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The European patient with Dravet syndrome: Results from a parent-reported survey on antiepileptic drug use in the European population with Dravet syndrome

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ABSTRACT

Dravet syndrome is a rare form of epilepsy largely refractory to current antiepileptic medications. The only precedents of randomized placebo-controlled trials in Dravet syndrome are the two small trials that led to the approval of stiripentol. With the arrival of new clinical trials for Dravet syndrome, we sought to determine the characteristics of the patient population with Dravet syndrome in Europe today, which has possibly evolved subsequent to the approval of stiripentol and the ability to diagnose milder clinical cases via genetic testing. From May to June 2014, we conducted an online parent-reported survey to collect information about the demographics, disease-specific clinical characteristics, as well as current and past use of antiepileptic medications by European patients with Dravet syndrome. We present data from 274 patients with Dravet syndrome from 15 European countries. Most patients were between 4 and 8 years of age, and 90% had known mutations in *SCN1A*. Their epilepsy was characterized by multiple seizure types, although only 45% had more than 4 tonic–clonic seizures per month on average. The most common drug combination was valproate, clobazam, and stiripentol, with 42% of the total population currently taking stiripentol. Over a third of patients with Dravet syndrome had taken sodium channel blockers in the past, and most had motor and behavioral comorbidities. Our study helps define the current typical European patient with Dravet syndrome. The results from this survey may have important implications for the design of future clinical trials that investigate new treatments for Dravet syndrome.

1. Introduction

Severe myoclonic epilepsy of infancy, also known as Dravet syndrome, is an epileptic encephalopathy that presents during the first year of life and affects 1 in 20,000 to 40,000 people [1–3]. Patients who have Dravet syndrome display multiple seizure types including tonic–clonic, myoclonic, absence, and focal seizures. A characteristic of this syndrome is that seizures can be provoked by fever and visual stimuli and can also lead to status epilepticus [1–3]. In addition to epilepsy, Dravet syndrome is associated with cognitive delays, behavioral disorders, and an elevated risk of sudden death [1–3].

Although traditionally diagnosed according to clinical criteria, genetic mutations are known to be a major cause of Dravet syndrome [4,5]. Mutations in the sodium channel-encoding gene *SCN1A* account for the majority of Dravet syndrome cases [6,7] and have also been found to cause milder forms of epilepsy, migraine, and autism without epilepsy [8–10]. Mutations in *SCN1B* [11], *SCN2A* [12], and *GABRG2* [13] are also known causes of Dravet syndrome, with additional genes such as *PCDH19* and *CHD2* found to cause Dravet-like phenotypes when mutated [14,15]. The discovery of these genes represents a major scientific advance, making it possible to perform genetic testing of patients with suspected Dravet syndrome that leads to the identification and diagnosis of milder or clinically "atypical" Dravet syndrome cases [5,16].

Despite these major advances with regard to the genetic causes of this rare disease, Dravet syndrome remains largely pharmacoresistant to antiepileptic drugs [17]. After more than 30 years since its initial description, only one drug has been approved for the treatment of Dravet syndrome (stiripentol, marketed by Biocodex as Diacomit® [18,19]). There remains, therefore, a high need for new therapeutics able to better control seizures as well as to preserve or improve cognition and behavior in Dravet syndrome.

Unprecedentedly, two new experimental drugs are expected to start clinical trials for Dravet syndrome in Europe between 2014 and 2015: cannabidiol, developed by GW Pharmaceuticals and INSYS Therapeutics, and fenfluramine, developed by Brabant Pharma. To date, all three have obtained orphan drug designation for Dravet

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syndrome by the US Food and Drug Administration while fenfluramine and cannabidiol developed by GW Pharmaceuticals have also obtained the designation as an orphan drug by the European Medicines Agency.

The only precedents of randomized placebo-controlled trials in Dravet syndrome are the two trials in France and Italy that led to the approval of stiripentol as an adjunctive treatment in Europe (2007), Canada (2012), and Japan (2012). The two studies combined involved 65 children between 3 and 18 years of age with Dravet syndrome and compared the efficacy of stiripentol with placebo when added to the children's existing treatment with valproate and clobazam. The use of a very homogeneous patient population made it possible for both trials to be strongly positive despite the small number of patients.

With the arrival of new clinical trials for Dravet syndrome, we sought to determine the characteristics of the patient population with Dravet syndrome in Europe today, which has possibly evolved subsequent to the approval of stiripentol and the ability to diagnose milder clinical cases through genetic testing. This parent-reported survey was set up to assess the most relevant demographic and disease-specific clinical characteristics, to collect information on the current and past use of antiepileptic medications by this population, and to try to define the current "typical European patient with Dravet syndrome".

2. Methods

2.1. Study design, assessment, and patient selection

The study was an international, voluntary, anonymous, single-assessment, web-based survey administered by the Dravet Syndrome Foundation Spain (http://www.dravetfoundation.eu/drugs-survey/, see Supplemental materials). It was distributed by European organizations for patients with Dravet syndrome through the Dravet Syndrome European Federation. The study took place from May to June 2014.

The study population consisted of patients with Dravet syndrome identified by patient organizations through their affiliated distribution lists. The questionnaire was developed in Spanish and English. Because of the cognitive state and generally low age of the identified patients with Dravet syndrome, the survey was completed by parents or caregivers. No ethics approval was required because of the anonymous nature of the study.

2.2. Data analysis

The data entered by responders though the webform were automatically collected in an Excel sheet. Both the Spanish and English versions of the survey were collected in a single file. A total of 278 entries from 15 countries were registered during the study period. After eliminating 4 duplicates, a total of 274 entries were used for the study. Data were numerical (e.g., age and number of seizures) or binary (e.g., having taken or not a specific drug) with the exception of two textboxes habilitated for responders to input additional medications not prespecified in the survey. The content of these boxes often corresponded to actual antiepileptic drugs that the responders failed to recognize in the prespecified list because of brand name variations between countries. These were manually curated to populate the appropriate cells in the file. Data are reported as total count or percentage for the different categories without performing any statistical analysis. Because clinical trials often have an inclusion criterion of minimum 4 tonic–clonic seizures per month on average, we analyzed antiepileptic drug use both for the total population and for this trial subpopulation.

3. Results

3.1. Demographics and clinical characteristics

Two hundred seventy-four patients from 15 European countries were included in our study (Table 1). One hundred fifty-seven patients were male and 117 female. The highest numbers of responses were from Spain, Netherlands, Italy, Germany, and France (Table 1). These countries have strong patient groups and/or physicians and a relatively high number of identified patients. The low number of UK patients in this cohort is due to the UK patient organizations not being yet affiliated with the Dravet Syndrome European Federation, which was used as the distribution channel for the survey, and has been described by Brunklaus et al. [20]. Genetic analysis was reported for 262/274 patients (Table 1). Of these, the large majority (246/262) had a confirmed mutation in *SCN1A*, accounting for 90% of the total population. Although the survey did not ask for mutations in other genes (see survey questions in Supplemental materials), data from the Spanish registry of patients with Dravet syndrome indicate that the 10% *SCN1A* negative population includes patients with mutations in *PCDH19*, *SCN1B*, and *SCN1B*, as well as patients with unknown genetic causes (unpublished data), with many of the patients carrying mutations in *PCDH19* choosing to become affiliated with specific patient organizations. Patients were aged between 1 and 47 years, with the largest group aged 4 to 8 years (Table 2). The adult subpopulation accounted for 15% of the responders (42/274).

Dravet syndrome is characterized by multiple seizure types, and a minimum of convulsive seizures per month is usually an eligibility criterion for participation in clinical trials. We, therefore, asked responders to list the average number of seizures per month that patients had, taking as a reference the last 6 months (Table 3). The most frequent seizure type was tonic–clonic, with 45% of the population reporting more than 4 seizures per month, followed by myoclonic, absence, partial, and atonic seizures (Table 3). By countries, the percentage of patients with Dravet syndrome with more than 4 tonic–clonic seizures per month was 26% for France, 67% for Germany, 56% for Italy, 54% for Netherlands, and 36% for Spain. A particularly dangerous type of seizures in patients with Dravet syndrome is status epilepticus, which can lead to mortality. We, therefore, asked responders about the number of times that the patients had been admitted to the emergency room as a result of status epilepticus during the previous 12 months (Table 4). In both the total population and the subpopulation with more than 4 tonic–clonic seizures per month, one-third of the patients had one or more status

Table 1
Country and genetic type of the survey population.

Country	Patients	*SCN1A* mutation		
		Yes	No	Not determined
Austria	3	2	1	0
Azerbaijan	1	1	0	0
Belgium	7	7	0	0
Czech Republic	1	1	0	0
France	22	15	3	4
Germany	30	27	0	3
Italy	50	44	5	1
Moldova	1	1	0	0
Netherlands	54	49	4	1
Poland	13	13	0	0
Portugal	10	10	0	0
Romania	10	9	0	1
Spain	59	54	3	2
Switzerland	11	11	0	0
United Kingdom	2	2	0	0
Total	274	246	16	12

Table 2
Age distribution of the survey population.

Age bands	Patients	%
>4	39	14
4–8	104	38
9–13	52	19
14–17	37	14
≤18	42	15
Total	274	100

Table 3
Frequency (average per month) of different seizure types by number and percentage of patients.

Seizure type	Patients (n)	%
Tonic–clonic		
0	62	23
1–3	88	32
≤4	124	45
Myoclonic		
0	159	58
1–3	27	10
≤4	88	32
Absence		
0	173	63
1–3	38	14
≤4	66	24
Partial		
0	185	68
1–3	41	15
≤4	48	18
Atonic		
0	237	86
1–3	23	8
≤4	14	5

epilepticus requiring admission to the emergency room during the last year. Ten percent of the population (28/274) reported 4 or more emergency room admissions, with numbers going up to 30 admissions per year as a result of status epilepticus.

In addition to epilepsy, Dravet syndrome is characterized by cognitive delays. The degree of cognitive delays varies from patient to patient, although it is reported to affect the majority of patients and to not correlate with the severity of the epilepsy [21,22]. In order to get a better picture of the nonseizure comorbidities of Dravet syndrome, we asked responders to report on the presence or absence of sleep disturbances, motor problems, and abnormal socialization in the patients (Table 5). Because the study measured parent-reported outcomes, the answers were subjective and percentages might vary from those reported by clinicians. Responders reported an incidence of sleep problems in nearly half of the patient population and motor impairment in up to 76% of the total population and 81% of the trial subpopulation (Table 5). Two-thirds of the patients were also reported to have abnormal socialization (Table 5).

3.2. Current and past use of antiepileptic medications

Responders were asked to select all of the current antiepileptic medications that the patients are taking from a list that included generic names as well as some of the most common brand names. In total, responses included 26 different approved medications as well as two experimental ones (CBD or cannabis oil, n = 3, and fenfluramine, n = 1). Each individual patient takes 0 to 6 concomitant antiepileptic medications. Only one patient was drug-free, and 14 (5%) were in monotherapy. On average, patients with Dravet syndrome take three antiepileptic drugs (40 and 41% in the total and trial populations, respectively), with a large percentage taking four drugs (25 and 31%, respectively). The most common antiepileptic drug currently used by patients with Dravet syndrome in Europe was valproate (85%), followed by clobazam (55%), topiramate (44%), and stiripentol (42%) (Table 6). In the subpopulation with four or more tonic–clonic seizures per month, stiripentol was the third most used drug, with 51% of the population currently taking this compound (Table 6). By countries, stiripentol use in the total population ranged from 55% in France to 31% in Netherlands, with consistently higher percentages in each country when the population was limited to those patients with four or more tonic–clonic seizures per month (Table 7). The most common drug combination was valproate, clobazam, and stiripentol, with or without additional antiepileptic drugs, taken by 29% of the total population (79/274) and 35% of the trial population (44/124).

To conclude our study, we asked responders to list all of the antiepileptic medications that the patients have ever tried from the same list used to determine their current medications (Table 8). A total of 16 antiepileptic drugs had been tried by more than 5% of the patients in addition to the ketogenic diet. The most commonly listed drug was levetiracetam, with more than half of the patients having tried it at some point in their treatment, and over a third of the European patients with Dravet syndrome had at some point taken the sodium channel blockers lamotrigine and carbamazepine.

Table 4
Admissions to the emergency room in the last year as a result of status epilepticus.

	Total population (n = 274)		Population > 4 TC (n = 124)	
	Patients (n)	%	Patients (n)	%
0	183	67	83	67
1	42	15	20	16
≤2	49	18	21	17

Table 5
Frequency of some nonseizure comorbidities by number and percentage of patients.

	Total population (n = 274)		Population > 4 TC (n = 124)	
	Patients (n)	%	Patients (n)	%
Disturbed sleep	128	47	67	54
Motor impairment	208	76	101	81
Abnormal socialization	179	65	83	67

4. Discussion

4.1. The most common characteristics of the population with Dravet syndrome

The results from our survey support that the typical European patient with Dravet syndrome is a young child with a confirmed mutation in *SCN1A*. Notably, only 15% of the responders included adult patients. This is consistent with our own observations from the Spanish registry of patients with Dravet syndrome where 16.5% of the patient population is over 18 years old (n = 127 patients, unpublished data). Because the Spanish registry has been running for 5 years, this suggests that the prevalence for the young population observed in the European survey is not biased by the 1-month survey response period. Instead, it is likely to accurately reflect the patient population affiliated with patient organizations, which served as our distribution channel. One potential reason is that parents and caregivers are more likely to become actively engaged with patient organizations in the years that follow their children's diagnosis or while their children are younger. Nevertheless, the availability of genetic tests for *SCN1A* and related genes has

Table 6
Current antiepileptic drug use by number and percentage of patients (>5% use only).

	Total population (n = 274)		Population > 4 TC (n = 124)	
	Patients (n)	%	Patients (n)	%
Valproate	237	86	104	84
Clobazam	151	55	77	62
Topiramate	120	44	38	31
Stiripentol	116	42	63	51
Levetiracetam	59	22	28	23
Bromide	29	11	22	18
Clonazepam	26	9	15	12

Table 7
Current stiripentol use by number and percentage of patients (countries with most survey responses).

Country	Total population (n = 215)		Population > 4 TC (n = 104)	
	Patients	%	Patients	%
France	12/22	55	4/6	67
Germany	14/30	47	10/20	50
Italy	24/50	48	16/28	57
Netherlands	17/54	31	10/29	34
Spain	20/59	34	11/21	52
Average		43		52

increased in recent years, leading to earlier diagnosis and an increase in the identification of younger patients in the general population with Dravet syndrome. An affiliation bias among the responders is also probably observed in the very high prevalence of patients carrying *SCN1A* mutations. The increased availability of genetic tests in recent years has led to the diagnosis of Dravet syndrome in patients with milder phenotypes, which, in the absence of a confirmed *SCN1A* mutation, might not have met the criteria for a clinical diagnosis and, therefore, enriched the population with Dravet syndrome with cases with *SCN1A* mutations. In our experience, these families also become affiliated with organizations for patients with Dravet syndrome at a higher rate than the families of those patients who do not have mutations in *SCN1A*, despite having the same clinical diagnosis. Therefore, children and adolescents carrying mutations in *SCN1A* are likely to account for the majority of Dravet syndrome cases, with both younger age and confirmed *SCN1A* mutations being even more prevalent among those affiliated with patient organizations.

Our data also confirm that the typical European patient with Dravet syndrome has severe epilepsy with multiple seizure types in addition to nonseizure comorbidities. Because families with a member that has Dravet syndrome are generally highly educated in the management of seizures and status epilepticus, including the use of rescue medications, the elevated frequency of emergency room admissions in these patients reflects the severity of the refractory epilepsy that most patients with Dravet syndrome have. Nevertheless, only 45% of the population reports an average of more than 4 tonic–clonic seizures per month. This number is of particular relevance for the design of clinical trials because a minimum of 4 tonic–clonic seizures is often an eligibility criterion for patient recruitment. Such a criterion might make the recruitment of suitable patients in a disease that has already a low incidence and that has a high rate of underdiagnosis difficult. Importantly, it would also limit the access of a large percentage of the population with Dravet syndrome to clinical trials. Therefore, clinical trials evaluating the efficacy of experimental treatments in other seizure types, such as myoclonic or absence seizures, should be considered in Dravet syndrome.

Although our survey was focused on establishing the age distribution, seizure frequency, and antiepileptic drug use of the European population with Dravet syndrome, all parameters used for inclusion in clinical trials, it also serves as a proof of concept for the potential of gathering patient data through an anonymous, web-based parent- or patient-reported survey. Using this approach, and engaging the collaboration of national organizations for patients with Dravet syndrome, we were able to collect 274 individual entries over a one-month period, a population size comparable to that of previously published large cohorts with Dravet syndrome over a five-year study period (e.g., Brunklaus et al., n = 241, [20]). The same survey approach could, therefore, be used in the future to get additional insight into Dravet syndrome pathophysiology, such as potential genotype–phenotype correlations or common electroencephalogram observations, by including questions about genetic and electroclinical findings.

4.2. Stiripentol is widely used by the European population with Dravet syndrome

Two of the key questions that we wanted to address regarding the use of antiepileptic medications were (1) what are the most frequent drugs and drug combinations used by the current European population with Dravet syndrome and (2) how widespread is the use of stiripentol, the only drug approved in Europe for the management of Dravet syndrome. Despite having a broad repertoire of antiepileptic medications, patients with Dravet syndrome in Europe are largely treated with only five of these medications: valproate, clobazam, topiramate, stiripentol, and levetiracetam, with most patients taking a combination of three or four of these drugs. These observations support the success of the stiripentol trials, which, seven years after stiripentol approval in Europe, have established the valproate, clobazam, and stiripentol combination as the gold standard for the management of Dravet syndrome.

The use of stiripentol was particularly high in the subpopulation with 4 or more tonic–clonic seizures per month. Because clinical trials are likely to target this specific subpopulation, European trials would need to include patients taking stiripentol, despite the drug being not yet approved in the United States, in order to appropriately capture the actual patient population. This is also important because stiripentol has known drug–drug interaction effects through inhibition of several cytochrome P450 isoenzymes [19] that should be clinically evaluated in combination with any new experimental drug before the latter reaches the market.

We also noted the use of some nonconventional treatments in this series including vagal nerve stimulation, the ketogenic diet, and the experimental drugs cannabidiol and fenfluramine. The more prevalent one was the ketogenic diet, with 5% of the patients with Dravet syndrome currently on the diet versus 17% of patients having tried it in the past. While the reduced number of patients on the ketogenic diet (13/274) prevents any efficacy claims, all patients were taking two to four concomitant antiepileptic drugs and were experiencing seizures, indicating that the ketogenic diet is likely to be only partly effective in this population as it occurs with antiepileptic medications. A total of 5 patients in this study reported using vagal nerve stimulators, three were taking cannabidiol or cannabis oil, and one was taking fenfluramine. All of these patients continued to have seizures and were taking concomitant medications, including combinations of nonconventional treatments such as vagal nerve stimulators and the ketogenic diet or vagal nerve stimulators and cannabidiol. Although the number of patients using these nonconventional treatments in our study was too small to make any efficacy observations, both vagal nerve stimulation and the ketogenic diet have been used with success in Dravet syndrome [23–25] and fenfluramine and cannabidiol are the two experimental treatments currently starting clinical trials for this population.

Table 8
Antiepileptic drugs tried by number and percentage of patients (>5% use only).

	Total population (n = 274)		Population > 4 TC (n = 124)	
	Patients (n)	%	Patients (n)	%
Levetiracetam	139	51	78	63
Valproate	132	48	63	51
Topiramate	125	46	70	56
Clobazam	117	43	64	52
Clonazepam	100	36	58	47
Lamotrigine	95	35	57	46
Carbamazepine	92	34	47	38
Phenobarbital	78	28	41	33
Stiripentol	73	27	37	30
Ketogenic diet	47	17	33	27
Ethosuximide	42	15	25	20
Vigabatrin	36	13	27	22
Oxcarbazepin	32	12	19	15
Zonisamide	25	9	21	17
Bromide	18	7	16	13
Phenytoin	14	5	13	10
Felbamate	11	4	7	6

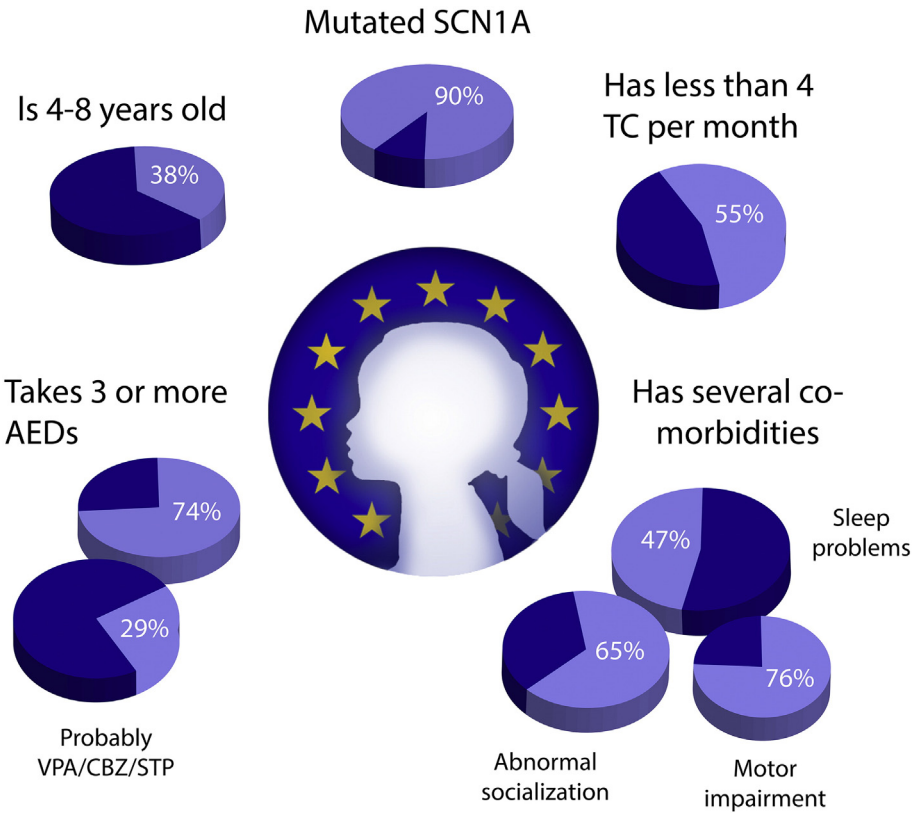

Fig. 1. The typical European patient with Dravet syndrome. Summary of the most representative demographic and clinical characteristics of patients with Dravet syndrome reported in the survey as well as the most frequently used antiepileptic medications.

4.3. Sodium channel blockers

When asked about the medications that patients had taken in the past, responders listed a number of antiepileptic drugs much larger than the list of drugs that they are currently taking, suggesting that after multiple trials, neurologists converge on a limited number of antiepileptic drugs for this population.

Interestingly, the most commonly listed drug was levetiracetam, with more than half of the patients having tried it at some point in their treatment. Although the potential efficacy of levetiracetam in this population has not been studied in placebo-controlled clinical trials, a preliminary open-label report concluded that it was effective as adjunctive therapy in Dravet syndrome [26] and it is a widely prescribed medication for multiple types of epilepsy, therefore being considered as one of the antiepileptic drugs recommended for this population [17,27].

Notably, over a third of the European patients with Dravet syndrome had at some point taken sodium channel blockers such as carbamazepine. With a population with confirmed *SCN1A* mutations in 90% of the patients, such treatment is not recommended and can lead to disease aggravation [20,27,28]. Although our survey cannot determine whether these drugs were administered only before or also after the patients' diagnosis of Dravet syndrome, the current number of patients using sodium channel blockers was below 2%. This suggests that either the lack of efficacy or a Dravet diagnosis leads to the discontinuation of these drugs. This number highlights the importance of an early genetic diagnosis to minimize exposing patients with Dravet syndrome to sodium channel blockers.

5. Conclusions

We present data from a parent-reported survey including 274 patients with Dravet syndrome from 15 European countries. This study establishes the typical European patient with Dravet syndrome who is 4 to 8 years old, has a mutation in *SCN1A*, has epilepsy characterized by multiple seizure types but usually no more than 4 tonic–clonic seizures per month, takes at least three antiepileptic drugs likely including stiripentol, and has a set of comorbidities that extends beyond mental retardation (Fig. 1). Our results stress the need to clinically evaluate any new experimental drug in combination with stiripentol and to consider the potential effect that it might have – positive or negative – on the nonseizure aspects of Dravet syndrome. We also identify that the usual trial inclusion criterion of minimum 4 tonic–clonic seizures per month is likely to reduce the already small patient population to half its size and the evaluation of other seizure types should be considered. The results from this study may have important implications for the design of future clinical trials that investigate new treatments for Dravet syndrome.

List of abbreviations

AEDs	antiepileptic drugs
CBZ	clobazam
CHD2	chromodomain helicase DNA binding protein 2
GABRG2	gamma-aminobutyric acid receptor subunit gamma-2
n	number
PCDH19	protocadherin 19
SCN1A	sodium channel, voltage-gated, type I, alpha subunit
SCN1B	sodium channel, voltage-gated, type I, beta subunit
SCN2A	sodium channel, voltage-gated, type II, alpha subunit
STP	stiripentol
TC	tonic–clonic seizure
VPA	valproate

Author's contributions

LMA, JI, and AMLM participated in the conception, organization, and execution of the study, as well as in data analysis. LMA and AMLM wrote the manuscript. All authors read and approved the final manuscript.

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Conflict of interests

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2014.12.028.

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