reduced cognitive functioning have a lower health-related quality of life (HRQoL) compared with those with TSC without seizures [2,12]. Furthermore, HRQoL is worse in individuals with TSC-associated seizures who experience more frequent and severe seizures compared with those with less frequent and/or severe seizures [13,14].

The burden of disease associated with epilepsy and TSC has been shown to extend to caregivers and broader family networks [15,16], with caregivers of individuals with TSC having significantly lower HRQoL than the healthy population [15]. Seizure frequency and neuropsychiatric disorders related to TSC have been shown to impact the number of hours spent caregiving, family functioning, and caregiver HRQoL [17]. Other studies have shown that the occurrence of TSC-associated seizures causes additional stress and significant direct and indirect costs for patients and families [18–20]. The impact of seizures on caregivers is also dependent on seizure type. While some studies have failed to show an association between caregiver burden and focal, generalized, or secondarily generalized seizures in patients with epilepsy [21], others focusing on disabling seizures, which include secondarily generalized seizures, have shown a greater impact than focal seizures on caregiver QoL due to increased seizure severity [22]. Although focal seizures are the most common seizure type in TSC [2], secondarily generalized seizures are also prevalent in patients with uncontrolled focal seizures [22]. Generalized seizures are therefore worthy of attention when considering epilepsy-related burden experienced by individuals with TSC and their caregivers [17].

In Sweden, the incidence of TSC has been estimated at ~5 per 100,000 individuals [23]; however, there are limited data on the burden of care related to TSC-associated seizures in a Swedish context, in particular the association between seizure frequency and time spent caregiving.

The objective of this study was to quantify the amount of time caregivers of individuals with TSC-associated seizures in Sweden spend on non-seizure-related care and generalized seizure-related care, and to identify the various types of caregiving activities provided. This study also aimed to determine the impact of generalized seizure frequency on time spent providing care.

2. Material and methods

2.1. Study design

A cross-sectional, non-interventional online survey study with caregivers of individuals experiencing TSC-associated seizures was conducted in Sweden. Participants were recruited over 4 weeks (July 9, 2021 to August 6, 2021) through Tuberös Skleros Complex-Sverige (TSC-Sverige), a TSC patient association. A study advertisement, including a link to a brief screening questionnaire, a consent form, and the online study survey (see Supplementary material), was placed on TSC-Sverige's social media platforms. For each recruited participant, a donation of 200 SEK was made to TSC-Sverige by GW Pharmaceuticals (now a part of Jazz Pharmaceuticals, Inc.).

2.2. Participants

Eligible participants were adults (aged ≥ 18 years) who were the primary unpaid caregivers of an individual with TSC-associated seizures and were willing and able to provide informed consent to participate in a 10- to 15-minute online survey. A target sample size was not set prior to recruitment, owing to the rarity of TSC and timing of the study during the coronavirus 2019 pandemic. As a result, the sample size was solely based on the number of participants who completed the survey after 4 weeks.

2.3. Survey

After completing the screening questionnaire, eligible respondents received an information sheet describing the study content, procedures, and their rights as participants. Respondents willing to participate completed a consent form before proceeding to the primary survey.

In the absence of a validated, structured instrument to report on seizure-related caregiver burden in TSC, a survey was specifically designed for this study with bespoke, de novo items informed by a literature review on caregiver burden associated with TSC, two previous unpublished surveys on caregiver burden associated with Lennox-Gastaut syndrome and Dravet syndrome in Sweden, and caregiver burden associated with TSC in the UK [17]. The survey was developed in English and reviewed by the chair of TSC-Sverige (Annika Hallberg Juhlin), a primary caregiver of an individual with TSC. The final survey was translated into Swedish, by a native Swedish speaker, alongside other study materials.

Survey questions pertained to the clinical and demographic characteristics of the individual with TSC-associated seizures, caregiver characteristics, and care provided by the primary caregiver and others. Patient clinical and demographic characteristics included current age, sex, type of school/education enrollment, employment status, age at diagnosis, number of generalized seizures in the last month, and variation in the frequency of generalized seizures (minimum/maximum) per month. In the survey, generalized seizures were described as affecting both sides of the brain, usually resulting in a loss of consciousness and an increased risk of falls and accidents. Additional detail was provided to caregivers concerning generalized 'motor' seizure types (e.g., tonic, atonic, clonic, tonic-clonic, and focal to bilateral tonic-clonic seizures) to facilitate their identification as a generalized seizure (see Supplementary material). For example, tonic-clonic seizures are those "where the muscles suddenly become stiff, then relax and tighten rhythmically so that the person jerks and shakes." Caregiver characteristics included their relationship to the patient, sex, age, occupation, and the number and relationship of other household members. Care activity details provided by the primary caregiver included the type and time spent (hours per week) on activities unrelated to any seizure types (e.g., assisting the individual with their routine medical care or daily activities) and on activities during and after a generalized seizure. Generalized seizure-related care included all care such as physical and emotional support, hospital visits, and cleaning. Caregivers also reported the variation in hours spent caregiving in relation to the frequency of generalized seizures. Further information collected included the number of caregivers involved in the care of the individual with TSC-associated seizures, the relationship of the caregivers involved, and the hours of professional care used.

To provide more contextualized information on the caregiver experience, the survey also contained optional open-text responses for caregivers to provide more detail regarding seizures and the hours spent caregiving for the individual with TSC-associated seizures. These data are in the Supplementary material.

2.4. Statistical analysis

Descriptive statistics, calculated using R version 4.3.1 software [24], are presented for all variables: count and percent data for categorical variables and for continuous variables, the median, interquartile range (IQR [Q1–Q3]), mean, standard deviation (SD), and range, are provided. To address potential bias, all survey responses were included in the analysis, irrespective of whether a survey participant had completed the entire survey; no missing data were imputed. Participants had to answer "required" questions before progressing in the survey, and they were able to return to previous pages to review their answers.

3. Results

In total, 31 respondents completed the screening questionnaire and met the inclusion criteria. Of the eligible participants, 23 consented to participate, with 21 (91 %) fully and two (9 %) partially completing the survey.

3.1. Demographic and clinical characteristics

3.1.1. Patient characteristics

Caregiver-reported patient demographic and clinical characteristics are presented in Table 1. The median (IQR) age of individuals with TSC-associated seizures was 15.0 (9.5–18.0) years old, and just over half were female (n = 13/23, 57 %). Individuals ≤16 years old required special needs support, with the majority attending a special needs school (n = 10/12, 83 %), one individual (8 %) requiring special needs support at a mainstream school, and one individual (8 %) reported as not in school. Over half of individuals aged >16 years were either in education or training (n = 3/11, 27 %), or were unable to work owing to their health (n = 3/11, 27 %). No individuals >16 years old were employed.

The median (IQR) age at first diagnosis of TSC was 0.5 (0.2–0.7) years. Around half of individuals (n = 12/23, 52 %) had experienced a generalized seizure in the last month, with a median (IQR) number of generalized seizures among these individuals of 40.0 (27.5–70.5) in the last month. Frequency of generalized seizures also varied over time, i.e. beyond the last month, with a minimum of 10.0 (0.0–30.0) and

maximum of 50.0 (11.5–85.0) seizures per month.

Caregivers provided open-text responses when asked to comment about the number and variation in the number of generalized seizures over time. These responses illustrated how the seizures could vary across a patient's lifespan, over a year, a day, or in response to seizure triggers, including puberty and stress (see Supplementary material for caregiver quotes).

3.1.2. Caregiver characteristics

Caregiver demographics are presented in Table 2. All caregivers were female, with a median (IQR) age of 42.0 (37.0–46.0) years. Almost all caregivers (n = 22/23, 96 %) were a parent of the individual with TSC-associated seizures and, of those who fully completed the survey, 12/21 (57 %) were not in full-time employment (part-time employment: n = 7/21, 33 %; full-time caregiver: n = 2, 10 %; long-term sick leave: n = 1, 5 %; in education or training: n = 1, 5 %; other: n = 1, 5 %). Most caregivers lived with their partner (n = 17/21, 81 %) and/or their other children (n = 14/21, 67 %).

In addition to the primary caregiver, care provided by other paid or unpaid caregivers is detailed in Table 3. Including the primary caregiver, each individual with TSC-associated seizures had a median (IQR) of 3 (2.0–5.0) caregivers (mean [SD]: 4.2 [3.5]), and only one individual (n = 1/21, 5 %) was cared for by the primary caregiver alone. In most cases, the caregiver's partner contributed to care (n = 16/20, 80 %); the caregiver's other children also commonly assisted with care (n = 8/20, 40 %). Professional/paid carers assisted half of the individuals (n = 10/

Table 1
Patient clinical and demographic characteristics.

Characteristic		
Demographics (n = 23)		
Age, years	Mean (SD)	14.0 (6.1)
	Median (IQR)	15.0 (9.5–18.0)
	Range	4.0, 23.0
Age category, n (%)	Child (0–11 years)	8 (35)
	Adolescent (12–17 years)	8 (35)
	Adult (>18 years)	7 (30)
Sex, n (%)	Female	13 (57)
	Male	10 (43)
Age at diagnosis of TSC, years	Mean (SD)	1.0 (1.8)
	Median (IQR)	0.5 (0.2–0.7)
	Range	0.0, 8.0
Educational status in individuals ≤16 years old (n = 12)		
Educational status, n (%)	Mainstream schooling	0
	Mainstream schooling with special needs support	1 (8)
	Special needs schooling	10 (83)
	Not in school	1 (8)
Occupational status in individuals >16 years old (n = 11)		
Occupational status, n (%)	In education or training	3 (27)
	Employed full/part time	0
	Unemployed / looking for work	1 (9)
	Unable to work owing to their health	3 (27)
	Other	4 (36)
Generalized seizure frequency (n = 23)		
Had a generalized seizure in the last month, n (%)	Yes	12 (52)
Number of generalized seizures in the last month (n = 12) ^a	Mean (SD)	49.7 (36.0)
	Median (IQR)	40.0 (27.5–70.5)
	Range	2.0, 120.0
Minimum number of generalized seizures per month (n = 15) ^b	Mean (SD)	19.7 (24.7)
	Median (IQR)	10.0 (0.0–30.0)
	Range	0.0, 80.0
Maximum number of generalized seizures per month (n = 15) ^b	Mean (SD)	65.7 (77.2)
	Median (IQR)	50.0 (11.5–85.0)
	Range	1.0, 300.0

IQR, interquartile range; SD, standard deviation; TSC, tuberous sclerosis complex.

^a Only reported by caregivers of individuals who had a generalized seizure in the last month.

^b Only reported by caregivers of individuals who have ever had generalized seizures and stated that the number of seizures had varied over time.

Table 2
Demographic characteristics of the primary caregiver.

Characteristic		
Relationship to patient (n = 23), n (%)	(Step-/foster-) parent	22 (96)
	Sibling	1 (4)
Sex (n = 21), n (%)	Female	21 (100)
	Male	0
Age (n = 21), years	Mean (SD)	42.8 (7.8)
	Median (IQR)	42.0 (37.0–46.0)
	Range	25.0, 56.0
Occupation (n = 21), n (%)	(Self-) employed full time	9 (43)
	(Self-) employed part time	7 (33)
	Full-time homemaker/caregiver	2 (10)
	Retired/unemployed	0
	Long-term sick leave	1 (5)
	In education or training	1 (5)
	Other	1 (5)
Other household members (n = 21), n (%)	Partner	17 (81)
	(Other) children	14 (67)
	Parent(s) or sibling(s)	1 (5)
	No one else	2 (10)

IQR, interquartile range; SD, standard deviation.

20, 50 %), providing a median (IQR) of 99.2 (73.5–127.5) hours of care per week.

3.2. Assessment of caregiver burden

3.2.1. Hours spent caregiving by primary caregiver

Primary caregiver hours and variation in hours spent providing care per week are shown in Table 4. Participants spent a median total (IQR) of 52.0 (25.7–100.0) hours providing care per week in the last month, with 46.7 (20.0–93.3) hours per week spent on non-seizure-related care. Caregivers of individuals who had a generalized seizure in the last month spent a median of 4.7 (1.7–15.8) hours per week on generalized seizure-related care.

The time caregivers spent on generalized seizure-related activities for an individual varied depending on the frequency of generalized seizures over time. During the caregiver's time caring for the individual, caregivers stated that the least amount of time spent on generalized seizure-related care was a median (IQR) of 1.9 (0.0–8.8) hours per week, whilst the most was 14.0 (0.5–77.0) hours per week. The median (IQR) difference between the best and worst seizure frequency periods was 7.0 (0.5–68.7) hours per week (Table 4).

Table 3
Care provided by others.

Characteristic		
Total number of caregivers involved in care (n = 21) ^a	Mean (SD)	4.2 (3.5)
	Median (IQR)	3.0 (2.0–5.0)
	Range	1.0, 16.0
Number of caregivers involved in care (n = 21) ^a , n (%)	1	1 (5)
	2	5 (24)
	3	8 (38)
	4+	7 (33)
Relationship of other caregivers to primary caregiver (n = 20) ^b , n (%)	Partner/spouse	16 (80)
	Parent/sibling	2 (10)
	(Other) child	8 (40)
	Other relative/friend	0
	Paid carer	10 (50)
Hours of professional/paid care per week (n = 10) ^c	Mean (SD)	99.3 (50.7)
	Median (IQR)	99.2 (73.5–127.5)
	Range	9.3, 168.0

IQR, interquartile range; SD, standard deviation.

^a Includes the primary caregiver and other household members.

^b Only caregivers who reported that at least one other caregiver is involved in the care.

^c Only caregivers who reported that care is provided by a paid carer.

Table 4
Hours and variation in hours of care for the primary caregiver per week.

Characteristic	n	Mean	Median	IQR	SD	Range
Seizure and non-seizure-related care hours per week in the last month						
Total hours of care ^a	21	62.1	52.0	25.7–100.0	47.7	5.0, 168.9
Non-seizure-related care hours	21	55.8	46.7	20.0–93.3	44.3	5.0, 168.0
Generalized seizure-related care hours ^b	12	11.1	4.7	1.7–15.8	14.3	0.5, 46.7
Generalized seizure-related care hours as a proportion of total hours of care (%) ^{a,b}	12	15.8	5.7	3.2–29.8	17.2	0.6, 50.0
Variation in generalized seizure-related care hours per week in the last month						
Minimum generalized seizure-related care hours ^c	15	4.8	1.9	0.0–8.8	6.4	0.0, 19.3
Maximum generalized seizure-related care hours ^c	15	41.7	14.0	0.5–77.0	59.5	0.0, 214.7
Difference between minimum and maximum generalized seizure-related care	15	36.9	7.0	0.5–68.7	58.7	0.0, 214.7

IQR, interquartile range; SD, standard deviation.

^a Sum of hours of non-seizure-related care and generalized seizure-related care per week in the past month.

^b Only caregivers of individuals who had a generalized seizure in the last month.

^c Only caregivers of individuals who have ever had generalized seizures and stated that the number of seizures had varied over time.

Caregivers provided open-text responses when asked to comment about the amount of time spent caring overall and the amount of time spent caring due to generalized seizures. These responses illustrated that the caregivers provide constant supervision, including during the night, due to the complex needs of the patient. During periods of frequent seizures, their caregiving time was affected, sometimes disproportionately considering the duration of seizures, and sometimes because of behavioral difficulties, or hospitalization (see Supplementary material for caregiver quotes).

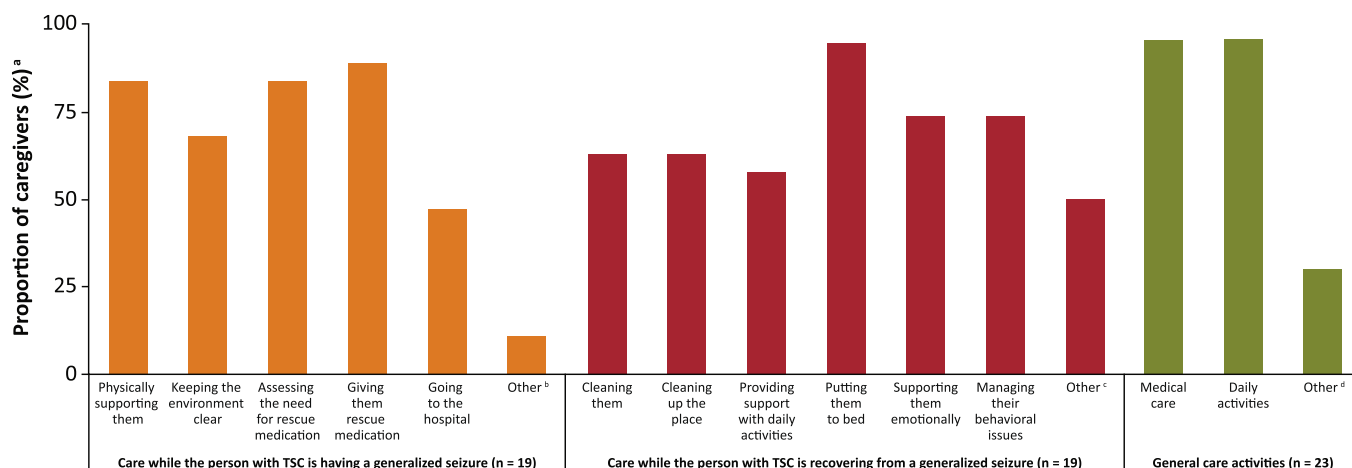


Fig. 1. Care activities undertaken by the primary caregiver. TSC, tuberous sclerosis complex. ^a Only caregivers of individuals who have ever had generalized seizures. ^b Other caregiving activities while the patient was having a generalized seizure included the use of a vagus nerve stimulation magnet (n = 1). ^c A free-text comment included having to “deal with severe self-harming behavior” in this situation (n = 1). ^d Other general care activities included assistance with self-care (n = 2), care related to learning difficulties (n = 1), and managing behavioral difficulties (n = 1).

3.2.2. Caregiving activities undertaken by primary caregiver

Non-seizure-related and generalized seizure-related care activities are illustrated in Fig. 1. Almost all caregivers reported activities irrespective of whether their care recipient had generalized seizures. These included assisting the individual with their routine medical care (n = 22, 96 %) and daily activities (n = 22, 96 %). “Other” reported non-seizure-related caregiving activities, reported by caregivers as part of a free-text comment, included assistance with self-care (n = 2), care related to learning difficulties (n = 1), and managing non-seizure-related behavioral difficulties (n = 1).

Among caregivers who stated that the individual has had generalized seizures in their lifetime, most reported giving them rescue medication (n = 17, 89 %), assessing their need for rescue medication (n = 16, 84 %), physically supporting them (n = 16, 84 %), and/or keeping their environment clear (n = 13, 68 %) while they were having a generalized seizure. The most common caregiving activities provided while the individual was recovering from a generalized seizure included putting them to bed (n = 18, 95 %), providing emotional support (n = 14, 74 %), and managing behavioral issues (n = 14, 74 %).

4. Discussion

This caregiver survey demonstrates the substantial caregiving needs of individuals with disabling TSC-associated seizures in Sweden. The need for round-the-clock care is highlighted by the large primary caregiver time burden, the presence of multiple caregivers per household, and the additional >90 hours of professional paid care provided per week. The complex and highly variable needs of caring for an individual with TSC-associated seizures is also highlighted. While care related to seizures constituted a substantial portion of caregiving time, non-seizure-related care contributed a larger proportion, likely reflecting the complexities resulting from this developmental epileptic encephalopathy and the diversity of TAND [25]. The high variation in seizure-related care indicates the unpredictability and stress reported by caregivers that impact their QoL [17,26].

Although there is likely overlap, the ~150 hours of total care time per week provided by primary (median 52.0 hours) and paid caregivers (median 99.2 hours) represent a substantial proportion of time, with paid caregiver time alone accounting for approximately 14 hours per day when averaged over a week. In comparison, in a systematic literature review investigating caregiving time for parents of children with complex needs, substantially less caregiving time was reported by parents of healthy children (0.6–3.3 hours per day or 4–23 hours per week)

[27] compared with the caregiving time reported here. The high level of support reported here is likely reflective of previous findings that have reported that individuals with TSC-associated epilepsy require continuous assistance with personal care needs and supervision with no respite, even during the night [17,19,28,29], and the potential for financial burden on the family. This was mirrored in the findings of the current study, where caregivers reported considerable caregiving time associated with managing behavioral issues or providing emotional support following seizures, as well as other non-seizure-related caregiving activities. These included providing routine medical care, care related to learning difficulties, and assisting with daily activities. The high level of support per week likely reflects the combined burden of generalized seizure-related activities (median 4.7 hours) and non-seizure-related activities (median 46.7 hours) on caregivers. This may have resulted in a higher burden for these caregivers compared with caregivers of the broader population of patients with TSC (with and without epilepsy). However, further research is required to address this question.

In caregivers of individuals with epilepsy, caregiver burden increases with a higher number of antiseizure medications taken by the patient and poorer patient neuropsychological outcomes [21]. As a result, caregivers HRQoL and emotional wellbeing are impacted negatively, with usual activities (e.g., home, social, leisure, and work productivity) limited for the caregiver and wider family [16]. While some caregivers may be required to make personal sacrifices by stopping working or reducing their working hours [17,18,20], others with paid caregiving and/or family support may be able to remain in full-time employment. In the present study, 43 % of primary caregivers were able to remain in full-time employment, which may also explain the large proportion of caregiving time provided by paid/professional caregivers and why a median of three people, most commonly the partner or other children of the primary caregiver, were involved in caregiving. This impact on the wider family has been reported previously [2,3,17,19]. Although the caregiving time of other unpaid caregivers (e.g., siblings and other family members) was not captured here, it can be anticipated that the total care time reported for primary and paid caregivers combined is an underestimate of the overall level of support offered.

In this study, caregivers reported that around half of individuals had experienced a generalized seizure within the last month. In these individuals, the median number of generalized seizures was high (40 in the last month), with a large range (2–120 seizures; IQR of 27.5–70.5) demonstrating the high variability of seizure frequency between individuals. Variability in generalized seizure frequency within

individuals over time was also reported, with caregivers reporting 10 and 50 generalized seizures per month, for periods when seizure frequency was at its lowest and highest, respectively. High variability in seizures has been reported previously in patients with TSC-associated epilepsy [9]. For generalized seizures, specifically, variability of seizures between different individuals has been reported in a UK caregiver survey where the IQR in the number of generalized seizures per week was 0–5 [17]. In the present study, seizure frequency was reported to vary and evolve over an individual's lifetime, with certain seizure triggers in particular, such as puberty and stress, being noted. Taken together, these findings align with and highlight the previously reported unpredictable nature of seizures associated with TSC and unmet needs regarding seizure control that can result in an increased burden for caregivers [19,20].

The present study highlights the potential for generalized seizure-related care to become an increasing source of caregiving burden. Mirroring the weekly variability in seizures, there was a large range between the minimum and maximum number of hours of generalized seizure-related care per week that could become a source of uncertainty for caregivers. The free-text comments in the present study support these findings, where caregivers expressed insights into how their time varied depending on the severity and frequency of the individual's seizures. This is also consistent with other TSC-associated epilepsy caregiver studies that demonstrate that an increase in the frequency of seizures is associated with a higher burden of care and a lower QoL for caregivers [2,3,15,17,26,28,30]. Highlighting the diversity of caregiving activities and the burden of illness of TSC-associated seizures, caregivers reported a large variety of activities during and after seizures, which included giving medication, physical and emotional support, and clearing the environment during a seizure. This aligns with many additional caregiver activities that have been reported elsewhere [17,31] and adds to the body of evidence outlining the extensive responsibilities for caregivers of individuals with TSC-associated seizures, including TAND manifestations, and the additional requirements during and after generalized seizures. Further research is needed to determine if the potential benefits of early preventative seizure control can be translated to improvements in cognitive decline and reduced caregiver burden.

There are several limitations that must be considered when interpreting the findings of this study. The small sample size of caregivers that responded to the survey, due to the coronavirus-pandemic-related recruitment challenges in the summer of 2021, is a potential source of bias and a key limitation of the study. Additionally, participants were recruited for the survey through an advert posted on the TSC-Sverige social media platforms, meaning it was not possible to determine a response rate, and caregivers recruited in this study may not represent those without access to social media. Despite this, our partnership with TSC-Sverige throughout survey development ensured that the questions in the final version were relevant to the TSC community. The availability of validated tools to examine seizure-related burden in caregivers of individuals with TSC is limited, requiring the creation of a bespoke survey for the present study. However, the small sample size made it impossible to robustly examine the association between seizure frequency and caregiver burden based on varying patient characteristics and generalized seizure frequencies.

Of note, this survey only captured the effect of generalized seizures on the burden of care; however, other seizure types, such as focal seizures, may also have an impact. While the present study reports a higher frequency of generalized seizures than a previous and similarly designed UK survey of caregivers of patients with TSC-associated epilepsy [14], the two studies reported similar generalized seizure (mean: 11.1 hours per week) vs general seizure-specific care times (mean: 7.4 hours per week), respectively. Therefore, any potential over-reporting of generalized seizures or subsequent impact on caregiving time is not expected to exclusively bias the findings of the present study. Moreover, the findings described herein remain important owing to the impact of

generalized seizures on the burden of illness experienced by caregivers and patients with TSC, further highlighted by their greater impact on caregiver QoL than focal seizures [22].

5. Conclusion

This survey highlights the substantial caregiver time spent on individuals with TSC-associated seizures in Sweden. In addition to the substantial support from professional paid carers, caregivers reported that a median of three people were involved in the care of the individual with TSC-associated seizures, highlighting the support network requirements beyond the primary caregiver. Primary caregivers reported spending a large amount of time on non-seizure-related care activities, with the amount of time spent providing seizure-related care varying depending on generalized seizure frequency. Furthermore, an extensive array of caregiving activities was demonstrated, including additional responsibilities during and after a generalized seizure. Overall, these findings highlight the importance of caregiver support and indicate the need for treatments with effectiveness in seizure and non-seizure outcomes.

A plain language summary of this study is available within the Supplementary material.

CRedit authorship contribution statement

Siu Hing Lo: Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Hanna Skrobanski:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Miranda Harrison:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Jamshaed Siddiqui:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Sally Bowditch:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SHL and HS are employees of Acaster Lloyd Consulting Ltd, which received payment from GW Pharmaceuticals, now a part of Jazz Pharmaceuticals, Inc., in the conduct of this study. MH, JS, and SB are employees of Jazz Pharmaceuticals UK Ltd and hold stock and/or stock options in Jazz Pharmaceuticals, plc.

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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.

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Declaration of Generative AI and AI-assisted technologies in the writing process

AI and AI-assisted technologies were not utilized in the preparation of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ebr.2024.100737>.

Data availability

All relevant data are provided within the manuscript and supporting files.

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