

# Families driven drug development and clinical trials: a pilot study in Dravet Syndrome to delineate what really matters

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## Research

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# Abstract

## Background

Dravet syndrome (DS) is a developmental and epileptic encephalopathy. Patients rapidly develop drug resistant seizures but patients with DS develop non-seizures disorders that are often age related. We aimed to identify the caregivers' opinion on the outcome measures that matters in clinical trials in individuals with DS and their correlation with the age of the individual with DS.

## Methods

We conducted a prospective international study with convenience sample based on a 11-closed questions survey developed with three European patients' advocacy groups (PAG) for DS (France, Italy and Germany). The items were about seizures and daily life outcomes that a clinical trial should target according to family opinion. Items were scored from 1 (not important at all) to 5 (highly important). Statistical analyses were performed to evaluate country (ANOVA and  $\chi^2$  tests) and age effect (Spearman's  $\rho$ ).

## Results

Hundred and fifty-three caregivers answered the survey (68%: France, 28%: Germany and 4%: Italy; affected individuals' characteristics: 86 males, age: 11.4 [25th -75th percentile:7-20.4] years). Demographic characteristics were not significantly different between countries. Families ranked as important almost all the items proposed. However, most of the items related to daily life had the highest rank in all 3 countries compared to items about seizures ( $p = 0.02$ ). Positive correlation between age and age at diagnosis ( $\rho = 0.26$ ,  $p = 0.02$ ) and negative correlations between age and targeting seizure duration and between age ( $\rho = -0.25$ ,  $p = 0.005$ ) and targeting the need of referral to hospital ( $\rho = -0.26$ ,  $p = 0.005$ ) were identified.

## Conclusions

This study emphasized the DS families' expectations from therapies beyond seizure efficacy. These data can help to adapt patients-centered outcome measures in future clinical and real-life trials in DS.

## 1. Background

Determining what really matters, i.e., the meaningful outcomes for the health of individuals, is a key point in clinical trials, especially for rare diseases. Indeed, rare diseases generally involve several organs with a high inter-individual variability leading to a great disparity in terms of clinical presentation and consequences in the daily life. The use of primary outcome measures (POMs) elaborated by practitioners might be simplistic and misrepresents the multiple facets of the impact of a disease [1].

Dravet Syndrome is a rare genetic epileptic syndrome with onset in first 15 months of life in normally developing infants, associated in > 85% of cases with a pathological variant of *SCN1A* leading to a loss-of-

function of voltage dependent sodium channel [2–6]. Convulsive febrile and afebrile seizures appear with recurrent status epilepticus. A second stage with drug resistant epilepsy with polymorphic seizure types, including myoclonic, focal and atypical absence follows after few months [7]. Psychomotor delay becomes evident from the second year of life together with motor and language disorders. Autism spectrum disorder is present in almost one third and behavioral disorders incidence increases with age [2, 3, 8]. Several additional features are frequently reported: eating and sleep disorders, gait deterioration, dysautonomia, and a higher predisposition to infections [9–11]. The long-term outcome of individuals with Dravet syndrome remains poor [12–15]. This syndrome is considered as the archetype of developmental and epileptic encephalopathy (DEE) [16]. This concept underline that the cognitive outcome might not be exclusively determined by seizures [17] but is also due to SCN1A dysfunction. Research into the impact of Dravet syndrome beyond seizures increased in the last years and allowed to describe the whole phenotype of this DEE based on families and practitioners reports [9, 10, 14, 15, 18, 19].

Evaluation of clinical trials in epilepsy is mainly based on primary outcome measures (POM) targeting efficacy to reduce seizure and safety, using incidence of adverse events (AEs) and withdrawals rate due to AEs [20, 21]. For example, POM on efficacy, at a given time, are quantified through the duration of seizures, the percentage of seizure frequency compared to the baseline, the responder rate (defined as the number of affected individuals with at least 50% reduction in total seizure frequency) and the proportion of subjects who achieved seizure-free status [22–25]. However, it is important to question the meaning of these endpoints, particularly in the context of developmental and epileptic encephalopathy (DEE) characterized by major drug resistance and associated comorbidities beyond seizures.

The aim of this study is to explore the domains that really matters for individuals with DS emphasizing that a therapy targeting these domains would have a positive meaningful impact on the outcome.

## **2. Methods**

### **1.1. Survey development**

The 11-closed questions survey analyzed in this report were developed with three national associations of Dravet syndrome families, namely “Alliance Syndrome Dravet” in France, “Dravet-Syndrom e.V.” in Germany and “Dravet Italia Onlus”. The choice of these domains were guided by our preliminary surveys [18, 26] and other literature reports [9, 10, 14]. This survey explored different items related to current seizures (frequency, duration, seizures requiring rescue therapy, seizures needing of referral to emergency room (ER) or intensive care unit (ICU)) and daily life (sleep, eating disorders, language, motor skills, daily activity, behavior, communication, and interaction). Each item was evaluated using a Likert’s scale from 1 to 5 (not important at all = 1, not important = 2, neutral = 3, important = 4 and highly important = 5).

### **1.2. Participants**

This study was a prospective cohort study with convenience sampling. Indeed, the survey was fill by caregivers during annual associations meeting in France and Germany. In Italy, the questionnaire was shared online with families for a period of 6 weeks (may to June 2019) with a reminder sent at week 4. For each individual with Dravet syndrome, a unique caregiver completed the survey.

## 1.3. Statistics

Results are expressed as the average  $\pm$  standard deviation in case of Likert's scale data and as median [25th -75th percentile] otherwise using descriptive statistics. We performed Levene's tests to evaluate homogeneity of the variance of the different quantitative responses between the different countries (France, Italy and Germany). When Levene's test met the assumption of homogeneity of variance, we used one-way analyses of variances (ANOVA) with following factor: France, Italy, and Germany. Significant ANOVAs were completed by Bonferroni post-hoc tests. In case of violation of homogeneity of the variance, we used a more robust test called Brown Forsythe test with the same factors [27]. A Tamhane's post-hoc tests were then applied in case of significance. For qualitative data,  $\chi^2$  tests were used to study the presence or the absence of significant difference between the different countries. We correlated different quantitative answers to affected individuals' age using Spearman's rank correlation coefficient (Rho) coefficients. To illustrate the possible correlation with age, we presented the data in relation to three age groups: <6 years, 6–12 years and > 12 years. In the event of missing data, percentages were calculated per number of responses obtained, item by item.

## 3. Results

A total of 153 surveys were filled by parents with 96.5% of response rate (missing data: 81/2295). Age of individuals with DS participating at the time of this survey ranged from 1.2 to 40 years (median: 11.4 [7–20.4] years, Table 1). The age at seizure onset was 5 [3.5–6.5] months and age at which their child was identified as having Dravet syndrome (DS diagnosis) was 18 [12–33.6] months. Fifty-six percent were male (86/153). Seventy-three were followed in France (47.7%), 43 in Germany (28.1%) and 37 in Italy (24.2%). There was no significant difference between the three countries regarding demographic characteristics (Table 1). However, concerning the age at diagnosis, a significant correlation with patients' age was identified (Table 2,  $\rho = 0.26$ ,  $p = 0.002$ ). A lower age of diagnosis was associated with younger age (13.2 [9.6–21.6] months for < 6 years, 18 [12-27.6] months for 6–12 years and 20.4 [12-60.5] months for > 12 years).

Table 1  
Demographic characteristics

	Total	France	Italy	Germany	<i>p</i>
n (%)	153	73 (47.7%)	37 (24.2%)	43 (28.1%)	
Sex (m/f)	86/67	41/32	19/18	26/17	<i>ns</i>
Current age (y)	11.4 [7–20.4]	11 [5-20.5]	10.8 [6.6–17.7]	12,8 [9-23.8]	<i>ns</i>
Age at seizure onset (m)	5 [3.5–6.5]	5 [3.5-7]	5 [3.5-6]	5 [3–6]	<i>ns</i>
Age at diagnosis (y)	18 [12–33.6]	13.2 [9.6–27.6]	18 [12–72]	21.6 [13.2–33.6]	<i>ns</i>

Table 2  
Impact of age on the different items of this study.

	Tot	< 6 years	From 6 to 12 years	> 12 years	Spearman's $\rho$	$p$
Countries (France/Italy/Germany)	73 / 37 / 43	22 / 3 / 9	19 / 14 / 14	32 / 20 / 20	-	-
Current age (year)	11.4 [7–20.4]	4 [3.3–4.5]	8.8 [8–10.7]	21 [16.3–26.5]	-	-
Age at seizure onset (month)	5 [3.5–6]	5.5 [4–6.8]	5 [3–6.7]	4 [3.5–6]	<i>ns</i>	<i>ns</i>
Age at diagnosis (month)	18 [12–33.6]	13.2 [9.6–21.6]	18 [12–27.6]	20.4 [12–60.5]	0.26	0.002
Behavior	4.52 +/- 0.7	4.55 +/- 0.64	4.43 +/- 0.85	4.58 +/- 0.56	<i>ns</i>	<i>ns</i>
Communication and interaction	4.54 +/- 0.67	4.55 +/- 0.71	4.47 +/- 0.72	4.59 +/- 0.51	<i>ns</i>	<i>ns</i>
Daily activity	4.31 +/- 0.7	4.24 +/- 0.75	4.39 +/- 0.61	4.28 +/- 0.71	<i>ns</i>	<i>ns</i>
Motor skills	4.29 +/- 0.65	4.24 +/- 0.7	4.36 +/- 0.64	4.26 +/- 0.57	<i>ns</i>	<i>ns</i>
Language	4.29 +/- 0.75	4.39 +/- 0.81	4.32 +/- 0.75	4.21 +/- 0.61	<i>ns</i>	<i>ns</i>
Sleep	4.27 +/- 0.83	4.52 +/- 0.85	4.2 +/- 0.96	4.21 +/- 0.51	<i>ns</i>	<i>ns</i>
Sz frequency	4.25 +/- 0.78	4.12 +/- 0.87	4.36 +/- 0.74	4.24 +/- 0.6	<i>ns</i>	<i>ns</i>
Sz duration	4.15 +/- 1.11	4.38 +/- 1.16	4.22 +/- 1.09	4 +/- 0.99	-0.25	0.005
Sz (Rescue therapy)	3.88 +/- 1.21	4.25 +/- 1.31	3.96 +/- 1.23	3.67 +/- 0.79	<i>ns</i>	<i>ns</i>
Eating disorders	3.7 +/- 1	3.65 +/- 1.17	3.68 +/- 0.88	3.72 +/- 0.73	<i>ns</i>	<i>ns</i>
Sz (referral to ER or ICU)	3.55 +/- 1.55	4.09 +/- 1.65	3.68 +/- 1.49	3.22 +/- 1.26	-0.26	0.005
The statistical impact of age was identified using Spearman's rank test and illustrated using three groups of affected individuals, namely < 6 years, between 6 and 12 years and > 12 years.						

Families ranked as important almost all the items proposed (Table 1). They rated similarly communication, sleep, behavior, daily activity, and motor skills (4.05 +/- 1.34) compared to lower scores for items related to seizures (3.96 +/- 1.22,  $p = 0.02$ ) (Fig. 1A, Table 2). For items regarding seizures, the highest score was achieved for seizure frequency (4.25 +/- 0.78) followed by seizure duration (4.15 +/- 1.11).

Caregivers in the three countries agreed on the importance with a descending order for sleep, communication, behavior, daily activities, motor skills, language, seizure duration, seizures requiring rescue therapy, and seizures needing of referral to ER or ICU. In relation to age, only seizure duration and the need of referral to ER or ICU were negatively correlated with affected individuals' age, i.e., the highest scores were reported in the youngest individuals ( $\rho = -0.25$ ,  $p = 0.005$  for seizure duration and  $\rho = -0.26$ ,  $p = 0.005$  for seizure with referral to ER or ICU) (Table 2 and Fig. 1C). There were few significant differences in the evaluation of the different items according to countries (Fig. 1B). These differences were mainly about seizure frequency, which had higher score in Italy compared to France (4.57 $\pm$ 0.55 in Italy and 4.03 $\pm$ 0.77 in France,  $p = 0.0005$ , Germany: 4.36 $\pm$ 0.72,  $p = \text{ns}$ ) and those of eating disorders, which was higher in France compared to Germany (3.89 $\pm$ 0.8 in France and 2.88 $\pm$ 1.45 in Germany,  $p = 0.004$ , Italy: 3.68 $\pm$ 0.95,  $p = \text{ns}$ ).

## 4. Discussion

This study shows the expectations of families of individuals with DS regarding the needs and expectations from therapy in a large transborder European cohort. The caregivers' expressed their major needs in improving behavior, communication, sleep, daily activity, motor skills and language. They rated the need to treat these impacts previously reported as major burden in previous studies [10, 15, 18, 26] higher than seizures. More importantly, seizures and seizures related issues were far from being the sole the effectiveness of medication. Although not surprising to date with the different reports on the impact of DS beyond seizures, this is the first direct results from families across 3 countries in Europe confirming smaller studies and hypothesis [18, 26]. These data should question the future designs of trials in DS and the use of primary endpoints based on POM including not solely seizures [22, 24, 25, 28, 29]. In addition, RCTs in DS have an age median or mean range between 7.6 and 9.3 years, an age range where seizures' related issues tend to be less scored than in earlier years. The difference between France and Germany (Italy) on the eating behavior can be anecdotal and related to the cultural place of the food and the "cuisine" in France and Italy.

In order to improve the evidence of efficacy in clinical trials, Food and Drug Agency in 2009 and the European Medicines Agency in 2010 [20, 30], have encouraged the Patient Reported Outcomes (PROs) as self-assessment of affected individuals' health status, and validated it as a possible secondary endpoint to complement the evaluation of clinical trials. Patients reported outcomes (PRO) are defined as "any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy" [31]. Gradually, the use of PROs in clinical trials has increased significantly since 2005 [32–34]. PROs can be used to determine affected individual's experience particularly concerning improvement or aggravation of subjective symptoms, to stratify participants, to refine clinical trial design and to illustrate the risk-benefit balance allowing to choose the personalized better treatment [34]. The development of specific PROs for Dravet syndrome may seem anecdotal because there are generic PROs that make it possible to evaluate the quality of life of patients, such as the Health-related quality of life. However, these questionnaires are not accurate enough to assess the quality of life of individuals with rare diseases and intellectual disability [35]. This is why, given the lack of standardized PROs dedicated to individuals with rare diseases, the International Rare Diseases Consortium (IRDiRC) has decided to set up the Patient-centered outcome measures (PCOMs) initiatives to develop [36]. Determining the domains that are important to individuals with Dravet syndrome and their families is the first step of PRO development [37, 38]. Indeed, this

study explored the direct health domains affected in individuals with DS and the expression of the families' need to target and improve these different domains by new therapies. We did not however tackle the impact on the caregivers that was already detailed in different studies at national [18], European [14] and international levels US foundation [10]. The PCOMs would be a combination of the items related directly to the patient health and to the burden on the families as proposed in the PCOMs development [39].

Our study showed that different preoccupation can emerge in individuals with Dravet syndrome and that the predominant problems can vary with age [6]. Reading these results is correlated to the 3-phases of natural history of individuals with DS [3]. In the first phase, during the first 15 to 18 months, seizures are mainly triggered by fever, are often prolonged evolving to status epilepticus, generalized or unilateral. In the second phase, till around 5–6 years, known as the “worsening phase”, individuals show different types of seizures as atypical absences, focal and tonic seizures with frequency drug resistant epilepsy in addition to, the emergence of developmental slowing and behavioral disorders. Finally, in the third phase, also called the “stabilization phase”, the frequency of seizures might decrease with sometimes the cessation of some types of seizures without seizure freedom in almost all [3, 14]. However, with age, most affected individuals remain with active epilepsy and major co-morbidities. But during this last phase, seizures often become nocturnal, tonic and brief [40]. Intellectual disability and behavior problems move to the front scene with the families struggling for the education and rehabilitation special needs [15]. In this survey, families rated a decreasing need with age for a therapy targeting seizures' reduction and referral to ER or ICU. This data was also in line with the natural history of this syndrome for which ER and ICU needs are reported to be significantly more frequent in infant and pre-school children compared to adolescents and adults [14]. However, the need of treatment to reduce seizure frequency and of the need to rescue treatment remains stable with age. These data highlighted the persistence of high drug resistance in this syndrome throughout life [41]. We report similar needs of treatment aiming to improve behavioral, sleep, communication and interaction disorders, daily activity, motor skills and language difficulties might emphasize the importance of these issues regardless of age. Indeed, communication problems, behavioral and motor impairments are present in affected individuals with Dravet syndrome since pre-school age and the proportion of affected individuals with these comorbidities remain relatively stable across the different age group [14, 15, 42].

Another key finding of this study is the age at diagnosis of affected individuals (18 [12-33.6] months), showing a significant decrease in the age of diagnosis in the youngest individuals compared to the oldest. These data confirm the improvement in age of diagnosis of Dravet syndrome over the last years [14, 43, 44]. This can be due to different factors, related to the monogenic character of this epilepsy due to *SCN1A* pathogenic mutation, to a large effort of dissemination due to development of specific orphan drug and a large empowerment of the PAGS. Importantly, this earlier diagnosis age might question a younger age of inclusion in RCTs where the median age of inclusion in recent trials was between 7.6 and 9.3 years [22, 24, 25, 28, 29]. An earlier efficient therapy can be a clue for a better neurodevelopment provided its use in the sensitive time window [45].

Some limits must be highlighted. This is a cross-sectional study to assess the impact of age on caregivers' expectations regarding what should treatment target. A longitudinal study will be probably more efficient to identify the evolution of caregivers' perspectives. However, to date, there is no study with this design probably due to its complexity and the rarity of this pathology. The convenient sample of this study might have led to a

selection bias. Indeed, the identification of affected individuals through national families' associations might encourage the recruitment of families with specific profile and individuals with possibly more severe phenotypes. This survey is not accompanied by a qualitative study of the patients' opinions using for example Delphi methodology [46], as we previously reported in Dravet syndrome [18, 26]. However, the design of this study is complex, time consuming, requires the definition of experts and does not allow us to have as large a population as in this study [47].

## **5. Conclusions**

The importance of the non-seizure issues in affected individuals with Dravet syndrome urges us to identify what matters most for the affected individuals and what impact most their everyday life. The next step would be to develop measurable and reproducible scales adding these items to seizures frequency, to constitute more direct evidence of drug benefit and can be used as an outcome measure for coming trials. This pilot study on DS can be translated to other DEEs as they share drug resistance seizures and development and motor problems beyond seizures. This shift in our thinking in developing outcomes measures and developing more participatory approaches in medicines is urgent to establish in the era of gene therapy. Indeed, these therapies based on possible or partial correction of the underlying genetic defect aim to change the present path of affected individuals achieving disease modifying therapies beyond seizures decrease [45].

## **Abbreviations**

AE: Adverse Event, ASM: AntiSeizure Medication, DEE: Developmental and Epileptic Encephalopathy, DS: Dravet Syndrome, ER: Emergency Room, ICU: Intensive Care Unit, PCOM: Patients-Centered Outcome Measure, PRO: Patients Reported Outcome, POM: Primary Outcome Measure, PR: PharmacoResistant, RCTs: Randomized Controlled Trials.

## **Declarations**

### **1 Ethics approval and consent to participate**

The studies involving human participants were reviewed and approved by Necker-enfants malades ethical committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

### **2 Consent for publication**

Not applicable

### **3 Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## 4 Competing interests

The authors declare that they have no competing interests.

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## 6 Authors' contributions

Study concept and design: TT, TLB, MK, RN. Data acquisition: TT, EM, ASH, IB, SF, NC. Data analysis and interpretation: TT, TLB, GdO, NC, MK, RN. Drafting manuscript: TT, MK, RN. Revising manuscript content: All. Approving final version of manuscript: All. All authors read and approved the final manuscript.

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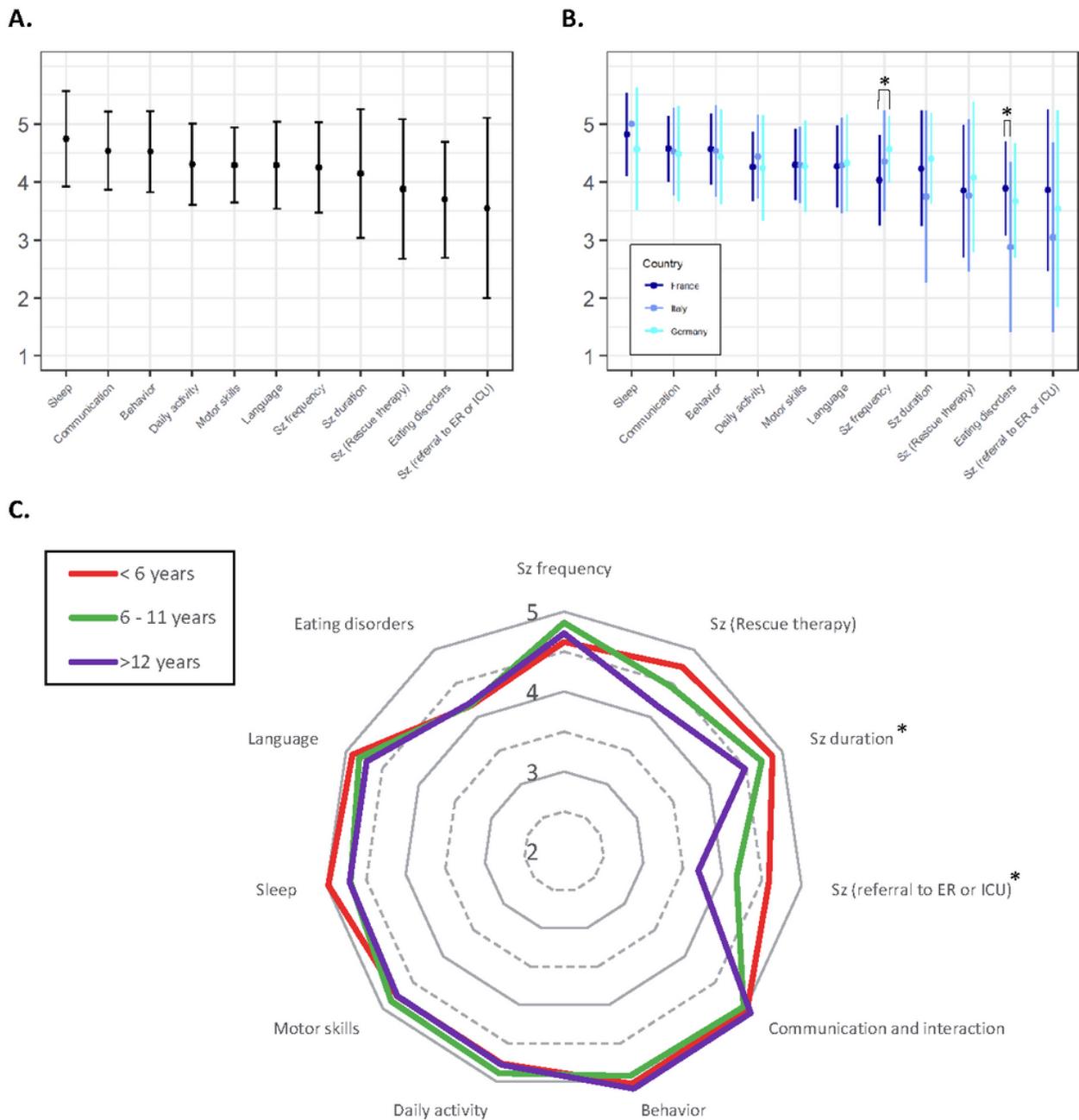
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## Figures



**Figure 1**

Caregivers' impressions (Likert's scales from 1: not at all to 5: very important) about the aspects that a tested antiseizure medicine drug has to ameliorate for their Children with Dravet syndrome (A), same results according to the different countries (B) and the different class of age of the affected individuals (C).

## Supplementary Files

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