Author/s:
Nabbout, R;Auvin, S;Chiron, C;Thiele, E;Cross, H;Scheffer, IE;Schneider, AL;Guerrini, R;Williamson, N;Irwin, J;Mistry, A;Grimes, R;Bennett, B

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DR RIMA NABBOUT (Orcid ID : 0000-0001-5877-4074)

PROFESSOR INGRID EILEEN SCHEFFER (Orcid ID : 0000-0002-2311-2174)

MISS NICOLA WILLIAMSON (Orcid ID : 0000-0002-9717-8563)

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Perception of impact of Dravet syndrome on children and caregivers in multiple countries: looking beyond seizures

RIMA NABBOUT[1]

STEPHANE AUVIN[2]

J CATHERINE CHIRON[1]

ELIZABETH THIELE[3]

J HELEN CROSS[4]

INGRID E SCHEFFER[5,6]

AMY L SCHNEIDER[5]

RENZO GUERRINI[7]

ZOGENIX AND ADELPHI VALUES STUDY GROUP*

1 Reference Centre for Rare Epilepsies, Necker-Enfants Malades and Inserm U1129, Paris; **2** Hôpital Robert Debré, APHP and Inserm U1141, Paris, France. **3** Herscot Center for

Tuberous Sclerosis Complex, Massachusetts General Hospital, MA, USA. **4** Great Ormond Street Institute of Child Health, University College London, London, UK. **5** Departments of Medicine and Paediatrics, University of Melbourne, Melbourne; **6** Royal Children's Hospital, Florey and Murdoch Children's Research Institute, Melbourne, Australia. **7** The Meyer Children's Hospital, University of Florence, Florence Italy.

Correspondence to Rima Nabbout, Department of Pediatric Neurology, Reference Center for Rare Epilepsies, Inserum U663, Necker Enfants Malades Hospital, Paris, France. E-mail: rimanabbout@yahoo.com

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ABBREVIATIONS

HRQoL Health-related quality of life

DEE Developmental and epileptic encephalopathy

AIM To assess the relevance and generalizability across countries of concepts of the impact of Dravet syndrome beyond seizures, as recognized by families.

METHOD Caregivers of children with Dravet syndrome in four countries (Australia [*n*=8]; USA, UK, and Italy [all *n*=4]) participated in 1-hour qualitative telephone interviews, identifying key Dravet syndrome concepts. Interviews were recorded, transcribed, and, where necessary, translated into English for thematic analysis. Conceptual saturation was assessed and findings compared to the previously developed French conceptual disease model.

RESULTS The most common seizure types reported by caregivers were tonic–clonic, absence, or focal-impaired awareness (localized/partial). Fever and physical activity were the most commonly reported triggers. Patient-relevant impacts included impairment in cognition, motor skills, communication, social skills, and behavioural functioning. Caregivers consistently reported negative social, physical, and family impacts. Concepts identified in the interviews showed similarity with the French conceptual model. Minor differences between countries are likely to reflect variations in health care systems.

INTERPRETATION Findings in Italy, Australia, UK, and USA confirm that the key impacts of Dravet syndrome on children and caregivers identified in France are generalizable across countries. Key symptom and impact concepts relevant to children and parents should be targeted as critical outcomes in new therapy evaluations.

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Concepts of Dravet Syndrome Impact *Rima Nabbout et al.*

[Boxed content to appear on page 2]

What this paper adds

- Relevance of the impact of Dravet syndrome on children and caregivers was confirmed across countries.
- Patient and caregiver-relevant Dravet syndrome impacts contribute to poorer health-related quality of life.
- Indirect seizure impacts were reported to be as important as direct impacts.
- Country-specific differences in concepts probably reflect differences in health care systems.

[Main text]

Dravet syndrome is a rare developmental and epileptic encephalopathy with onset during the first year of life in previously typically developing infants.[1] It is primarily associated with a de novo mutation of the *SCN1A* gene.[2] Prevalence is estimated to be 1 in 17 000, although in the absence of sizeable epidemiological studies, this figure may be underestimated. Dravet syndrome is characterized by frequent febrile seizures, followed by afebrile seizures, mainly clonic and unilateral, of long duration, and with frequent status epilepticus.[3] Although progression is variable, additional seizure types emerge over time; myoclonic, focal, and atypical absence seizures commonly develop with age.[4] Seizures can be life-threatening with a high risk of status epilepticus and sudden unexpected death in epilepsy.[5]

There are numerous other, non-fatal Dravet syndrome features that carry significant consequences for the patient. Children often have severe developmental impairments impacting all domains of life. Issues arise with fine motor skills and gross motor function, including abnormal gait that have an impact on physical function.[6–8] Adolescents and adults with Dravet syndrome may struggle to integrate with peers due to impaired cognition and communication difficulties, causing social isolation.[3] Adult survivors are almost entirely dependent on others for aspects of care.[9] All these factors contribute to poor health-related quality of life (HRQoL) for individuals with Dravet syndrome.[3]

Current treatment of Dravet syndrome focuses on alleviating the associated seizure burden. Antiepileptic drugs are non-curative and are often used in combination.[10] Treatment side effects include fatigue, cognitive impairment, and behavioural issues.[10] Additionally, complexity of treatment administration can impact on the caregiver's daily life.[11] For patients with Dravet syndrome, there are complex care needs that can have a detrimental impact on caregiver quality of life at each developmental stage.[12] Consequently, there is a clear unmet need for more effective Dravet syndrome treatments that may not only improve the patient's HRQoL, but also the caregiver's quality of life.

Research into the impact of Dravet syndrome on both patients and caregivers is increasing,[13] including recent work conducted by Nabbout et al.[14] This small-scale study explored the wider impact of Dravet syndrome in both children and their caregivers, using qualitative interviews. Its aim was to create a broader picture of the condition beyond seizures and to identify potential endpoints that should be considered in devising a future composite

endpoint for Dravet syndrome clinical trials. Qualitative, open-ended caregiver interviews were conducted with 11 caregivers of children with Dravet syndrome in France that allowed for spontaneous reporting of caregiver-relevant concepts.[14] A broad range of patient-relevant and caregiver impacts were reported, including impacts on daily activities, work, family relationships, emotional well-being, and sleep. Although this research identified a wider potential impact of Dravet syndrome, a shortcoming of the study was that data were collected only in France. There may be country-specific impacts associated with caring for a child with a chronic condition and, as such, findings of the French study may not be widely generalizable. Therefore, in this study we assessed the relevance of the initial concepts identified by Nabbout et al.[14] with caregivers of children with Dravet syndrome in the UK, USA, Italy, and Australia. The findings of this study can be used to support the relevance and generalizability of the findings identified in the French cohort.[14]

METHOD

Study design

A qualitative study was conducted with caregivers of children (age 2–18y) with Dravet syndrome. This age range was selected as diagnosis is rarely confirmed before 2 years of age.[15] One-hour long telephone interviews to elicit the concepts were conducted using a semi-structured interview guide. The methodology of this study was developed to reflect the French study,[14] to allow for clear comparisons to be made between the studies. This ensured that any differences in findings between the French study and this study could be better attributed to differences between countries rather than to potential bias and measurement error. As such, the interview guide used was the one previously developed for the French study.[14] Questions were selected based on key findings in the Dravet syndrome literature. Clinical experts provided input on the clinical relevance of topics. Questions assessing core aspects of HRQoL were included, as they were considered relevant to Dravet syndrome.

Sample

Participants recruited were caregivers of children with Dravet syndrome. Children from a range of age groups were selected to capture different developmental issues, as the disease profile and challenges associated with caring for a child with Dravet syndrome change with age.[9] Caregivers were interviewed in the USA, UK, Italy (all n=4) and Australia (n=8), with a

total target sample of 20 participants. A larger sample size was chosen in Australia because of the greater recruitment opportunities in that country for this rare disease.

To be included in this study, participants had to be caregivers of a child with Dravet syndrome, aged 18 years or older, fluent in the language of the country in which they were interviewed, and able to participate in an interview lasting up to 60 minutes. Caregivers were excluded from participation if they had difficulty hearing, reading, had severe neurological or cognitive deficits, or an uncontrolled psychiatric condition affecting their ability to participate.

Recruitment

Caregivers in the USA, Italy and Australia were recruited at clinical sites. They were invited to take part in the study during a routine appointment and given a letter detailing the aims and purposes of the interview. After this, if caregivers were comfortable participating they provided written consent by completing an informed consent form and another form for detailing background and demographic information. Caregivers in the UK were identified and recruited through a patient advocacy group – Dravet Syndrome UK. Eligible caregivers were invited to participate in a 1-hour telephone interview. Specific recruitment quotas ensured a diverse sample regarding age and sex of patient and caregiver. Caregivers were remunerated for participating.

The study was conducted in accordance with the Declaration of Helsinki. Local ethical approval was obtained at each clinical site. Site-specific ethical approval was obtained in Italy (reference 146/2016) and Australia (reference HREC/16/Austin/282). Centralized approval was obtained from an independent review board to conduct the study at a USA clinical site (reference 31466/1). As caregivers in the UK were recruited through a patient advocacy group, no site-specific ethical approval was required. However, the study protocol, including the design and methodology applied to all countries, was approved by the Quorum Independent Review Board.

Data collection

The methodology used for the qualitative interviews was the same as that used in the French study.[14] During the interviews, open-ended questions captured spontaneous accounts of caregiver experience. Trained researchers conducted interviews using a pre-existing interview guide.[14] Interviewers had limited prior knowledge of Dravet syndrome, in order to maximize spontaneous elicitation of participant-relevant information, and minimize potential

interviewer bias. To cover all relevant topics, participants were then asked more focused questions, included in the interview guide as 'probes'. Each interview included topics on diagnosis, treatment, symptoms/signs, child and caregiver impacts, and coping/relief strategies. Interviews were conducted in the native language of each country, audio-recorded, transcribed, and translated into English where necessary. Transcripts were quality-checked by the interviewer, ensuring consistent, accurate transcription before analysis.

Analysis

Qualitative analysis of transcripts was conducted using ATLAS.ti computerized software (Scientific Software Development, GmbH, Germany). Interviews were analysed using thematic analysis.[13,16,17] This rigorous analysis technique is ideally suited to qualitative research, particularly clinical outcome assessments, including the caregiver-reported outcomes used here.[17] As a data-driven, theory-free approach, this method was chosen as it provides rich data meeting a specific aim.[16,17] All themes identified were data-driven rather than prespecified a priori, ensuring the analysis was firmly grounded in data, focusing on topics important to caregivers.[18] A coding tree was developed before analysis to structure the coding of concepts and subconcepts. The coding tree was used consistently to guide coding of the interviews (Fig. S1, online supporting information). Two experienced qualitative researchers coded the transcripts using a constant comparative method[19] to ensure consistency. Any discrepancies in coding were discussed by the research team and resolved by the project lead.

After interview analyses, conceptual mapping was performed using the French conceptual model[14] and concepts emerging from this study. The conceptual model details key concepts (i.e. symptoms/signs, impact, trigger, and coping strategies) and subconcepts (i.e. specific types of concepts) identified, and hypothesized relationships between them. For example, absence seizures (subconcept) are a type of symptom/sign (seizure) (concept). This allowed comparisons between studies to identify new concepts emerging from these interviews and highlighted differences between countries.

After conceptual mapping, conceptual saturation was assessed to determine sample size adequacy. Conceptual saturation is defined as the point at which no new concepts spontaneously emerge from additional interviews,[20] therefore, the researcher can be confident that the question has been fully answered and the sample size is sufficient. Research suggests conceptual saturation can be achieved in just 12 interviews.[20] A sample of 20 caregivers was

selected to comfortably exceed the minimum sample size required for successful conceptual saturation. Additionally, sample size was chosen to ensure a demographically diverse sample, including the age and sex of the patient and caregiver.

Conceptual saturation was assessed for the overall sample as follows. Caregivers were split into three approximately even-sized groups, based on order of interview completion. For conceptual saturation to have been achieved, concepts had to be mentioned by the end of analysis of the second group. If any new concepts were elicited in the third group, the sample size would be deemed insufficient for the results to have fully captured all caregiver-relevant concepts. Exploratory conceptual saturation analyses were also assessed for each country separately.

RESULTS

Demographics

Twenty caregivers were interviewed across the four countries (13 females, 7 males; mean age 43y 4mo; range 34–55y; Table SI, online supporting information). Twenty children (12 females, eight males) with Dravet syndrome were recruited in each age category (2–4y, 5–8y, 9–11y, 12–18y). Mean age at diagnosis was 34 months; however, this varied considerably by country. Time to Dravet syndrome diagnosis was considerably longer in the UK and USA (4y 2mo and 5y respectively) compared to Italy and Australia (1y 1mo and 2y respectively).

Concept elicitation findings

The most frequently reported symptom was seizures, volunteered by all caregivers (*n*=20; Fig. 1); specifically, absence (*n*=15) and tonic–clonic seizures (*n*=14) were the most common seizure types across all age groups. Seizures lasted from a few minutes (*n*=5) to up to an hour (*n*=6). Seizure frequency varied greatly from a few times per year to a few every night, with no clear pattern. Timing of seizures varied greatly: more caregivers reported their child experiencing night-time seizures (*n*=11) than in the morning or during the day (*n*=6). Several factors triggered seizures including temperature caused by illness or fever (*n*=15) and changes in external temperature (*n*=15). Less frequent triggers included physical activity (*n*=9) and water immersion (*n*=8). These were consistent across countries.

A range of child impacts were reported relating to cognitive functioning, motor skills, behavioural functioning, and other secondary impacts (Fig. 2), with minimal differences

between countries. The most commonly reported patient-relevant impacts were social functioning (*n*=20) and gross motor function (*n*=19). Problems with fine motor skills, expressive communication, and learning were also frequent (*n*=18 respectively). Less commonly mentioned concepts included impacts on emotional expression (*n*=8) and 'treatment impacts' due to drug side effects or resistance (*n*=10).

Variation across countries of the impact on eating was found. For example, in Italy subconcepts such as 'being a fussy eater', 'having no interest in food', or 'lack of appetite' were elicited in every interview (*n*=4). Although the subconcept of 'selective eating' was also reported by most participants in the UK (*n*=3), in Australia it was only mentioned in four of eight interviews. With regard to emotional expression, all caregivers in the USA reported this to impact on their child negatively (*n*=4), however, it was less prevalent in the UK (*n*=3) and Australia (*n*=5). No caregiver in Italy reported this impact. Although there was no between-country difference in sleep impact generally, a larger proportion of caregivers in the UK (*n*=3) reported their child's daytime somnolence, compared to other countries. There were minimal differences between countries for other child impacts.

Caregivers described the impact caring for a child with Dravet syndrome has on their personal lives (Fig. 3). The most significant caregiver-reported impacts were on relationships with partners and other family members (*n*=18) and 'work' (*n*=18). Caregivers also reported impacts on leisure activities (*n*=16), finances (*n*=16), sleep (*n*=15), daily activities (*n*=13), and physical functioning (*n*=14). Less frequently reported impacts included 'social life' (*n*=12) and emotional well-being (*n*=10). There were between-country differences for caregiver impacts. For example, in Australia the emotional subconcept 'worry' was spontaneously mentioned by six caregivers, whereas only one caregiver in each of the three other countries spontaneously mentioned 'worry'. Interestingly, 'stress' was reported by caregivers in the USA (*n*=2) and Australia (*n*=3) but not by caregivers in the UK and Italy. A larger proportion of caregivers in Italy (*n*=3) reported the physical impact of 'feeling tired' due to caring for a child with Dravet syndrome than caregivers in other countries (Australia *n*=2, UK *n*=1, USA *n*=1). Financial impacts were elicited by most caregivers in the UK (*n*=3), Australia (*n*=7), and the USA (*n*=4); however, only half of caregivers in Italy reported this (*n*=2).

Caregivers described adopting coping strategies. Most gained help from a child minder or family member (*n*=17) to look after their child and provide respite for parents. Other approaches included avoidance strategies, such as not going outside in hot weather

(*n*=17) and making home adjustments (*n*=15), such as installing air-conditioning, having the child's bedroom on the ground floor, and seizure monitors to alert caregivers. Although caregivers reported numerous coping strategies, none described their effectiveness spontaneously.

Conceptual model

Mapping of the concepts to the French conceptual model[14] highlighted that the topline symptoms/signs, trigger, impact, and coping strategy concepts were similar. Several subconcepts were identified in our analysis that were not previously captured (Fig. S2, online supporting information). For example, focal impaired awareness seizures (previously called complex partial seizures) were reported by two caregivers in the UK and one from the USA. Two caregivers in Australia and one in the UK reported that their child (aged 8y and 9y respectively) often experienced fear of having a seizure.

Conceptual saturation

Conceptual saturation was assessed for the total sample (*n*=20). The conceptual saturation figure shows that for the whole sample, every concept was initially mentioned in the first two groups of participants, indicating that conceptual saturation had been achieved and that the overall sample size was appropriate (Fig. S3, online supporting information). Exploratory conceptual saturation was also calculated separately in the individual country samples. As the minimum sample size required for successful conceptual saturation is 12 and the country subgroups contained four to eight caregivers, conceptual saturation per country was not expected. However, of all concepts mentioned, 99% were mentioned in the first two groups in Australia, 82% in the USA, 68% in the UK, and 66% in Italy.

DISCUSSION

We aimed to assess the relevance[21] of the broader impact of Dravet syndrome on children and their caregivers of the conceptual model developed in French families[14] across multiple countries. While there is a growing body of literature on the child and caregiver experience of Dravet syndrome,[12,14,22–24] many reports relate to survey-based studies. We wished to identify subtle features that may not have been captured via that methodology. Our findings deepen understanding of this complex area and support the broader relevance of concepts previously reported in one European country to other regions of the world.[14]

Our findings show that patient and caregiver-relevant impacts contribute to poorer HRQoL and that these issues are generalizable to other developed countries. As anticipated, caregivers reported that seizures were the most important concept. However, we also identified the wider impact of Dravet syndrome. Frequencies of spontaneous reporting about the child's social functioning and seizures were similar, mirroring recent research that shows that psychological and social factors accounted for more differences in HRQoL than seizures and treatment.[25]

A key finding from the interviews was that most caregivers in the UK, USA, and Australia reported financial impacts, compared to caregivers in Italy. Although it is difficult to draw conclusions, given the relatively small per-country sample, this finding may suggest a greater perceived financial burden in these countries than in Italy, potentially due to differences in health care systems. This is consistent with previous research highlighting that cost and access barriers to health care, particularly in the USA, affect patient care and, thus, caregiver experience.[26] Perceived differences between health care systems are broadly supported by the finding that age at diagnosis varied considerably per country, with children in the UK and USA diagnosed considerably later than children in Italy and Australia. The mean age of diagnosis in France was comparable with that in Italy and Australia (e.g. 15mo).

Caregivers perceived indirect impacts (i.e. impacts not directly attributable to the condition) to be as important as the direct impact of seizures, and that Dravet syndrome affected multiple domains of their lives.[12,14] These findings emphasize that a biopsychosocial approach to treatment should be developed for Dravet syndrome, with the implementation and evaluation of combined pharmacological and psychosocial interventions. A biopsychosocial approach in epilepsy is not a new concept. More than 50 years ago it was suggested that treatment should move beyond seizure control (medical model) to incorporate the physical, mental, and social aspects of health (biopsychosocial model).[27] This approach has been reiterated recently as a need to focus on treating the whole person.[28] Therefore, this should now be extended to include the caregivers of persons with epilepsy, especially in the developmental and epileptic encephalopathies such as Dravet syndrome. A key example of a biopsychosocial model that identifies a range of aspects of health is the World Health Organization's International Classification of Functioning, Disability and Health. However, although this framework is widely used to paint a comprehensive picture of disease, when developing a disease-specific, end-point approach it may not always be preferable to adopt a generalized approach.[29] It was felt that existing, generic frameworks would not be appropriate

to assess the key Dravet syndrome concepts, as these would lack full coverage of the range of concepts identified in this research, including the impact on the caregiver.

This emphasizes the need for improved endpoint concepts, including patient-centered and caregiver-nuanced outcomes, in addition to medically relevant outcomes. A selected endpoint model must paint a comprehensive picture of the condition, incorporating aspects such as symptoms and the impact on the child and the caregiver. In the previous study by Nabbout et al.[14] several instruments were identified to assess the key patient-relevant and caregiver reported concepts relevant to Dravet syndrome. The findings reported here are consistent with the previous study and indicate that the instruments identified previously are still relevant and should be measured in future clinical trials on Dravet syndrome. These include the Pediatric Quality of Life Inventory,[30] the Behavior Rating Inventory of Executive Function,[31] the Quality of Life in Childhood Epilepsy Scale,[32] the Karolinska Sleepiness Scale,[33] the Pediatric Quality of Life Inventory-Family Impact Module,[34] and the EuroQoL Five-Dimension, Five-Level instrument.[35]

Conceptual saturation analyses confirmed that all the important concepts had been identified, with no new concepts emerging in the third group of caregiver interviews, indicating that the sample size was sufficient to address the research question. The findings can be considered broadly representative of the Dravet syndrome population. Despite achieving group-level saturation, not all concepts were fully saturated at the individual country level as expected, given the small size of each country's sample (n=4–8).

Patient and caregiver-relevant concepts identified were broadly generalizable across the countries included in this study and highlight the wider impacts of Dravet syndrome. These concepts could be incorporated into a more meaningful composite endpoint for use in clinical trials. Measuring change in these concepts in a clinical trial of a new treatment would help to evaluate its efficacy. Future research would be required to fully develop a composite endpoint. Using the conceptual framework developed in this research alongside additional rounds of testing, an endpoint strategy and scoring method can be generated that combine relevant clinical measures of interest to create an overall endpoint. Future research is also recommended that would use larger sample sizes of caregivers in each country, to substantiate the findings reported here. Additional research could also involve a greater range of countries in the sample, including non-Western societies, to further evaluate the generalizability of findings. The countries included in this study were comparatively similar culturally, meaning that cross-cultural comparisons could not be drawn from this research.

Finally, future work could explore the caregiver and patient experience of other developmental and epileptic encephalopathies using a qualitative methodology. This research highlights the importance of disease-specific endpoint models.

Limitations

A key limitation of this study is the sample size of caregivers recruited per country, limiting the generalizability of the findings at the country-level, particularly in the USA, UK, and Italy. Although in qualitative research, a small sample size is not always a limitation, in this instance it is considered a limitation as not every concept was saturated at the country-level. The sample was homogenous in their reporting, but the results reflect a purely Western societal perspective on the impact of Dravet syndrome. Therefore, the experience of caregivers of children with Dravet syndrome in countries where health care systems may be less developed or different cultural attitudes affect impact (e.g. Africa, Asia or Eastern Europe), is unknown. Additionally, it must be noted that differences identified between countries may reflect fundamental differences regarding patient (e.g. Dravet syndrome severity, treatment type) and caregiver demographic characteristics (e.g. sex, age) given the smaller sample size.

Conclusion

It is generally accepted that the impact of epilepsies, and mainly developmental and epileptic encephalopathies, reaches far beyond seizures and clinical features.[36] This study evidences the significance of these far-reaching concepts to both patients and caregivers in a Dravet syndrome-specific population. The concepts identified in the French study regarding patient and caregiver impact of Dravet syndrome are broadly relevant across countries and have identified key concepts that could be important to incorporate into a future composite endpoint. Future research is required to develop a composite endpoint, with validated scoring and acceptable psychometric properties, before use in a Dravet syndrome clinical trial.

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UK). The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

SUPPORTING INFORMATION

The following additional material may be found online:

Table SI: Demographic characteristics

Figure S1: Example of a coding tree.

Figure S2: Revised conceptual model.

Figure S3: Conceptual saturation analysis results.

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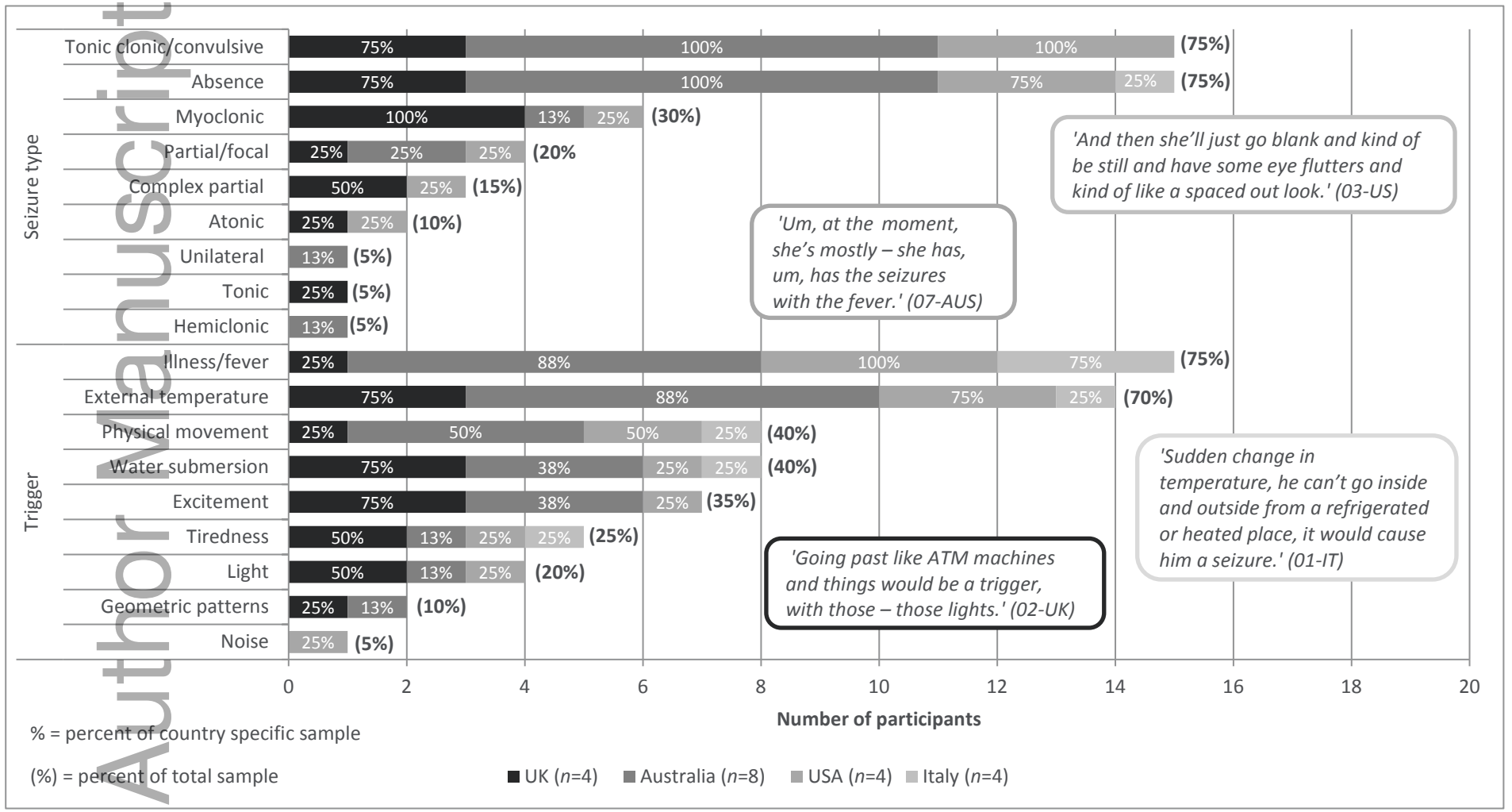
[Figure Legends]

Figure 1: Seizure and trigger concepts reported by caregivers in the UK, Australia, USA, and Italy.

Figure 2: Patient-relevant impacts reported by caregivers in the UK, Australia, USA, and Italy.

Figure 3: Caregiver reported impacts by caregivers in the UK, Australia, USA, and Italy.



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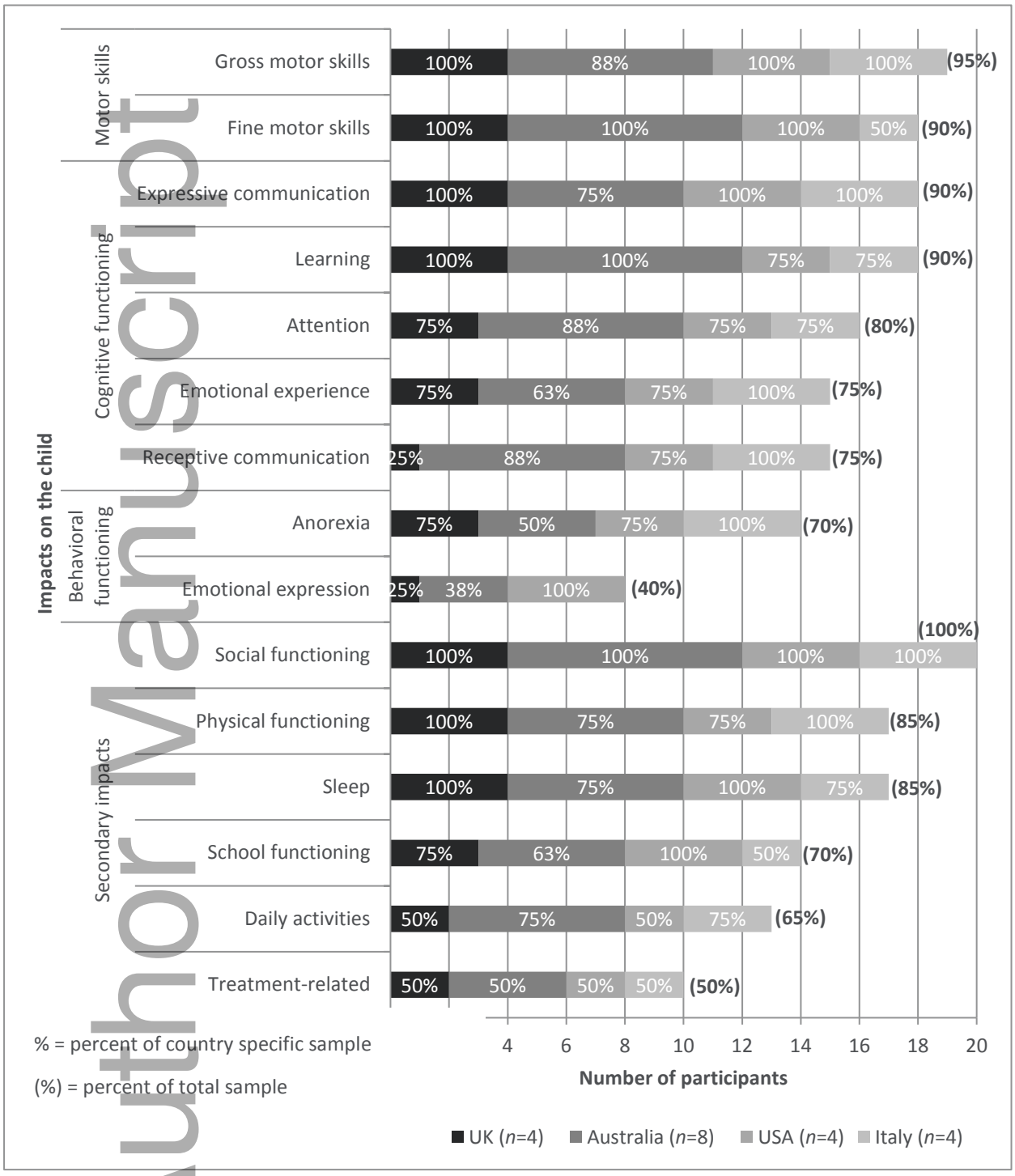

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