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The humanistic and economic burden of Dravet Syndrome on caregivers and families:
Implications for future research

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Abstract

The aim of this article was to review the current literature with respect to the humanistic and financial burden of Dravet Syndrome (DS) on the caregivers of children with DS, in order to (1) identify key unanswered questions or gaps in knowledge that need to be addressed and then, based on these knowledge gaps, (2) propose a research agenda for the scientific community to address in the coming decade. The findings support the conclusion that caring for a child with DS is associated with significant humanistic burden and direct costs. However, due in part to the paucity of studies, as well as the lack of measures of specific burden domains, there remains much that is not known regarding the burden of caregiving for children with DS. To address the significant knowledge gaps in this area, research is needed that will: (1) identify the specific domains of caregivers' lives that are impacted by caring for a child with DS; (2) identify or, if needed, develop measures of caregiving impact in this area; (3) identify the factors that influence DS caregiving burden; (4) develop and evaluate the efficacy of treatments for reducing the negative impact of DS and its comorbidities on DS caregivers; (5) quantify the direct medical costs associated with DS and DS comorbidities and identify the factors that influence these costs; and (6) quantify and fully explore the indirect costs of DS. Research that addresses these goals will provide the empirical foundation needed for improving the quality of life of children with DS and their families.

Keywords: Dravet Syndrome, Severe Myoclonic Epilepsy in Infancy, Caregiver burden, Costs

Abbreviations

DS, Dravet Syndrome.

1. Introduction

Dravet syndrome (DS) is a severe form of epilepsy that usually emerges in the first year of life.[1] DS is relatively rare, with early estimates of the incidence ranging from 1 in 20,000 to 1 in 40,000;[2] however, more recent research suggests it may affect one out of every 15,700 live births in the US.[3] Although children with DS usually evidence normal early development in the first few months of life, they soon develop prolonged febrile and afebrile generalized clonic or hemiclonic seizures.[4] After the first year of age a variety of seizure types can emerge including myoclonic, focal and atypical absences and the epilepsy is usually resistant to treatment. Episodes of status epilepticus are common, and children often develop significant cognitive impairment and behavioral disorders.[4-7] The mortality risk is high and childhood death is frequently caused by sudden unexpected death in epilepsy. The estimated mean annual rate of sudden unexpected death in epilepsy in DS is 0.6% (i.e., 6 per 1000 person years) of which is significantly higher than that reported in the overall population of patients with epilepsy (< 0.1%; i.e., less than 1 per 1000 person years).[8] Long-term outcome of DS is unfavorable, with children evidencing neurodevelopmental, behavioral and motor impairments and ongoing seizures of multiple types.[4, 6, 9-11]

A recently published comprehensive study assessing health-related quality of life in DS patients demonstrated a severe negative impact relative to normative data for matched age groups.[10] These investigators found that the scores of DS patients on the Impact of Pediatric Epilepsy Scale (IPES) were significantly higher than scores measured in the original validation sample of children with epilepsy, with and without learning difficulties. Large numbers of the parents of the DS patients also indicated

significant difficulties, including scoring in the abnormal range of the Strength and Difficulties Questionnaire (SDQ) for “conduct problems” (35%), “hyperactivity/inattention” (66%), and problems in “peer relationships” (76%). Epilepsy/seizure severity, presence of myoclonic seizures, and age at onset of seizures were among the strongest independent predictors of poor HRQOL, further underscoring the urgency and need for more effective antiepileptic treatment options for this patient population.[3] Other studies have found that DS is associated with significant financial costs to the family and to society,[8, 12] significant behavioral and medical comorbidities (such as autism spectrum characteristics, communication impairments, cardiovascular conditions, dysautonomia, cognitive dysfunction, disturbed sleep, and motor impairment, among many others),[4, 8, 10, 13] and negative impact on the quality of life of their caregivers.[4, 8]

Despite these findings suggesting a significant humanistic and economic burden of DS, there is a dearth of existing literature on the broader impact of DS on caregivers and the entire family unit. If the humanistic and financial burden of DS is as severe as has been suggested, this burden could contribute to greater psychological and health problems among the caregivers of children with DS, and even likely to other family members. These problems could in turn interfere with caregivers’ ability to care for children with DS; an effect which could then lessen the quality of life of the children and the entire family system. It would therefore be useful to better understand what we now know about the burden of caregiving for children with DS, and from this determine the knowledge gaps that need to be filled, in order to ensure that the needs of children with DS and their families are being adequately addressed.

The primary aim of the current article is to address the need for greater understanding in this area by reviewing the current literature with respect to the humanistic and financial burden of DS on the caregivers of children with DS, in order to (1) identify key unanswered questions or gaps in knowledge that need to be addressed and then, based on these knowledge gaps, (2) propose a research agenda for the scientific community to address in the coming decade.

2. Methods

2.1. Search strategy

We first performed a search of four electronic databases (MEDLINE [via PubMed], EMBASE, CINAHL, and PsychInfo) for articles published in indexed peer reviewed journals and that presented original findings regarding the humanistic and financial burden of DS on November, 2016 for all articles that had “Dravet syndrome”, “Severe Myoclonic Epilepsy in Infancy” or “SMEI” in the title. This search yielded 447 (MEDLINE), 570 (EMBASE), 72 (CINAHL) and 116 (PsychInfo) articles, respectively. The titles of all English language articles were reviewed, and any that had a title suggesting that the article might present information regarding the burden or cost of caregiving for a child with DS were read by one of the authors (MPJ). Of these, six were identified which presented data regarding these burdens, five of which presented information regarding the humanistic burden on caregivers,[8, 14-17] and one of which presented data regarding the financial burden of DS.[12] Three of these papers presented findings from three different perspectives using data from a single study.[14-16]

3. Results

3.1. Humanistic burden of caregiving for children with Dravet Syndrome

The five papers reporting on the humanistic burden of DS included one that used both a quantitative (administration of a validated measure of the impact of epilepsy) and qualitative (semi-structured interviews) approach, the findings of which were presented in three articles,[14-16] one open-ended paper-and-paper questionnaire study,[17] and one survey study.[8] The quantitative/qualitative study recruited a convenience sample of 28 parents of 24 children with DS. In this study, 20 semi-structured interviews were conducted with the mother only, and four with both parents. Seventeen parents were administered the Impact of Child Neurologic Disability Scale (ICND), which is a 44-item measure assessing the impact of epilepsy on children and their families in four domains: epilepsy, cognition, behavior, and physical/neurological function.[18] The children with DS of the participants had to be 12 months old or older and have been diagnosed by a pediatric neurologist. During the interviews, the parent participants were asked to describe their experience for each of three stages of DS: (1) Stage 1, which begins in the first year of life, usually with the emergence of prolonged febrile status epilepticus; (2) Stage 2, which begins around one year of age with the emergence of other seizure types and often with subsequent behavioral problems; and (3) Stage 3, which begins when children reach early adolescent with seizure types often decreasing and some improvement in behavioral problems (for a subset of children). Specifically, the parents were asked to describe "...their child's illness, personal experiences, perceptions of their child's healthcare, and coping mechanisms or support, both effective and lacking" (p. 762[15]). They were also asked to "...report spontaneously events or experiences that were particularly positive or negative in caring for their child" (p. 762[15]). The first

report from this study summarized the findings regarding the impact of caregiving for a child with DS separately for each stage.[15]

The focus of the impact of DS on caregivers during Stage 1 was on the relationships of the parents to others. The investigators reported that 14 (58%) of the mothers (N = 20) or mother/father units (N = 4; the interview data from the four mother/father parent couples who participated were combined as a single respondent for purposes of analyses) reported no changes in their relationships with friends during Stage 1, while one parent (4%) reported a positive impact on their friendships. It was not clear if any (and if so, how many) mentioned a negative impact of caregiving on friendships; none were mentioned in the articles. Sixteen (67%) reported no changes in extended or nuclear family relationships, five (21%) reported improved family relationships, and only two (8%) reported negative effects (e.g., increased strain, loss of relationship). Changes in spousal relationships were most common, with 8 (33%) reporting no change, seven (29%) reporting improved relationships, and nine (38%) reporting a negative impact.

With respect to Stage 2, 13 (54%) parents described Stage 2 as being a “particularly difficult” time, and noted more negative experiences during Stage 2 than Stage 1. However, the parents were also more likely to report at least one positive experience associated with caretaking during Stage 2; specifically, 19 (79%) spontaneously noted at least one positive experience. However, the positive experiences that were mentioned by the parents were not described in the articles. The most common negative experiences were associated with negative impacts on relationships with family (9 or 38%), friends (15 or 63%) and spouse (13 or 54%), all

significantly more common during Stage 2 than during Stage 1. Sleep problems were particularly common during Stage 2 (although it was not clear whether these referred to sleep problems with the children or parents – presumably both), with almost all (22 or 92%) reporting significant sleep problems during this stage.

Fourteen of the children had reached Stage 3 at the time the interviews were conducted, so information regarding the impact of caregiving on parents during this stage was available for only 14 of the parent participants. Increasing difficulties in the friendships of children with DS were reported by 11 (79%) of carers. Reports of negative relationships with family members and spouses were similar during Stage 2 and 3.

Two subsequent papers describing additional findings from these interviews focused on suggestions that emerged from the interviews which could help families better cope with caregiver burden.[14, 16] However, they also provided additional findings from these interviews about the impact of caregiving not reported in the original paper. The first of these mentioned social isolation from family, friends, and spouses as a source of significant distress, due primarily to the increasing amount of time it took to care for their child.[16] Stress associated with the costs of care were mentioned in the second additional report.[14]

The open-ended questionnaire study focused on parental perceptions of fever (a common trigger of seizures in children with DS) and fever management in a sample of 20 parents of children with DS.[17] The questions asked in the interview for this study included questions about (1) parental copings responses when the child has fever and (2) parent anxiety levels associated with child fever. All of the parents reported behavior

changes when their child has a fever, including: (1) sleeping in the child's room (63%); (2) waking the child at night to monitor body temperature and/or administer antipyretics (42%); and (3) staying at home while with the child as long as the fever persists (89%). In addition, all parents reported feeling anxious when their child has a fever. Almost all of the participants (89%) reported that their child's fever had a significant impact on their social life (i.e., less social interaction during fever attacks) and almost as many (84%) reported that fever had an impact on their professional life.

The single survey study we identified that examined the impacts of caregiving on parents focused on assessing comorbidities associated with DS from the parent's perspective.[8] However, in one of two surveys performed, 57 parents of children with DS answered questions "...regarding grief and adaptation with respect to their children's DS" (p. 99 [8]). The great majority of respondents (86%) acknowledged experiencing grief associated with their child's condition. The majority (89%) also endorsed a need for more support for managing the ongoing stress of caring for their affected child; an indirect acknowledgement that they experience caregiving as stressful.

3.2. Financial burden of Dravet Syndrome

Only one article was identified that presented findings regarding the financial costs of DS.[12] In this study, Strzelczyk and colleagues retrospectively evaluated all patients with DS treated in a single clinical center in Germany between 2007 and 2010 (N = 13).[12] These investigators determined the costs, in 2011 Euro amounts, of hospitalizations, medications, outpatient treatments, diagnostic procedures, and emergency transport based on data provided by the parents of the DS patients. The goal was to assess the use of health care services and their costs during both (1) a 1-

year baseline period and then (2) a follow-up year among patients whose seizures were not adequately controlled with the standard care at the time (using clobazam and valproate) and thus were switched to stiripentol, which had recently been made available. With respect to the costs of DS, they computed the direct costs due to DS only, as distinct from costs associated with other health problems or conditions that the children may have. However, this study did not assess indirect costs associated with DS such as lost work days, the possibility that one or both parents may have had to quit working partially or all together, need for specialized caregivers to watch children (i.e. nurses), presentism and lost productivity while at work due to extreme exhaustion and lack of sleep, etc.

During first (baseline) 1-year period, Strzelczyk and colleagues found the total direct costs to be €6,506, on average (range, €1,174 to €12,980 [about US\$1,300 to US\$14,500] in 2011 values)[12]. Twenty-four percent of this was due to the costs of medications, and 76% (€4,946 [about US\$5,300]) were due to non-medication costs, including hospital care costs (€4,483), emergency transportation (€389), outpatient care (€46), and diagnostic procedures (€26). During the next year, after a number of the children were switched to the new medication regimen (stiripentol), the average costs increased substantially (by €3,561 [about US\$3,800]), mostly due to the cost of the newly introduced medication. However, this was offset by some degree by a reduction in non-medication costs (a reduction of €2,587 [about US\$2,800]), including fewer inpatient admissions, and decreases in the costs of emergency transportation, outpatient treatment, and diagnostic procedures.

4. Discussion

The findings from this review, although based on just four studies (with findings presented in six articles), are consistent with the hypothesis that caring for a child with DS is associated with significant humanistic and financial burdens. With respect to the humanistic impact, the impact on relationships with friends, family, and the spouse (and related social isolation), sleep problems, financial stress, work, and emotional stress were identified from the qualitative interview and questionnaire studies. The presence of grief and general emotional stress among caregivers were identified in the survey study. These findings regarding the humanistic burden of DS are entirely consistent with the experience of clinicians who provide care for patients with DS and their families.[4] With respect to the financial burden, the findings indicate that direct costs are substantial, but are also variable, at least as identified in a sample of patients from a single clinic in Germany. No studies were identified that quantified the indirect costs associated with DS. In sum, the available research is limited but confirms that caregiving for a child with DS has significant humanistic and financial costs, but provide incomplete details beyond this general conclusion, and therefore highlight the significant knowledge gaps in this area.

4.1. Humanistic burden: Knowledge gaps and future directions

4.1.1. Identifying burden domains

The initial list of caregiver concerns that emerged from the studies reviewed here are consistent with the findings from other focus group and survey studies of parents of youth with epilepsy (but not DS, specifically), which identify sleep problems, stress, depression, ongoing anxiety and fear, disruptions/changes in careers and relationships, and disruptions in usual family activities as areas impacted following the diagnosis of a

child with epilepsy.[19-22] For many years previously not having a confirmed (genetic) diagnosis in Dravet syndrome also added to significant caregiver anxiety.[23] However, to our knowledge, no research has yet been conducted that would systematically identify the most important caregiver domains that are impacted by caring for a child with epilepsy in general, or DS in particular. Moreover, no research has yet quantified the impact of caregiving on caregivers of children with DS, relative to caregiving for other chronic health conditions, including other forms of epilepsy.

Research to address these questions is important for a number of reasons. First, it would provide a more comprehensive and empirically supported understanding of the true impact of DS on caregivers' lives. This would help clinicians, scientists, and healthcare systems determine which impact domains should be the target of treatment and research, given the limited clinical and research resources that are available. Second, given the likely significant role of caregiver burden on the lives of the families of and children with DS and other epilepsy conditions,[24, 25] research that systematically identifies the range of psychosocial, educational, and parenting/family stresses could be used to provide an empirical basis for the development of effective interventions. For example, sleep disorders are known to a prevalent problem for children with seizures and learning disability, and can be associated with daytime learning problems and impacts on parental relationships.[26] Designing care pathways that can access appropriate assessment and intervention would be informed by research to identify the key burden or impact domains, and the relative importance of each from the caregiver's perspective, and a critical research goal in this area (see Table 1).

[Insert Table 1 about here]

In addition, there is a need to study the impact of DS on caregivers relative to other chronic health conditions, including other forms of epilepsy. We would expect that this research would demonstrate significantly greater caregiver impact for DS given that DS represents a form of epilepsy that also has severe neurodevelopmental, behavioral, and motor impairments as part of the condition. For example, the severity and refractory nature of seizures in DS is higher than other epilepsy conditions. Children with DS have a high frequency of comorbid diagnoses including autism [27], attention deficit disorder [10], and developmental delay.[11, 28] They also evidence significant motor problems including deterioration in gait,[29] behavioral/conduct problems, [10, 30] and communication problems.[28] In essence, caring for a child with DS requires that carer's contend with a range of cognitive, communication and behavior problems beyond managing seizures.[4] Research would allow for the testing of this hypothesis and, if supported, would provide important findings that could be used to inform the development of interventions for reducing the impact of caregiving for a child with DS (see discussion of the need for clinical trials research, below).

4.1.2. Identifying or developing psychometrically sound measures of DS caregiver burden

Once the key burden or impact domains for caregivers of DS are identified, an important next step is to determine if there are measures of burden or impact that adequately assess each of these domains. A large number of caregiver burden measures exist.[31] However, none of the existing measures were specifically developed for assessing caregiver burden for children with epilepsy in general or DS in particular. Thus, in order to move our scientific understanding in this area forward, an

important next step would be to compare the list of burden domains identified as a result of addressing the first research agenda items against the available caregiver burden measures and either (1) identify a measure or set of measures that assess the most common and important DS caregiver burden or (2) develop such a measure or set of measures (see recommendation 2, Table 1). A valid and reliable measure of DS burden is essential for enhancing our understanding the effects of this burden on the children's lives and long term function, identifying the effects of epilepsy treatments on this burden (i.e., as secondary outcome measures in clinical trials), and assessing the potential benefits of interventions that could address this burden. Without adequate measurement, scientific progress cannot be made.

4.1.3. Identify the factors that influence DS caregiving burden as well as the subsequent effects of DS burden on the child's health and function

The lack of valid and reliable measures of DS caregiving burden means that we know virtually nothing about the factors that impact this burden as well as the subsequent effects of this burden on patient quality of life. The third research recommendation (see Table 1) addresses this knowledge gap.

Given the typical time course of DS (e.g., Stage 1 in the first year with the first emergence of seizures; Stage 2, when the frequency and severity of seizures increases along with behavioral and cognitive problems; Stage 3, when seizure frequency begins to decrease and the problems that have emerged begin to stabilize [15]), it would be reasonable to hypothesize that the nature and amount of burden changes over time as the child ages. Knowing this would allow us to better develop interventions that would

help caregivers and their children better manage the specific causes and types of burden at each stage; one size does not fit all.

It is also possible, even likely, that the impact of DS varies depending on the caregiver's specific relationship to the child with DS; for example, burden may be different for different members of the family unit given their roles and responsibilities in the family; parents, grandparents, and siblings or other family members may therefore require different types or intensity of assistance and treatment. The availability of a valid and reliable caregiving impact measure would be useful for clinicians to help identify the specific needs of each family member.

In addition to developing a greater scientific understanding of the factors that influence burden, research is also needed to understand the subsequent effects of this burden on the children with DS. Research supporting the importance of knowledge in this area comes from studies demonstrating that caregiver burden is significantly associated with the child who has epilepsy's quality of life.[21, 24, 32] For example, in one study the level of a mother's caregiver stress was found to be moderately to strongly associated with behavior problems in the child.[21] Yet, we do not yet know which caregiver burden domains (e.g., depression, anxiety, sleep difficulties, marital stress, financial difficulties), or combination of domains, are most strongly associated with which child quality of life domains (e.g., psychological function, physical function, health outcomes). In order to inform the development of effective interventions, such knowledge is critical.

4.1.4. Develop and evaluate the efficacy of treatments for reducing the negative impact of DS and its comorbidities on DS caregivers

Ultimately, the most long-term goal of research in this area is to identify and then implement effective strategies for reducing the negative impact of caregiving on caregivers, their families and of course their afflicted children; this is our fourth research agenda (see Table 1). Unfortunately, to date, there have been no studies that have sought to evaluate the efficacy of treatments for caregivers of children with DS, and only a small handful of pilot studies that describe or report on interventions for caregivers of children with epilepsy in general.

The earliest study we were able to identify was a report that described a pair of education programs, one of which was developed to be provided to children with epilepsy and their parents.[33] The investigators report that these 6-session programs were easily implemented in a variety of epilepsy centers, which speaks to the feasibility of such program, but did not provide efficacy data.[33] A second uncontrolled pre- to post-treatment pilot study was performed to evaluate the potential benefits of an 8-session group intervention designed to improve coping skills, self-efficacy, and self-reliance in children with epilepsy and their parents.[34, 35] Nine youth and their parents completed the program, and reported high level of satisfaction with the intervention. Pre- to post-treatment improvements were also noted in parent ratings of children's coping skills, as well as improvements in child-rated self-efficacy for seizure knowledge and knowledge about epilepsy. The extent to which this intervention reduced key caregiver burden in the parents was not clear, although it one might expect that noticeable improvements in the children would translate to less stress in the parents.

The only controlled trial we were able to identify randomly assigned 46 parents of children with epilepsy and their children to either (1) usual care or (2) an intervention provided to both parents and children in three phases: (a) information about epilepsy and how caregivers could facilitate the child's adjustment provided during a hospital admission; (b) a telephone call made three days after hospital discharge to reinforce the information provided during hospitalization; and (c) the provision of a parent-child activity workbook that taught parents how to use therapeutic play to help the child cope.[36] Only one statistically significant treatment effect emerged for the treatment group (parent-rated children's "internalized behavior"), although there were non-significant trends for the treatment group to report greater improvement in a number of other outcome variables than the control condition. The authors concluded that although there were indications that the treatment may have been helpful, they also noted that the intervention may not have been beneficial for a number of outcomes because it did not address many of the areas of concern for parents and caregivers, such as the provision of information regarding the medical management of their child's condition. In short, despite the negative impacts caregiving of a child with epilepsy in general and DS in particular and some preliminary efforts in this area, there is not yet a single intervention for parents and children that is known to effectively address these impacts.

Given that the most important domains of DS caregiver burden have yet to be identified (recommendation 1), the lack of identified measures to assess these burden domains (recommendation 2), and our lack of understanding of the factors that impact DS caregiver burden and how DS caregiver burden impacts child health and function, it might be premature to develop interventions.[36] However, we view the development of

interventions, and appropriate scientific evaluation of their efficacy, as an important long-term research agenda (recommendation 4, see Table 1).

4.2. Financial burden

4.2.1. *Direct costs of DS*

We know from one study performed in Germany that caring for a child with DS has significant direct financial costs and that those costs are widely variable.[12] However, we do not know if the findings from this study from a single clinic generalize to the families of children with DS in other parts of Germany or to clinics in other countries with different medical systems. One recent systematic review of the direct costs of epilepsy in general (including children and adults) in the US found direct epilepsy costs to range from \$1,022 to \$19,749 [about €950 to €18,500] over a one year period.[37] Another study of the direct and indirect costs of epilepsy in general in Germany found the mean direct costs to be €1,619 in a 3-month period (€6,476 over 12 months) and the 3-month maternal and paternal indirect costs to be €1,231 and €83 in 2011 amounts [estimated annual indirect costs €4,924 and €332], respectively.[38] The findings from both of these studies are in line with the DS study from Germany. Importantly, both studies also found markedly higher direct costs for patients with uncontrolled or more refractory epilepsy and for patients with comorbidities; both of which are aspects of DS. [8, 10, 13] Thus, we can expect that the costs associated with caring for a child with DS would be significantly higher than the costs associated with caring for a child with a less severe form of epilepsy or many other medical conditions; research is needed to evaluate this possibility.

Thus, our fifth research recommendation (see Table 1) is to quantify the direct costs associated with DS and DS comorbidities (including medication costs and outpatient and inpatient treatment costs, ER visits, ambulance costs). Such research could also determine how these costs vary as a function of (1) patient age (e.g., we might expect the costs to be greater during Stage 2[15]), (2) severity of the condition and comorbidities (we would expect the costs to be greater with greater severity – but how much greater?), (3) insurance coverage and out-of-pocket expenses (people might be less willing to pay for needed services if they have limited insurance coverage), (4) socioeconomic status (given evidence that children from families with lower socioeconomic status tend to receive less epilepsy-related medical care from neurologists and more from emergency department visits and hospitalizations, which are major drivers for the direct costs of epilepsy[39]) and (5) state/country of residence (short-term expenses might be higher in states or countries who provide more coverage for services, but long-term expenses might be lower, due to better ongoing management of the condition). More knowledge in this area, in particular knowledge regarding the role of insurance coverage and state or country differences in health policies, could inform policy makers regarding how to best provide care that is most cost effective.

One of the intriguing findings from the single direct cost study performed was the high variability in costs across the 13 DS families studied, ranging from annual costs from €1,174 to €12,980.[12] It would be important to learn more about the factors that contribute to this high level of variability. Of course, and as mentioned, one factor is most likely to be the severity of epilepsy, as reflected by the number and severity of

seizures.[37, 38] But there may be other factors as well, such as the financial resources of the parents, the age (stage of DS) of the child, responsiveness of seizures to therapies, severity of comorbidities, and of social support and extent of the social support network of the family. Research in this area would help to provide an empirical basis for determining the help that families may need in order to prepare for and minimize those costs in the long run.

4.2.2. Indirect costs of DS

Currently, we know virtually nothing about the indirect costs of DS, which would include lost work days (with the real possibility that one or both parents may have to quit working partially or all together), the costs associated with for specialized caregivers to watch children (i.e. nurses), presentism and lost productivity while at work due to extreme exhaustion and lack of sleep, among other possible indirect costs.

We know from studies about the costs of epilepsy in general (in adults and children) that indirect costs can vary widely – from between 12% and 85% of the total costs of epilepsy – depending on the population studied, the country where the costs were derived from, and the procedures used to assess those costs.[40] For example, in one carefully performed population-based study of consecutive children and adolescents with epilepsy performed in two German states, 3-month indirect costs (€1,314) were 81% of the direct costs during this same time period (€1,618).[38] We also know that childhood epilepsy has greater cost burdens than other prevalent childhood conditions.[41] Given the severity of DS, in particular, it is reasonable to hypothesize that DS will have relatively high direct and indirect financial cost. Research is needed to better understand the total cost burden associated with DS; hence, our

sixth research recommendation is to quantify and explore the indirect costs of DS (see Table 1).

Establishing baseline data on both direct and indirect costs will also allow us to determine how they might change as resources become more (or less) available to the families of children with DS, as well as determining how these costs change or shift as new (hopefully more effective) treatments are introduced (cf. [12]).

4.3. Study limitations

We limited our search to findings that had been published in indexed peer reviewed journals, and did not include “grey literature” (e.g., conference proceedings, white papers, reports written for foundations or agencies) in the search. Thus, the findings reported here provide only a partial review of current knowledge. In addition, given the paucity of research in this area overall, it is possible that there are other impacts of DS on the lives of caregivers that have not yet been identified. This provides additional support for the need for more systematic research in this area.

4.4. Summary and conclusions

The research studies reviewed here supports the conclusion that caring for a child with DS is associated with significant humanistic burden and direct financial costs. However, due in part to the paucity of studies, as well as the lack of measures of specific burden domains, there remains much that is not known regarding the humanistic and financial burden of caregiving for children with DS. To address this knowledge gap, research is needed that will: (1) identify the specific domains of caregivers’ lives that are impacted by caring for a child with DS; (2) identify or, if needed, develop measures of caregiving impact in this area; (3) identify the factors that

influence DS caregiving burden; (4) develop and evaluate the efficacy of treatments for reducing the negative impact of DS and its comorbidities on DS caregivers; (5) quantify the direct medical costs associated with DS and DS comorbidities and identify the factors that influence these costs; and (6) quantify and fully explore the indirect costs of DS. Research that addresses these goals will help us to better understand the magnitude and effects of the burden of DS, and provide the empirical foundation needed for improving the quality of life of children with DS and their families.

Conflicts of interest

Mark P. Jensen received financial support from Zogenix, Inc., for the research reported here. Andreas Brunklaus declares no conflicts with respect to this paper. Liam Dorris receives research support from UCB Pharma, NIHR, and Glasgow Childrens Hospital Charity. Sameer M. Zuberi is Editor-in Chief of the *European Journal Paediatric Neurology*, for which he receives an honorarium from Elsevier, Ltd. He also receives research support from Epilepsy Research UK, Dravet Syndrome UK, and Glasgow Childrens Hospital Charity, and has served on advisory boards for GW Pharma, Biocodex, and Zogenix, Inc. Kelly G. Knupp has received research support from Colorado Department of Public Health and Environment and Zogenix Inc. Sameer M. Zuberi, Liam Dorris, Andreas Brunklaus, and Kelly G. Knupp received no financial support from Zogenix, Inc. in relation to their contribution to this manuscript. Bradley S. Galer and Arnold R. Gammaitoni are employees of Zogenix, Inc.

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