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Short communication

Prevalence and healthcare resource utilization of patients with Dravet syndrome: Retrospective linkage cohort study

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ABSTRACT

Purpose: Prevalence, demography, antiseizure medication (ASM) usage, healthcare resource utilization (HCRU), and mortality of Dravet syndrome (DS) in the UK were investigated using primary and secondary care data in this retrospective cohort study.

Methods: Patients with confirmed DS were anonymously identified from the UK Clinical Practice Research Datalink (CPRD) GOLD database (01/01/1987–31/10/2018) using the DS Read Codes (F25G.11 or F25G.00). Probable DS was identified using the International Classification of Diseases-10/Read Code for epilepsy plus stiripentol or potassium bromide prescription. CPRD data were linked to the Hospital Episode Statistics database and Office for National Statistics to calculate HCRU and mortality.

Results: The prevalence of confirmed ($n = 32$; 1.1/100,000) and probable ($n = 22$; 0.6/100,000) DS in 2017 was 1.5/100,000. Most patients with DS (confirmed, $n = 22/28$; probable, $n = 8/14$) were aged <18 years in 2017. Mean (standard deviation) ASM usage was 5.5 (2.7) in confirmed DS and 7.6 (3.8) in probable DS, over 3.4 (3.5) years and 10.0 (6.2) years of follow-up, respectively. HCRU (per patient-year) was similarly high in patients with confirmed and probable DS; mainly consisting of general practitioner consultations (mean, 4.8–7.9), outpatient visits (5.6–8.3), hospital admissions (0.9–4), and emergency department visits (0.3–2.3). Fewer than five deaths were recorded in patients with confirmed and probable DS.

Conclusion: Using linked national healthcare databases, our study showed that the UK prevalence of DS recorded in primary care was low, and most cases were in patients aged <18 years. HCRU and ASM usage were similarly high in confirmed or probable DS.

1. Introduction

Dravet syndrome (DS) is a rare childhood-onset epilepsy often caused by *SCN1A* mutations, and characterized by multiple intractable seizure types [1]. Patients with DS usually develop intellectual disability [2], comorbidities are common [3], and the premature mortality rate is high [2]. Despite treatment with multiple antiseizure medications (ASMs), disease management is poor [3], and misdiagnosis for focal epilepsy results in incorrectly prescribed ASMs [4]. Patients with DS have high healthcare resource utilization (HCRU).

UK primary and secondary healthcare data are captured in electronic medical records (EMRs), with diagnoses recorded in primary care using

Abbreviations: ASM, antiseizure medication; CPRD, Clinical Practice Research Datalink; DS, Dravet syndrome; ED, emergency department; EMR, electronic medical record; GP, general practitioner; HCRU, healthcare resource utilization; HES, Hospital Episode Statistics; ICD, International Classification of Diseases; ONS, Office for National Statistics; SMEI, severe myoclonic epilepsy in infancy.

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a clinical terminology coding system (Read Codes) [5,6]. A DS Read Code was established in 2014, predated by a Read Code for severe myoclonic epilepsy in infancy (SMEI), the previous name for DS [1]. As established by a study in Lennox-Gastaut syndrome [7], Read Code data, accessible from the Clinical Practice Research Datalink (CPRD), enable improved understanding of prevalence and HCRU in rare childhood-onset epilepsies.

Using linked CPRD data, this retrospective cohort study aimed to examine prevalence, ASM usage, HCRU and mortality of patients with DS.

2. Methods

2.1. Data source

Data were sourced from the latest build of CPRD-GOLD (11/03/2019) [8], containing 13.7 million de-identified EMRs collected between 01/01/1987–28/02/2019, and were linked to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) data. The data sources align with those in our previous study [7]; further details are described in the Supplementary Methods.

2.2. Patient population

Data were included for patients with records between 01/01/1987–31/10/2018, who had at least one EMR containing a Read Code for DS (CPRD-GOLD; **F25G.11**) or SMEI (CPRD-GOLD; **F25G.00**) indicating confirmed DS; or an EMR containing an International Classification of Diseases (ICD)-10 code (HES) or Read Code (CPRD) for epilepsy, and a formulary product code for stiripentol or potassium bromide within the same year or year after being coded for epilepsy with an ICD-10 code or Read Code, indicating probable DS. Prescriptions of stiripentol or potassium bromide were deemed the best indicators of DS in patients with epilepsy; stiripentol is specifically indicated for patients with DS [9], while potassium bromide (which was available prior to the introduction of stiripentol) [10] has historically been used to treat patients with DS [4,9].

Further details on the identification, classification, and diagnosis index date for DS are summarized in the Supplementary Methods and Fig. S1.

2.3. Outcomes

The primary outcome was DS period prevalence in 2017. Secondary outcomes were ASM prescriptions, HCRU (primary care consultations, hospital outpatient visits, hospital admissions, and emergency department [ED] visits), and mortality during the follow-up period. Baseline characteristics included age (at index and diagnosis of epilepsy), follow-up duration, and sex.

2.4. Data analyses

Analyses were exploratory due to the small numbers of patients. Outcomes were stratified as follows: prevalence, by age in 2017 (<18 years and ≥18 years); HCRU, by age at follow-up (<12 years and ≥12 years); and hospital admissions, by total or epilepsy-related (primary admission diagnosis with ICD-10 code G40*).

2.5. Ethics and guidelines

The UK Health Research Authority Research Ethics Committee provided ethics approval for CPRD to provide primary care and linked data for observational research [6,11]. This study received approval from an Independent Scientific Advisory Committee (reference number: 18_236R) and followed Strengthening the Reporting of Observational Studies in Epidemiology guidelines [12].

3. Results

3.1. Baseline characteristics

Fifty-four patients were identified with confirmed (n = 32) or probable DS (n = 22). Of patients with probable DS, fewer than five were indicated by a product code for potassium bromide; the exact numbers cannot be disclosed to protect against potential reidentification. An overview of all screened patients and baseline characteristics are presented in Fig. S2 and Table S1. Median (range) ages at DS diagnosis were higher for patients with confirmed DS (5.5 [0.0–45.0] years) compared with probable DS (1.0 [0.0–40.0] years). Age at first epilepsy diagnosis was similar between patients with confirmed (1.0 [0.0–33.0] years) and probable DS (1.0 [0.0–40.0] years). Median (range) years of follow-up data were 2.6 (0.1–18.3) and 11.0 (1.5–25.2), respectively.

3.2. Prevalence

Of 54 patients with confirmed or probable DS, 12 were lost to follow-up before 2017, leaving 42 patients (28 confirmed) for calculating period prevalence (Fig. S2 and Table S2). DS period prevalence for 2017 was 1.5/100,000 (confirmed, 1.1/100,000; probable, 0.6/100,000). Most patients with DS (confirmed, n = 22/28; probable, n = 8/14) were aged <18 years in 2017 (Table S2).

Confirmed DS diagnosis was rare before 2010 (Fig. S3), peaking in 2013–14 (n = 13), which coincides with the introduction of SMEI (2013) and DS (2014) Read Codes. The first probable DS case was registered in 1989, and none were registered after SMEI and DS Read Codes were introduced.

3.3. ASM usage

ASM usage was assessed for all patients (confirmed, n = 32; probable, n = 22). Fifteen ASMs were used by ≥10% of patients with DS during follow-up (Fig. 1A). For confirmed DS, the most frequently prescribed ASMs were midazolam (88%), valproate (81%), and clobazam (72%). For probable DS, stiripentol (91%) was the most frequently prescribed ASM followed by valproate (86%), and clobazam (86%). Mean (standard deviation; range) number of ASMs used by patients with confirmed and probable DS were similar (5.5 [2.7; 1–12] and 7.6 [3.8; 3–15]; Fig. 1B), and approximately one ASM was prescribed each year of follow-up.

3.4. Healthcare resource utilization

HCRU was assessed for all patients for primary care (confirmed, n = 32; probable n = 22) and for those with HES/ONS linkage for secondary care (confirmed, n = 13; probable n = 14). In primary care, general practitioner (GP) consultation was the most common contact, followed by GP home visits and nurse consultations (Table 1A). Probable DS had slightly more primary care consultations than confirmed DS (regardless of age). In secondary care, outpatient visits were the most common HCRU type (similar between confirmed and probable DS, regardless of age), followed by hospital admissions and ED visits (Table 1B). Patients with probable DS had more total and epilepsy-related hospital admissions, and ED visits, than confirmed DS in patients <12 years, but similar numbers in patients ≥12 years. Length of hospital stay was similar between patients <12 years with confirmed and probable DS, but longer in patients with probable DS compared with confirmed DS in those ≥12 years.

3.5. Mortality

Few deaths were reported. The exact number cannot be disclosed to protect against potential reidentification.

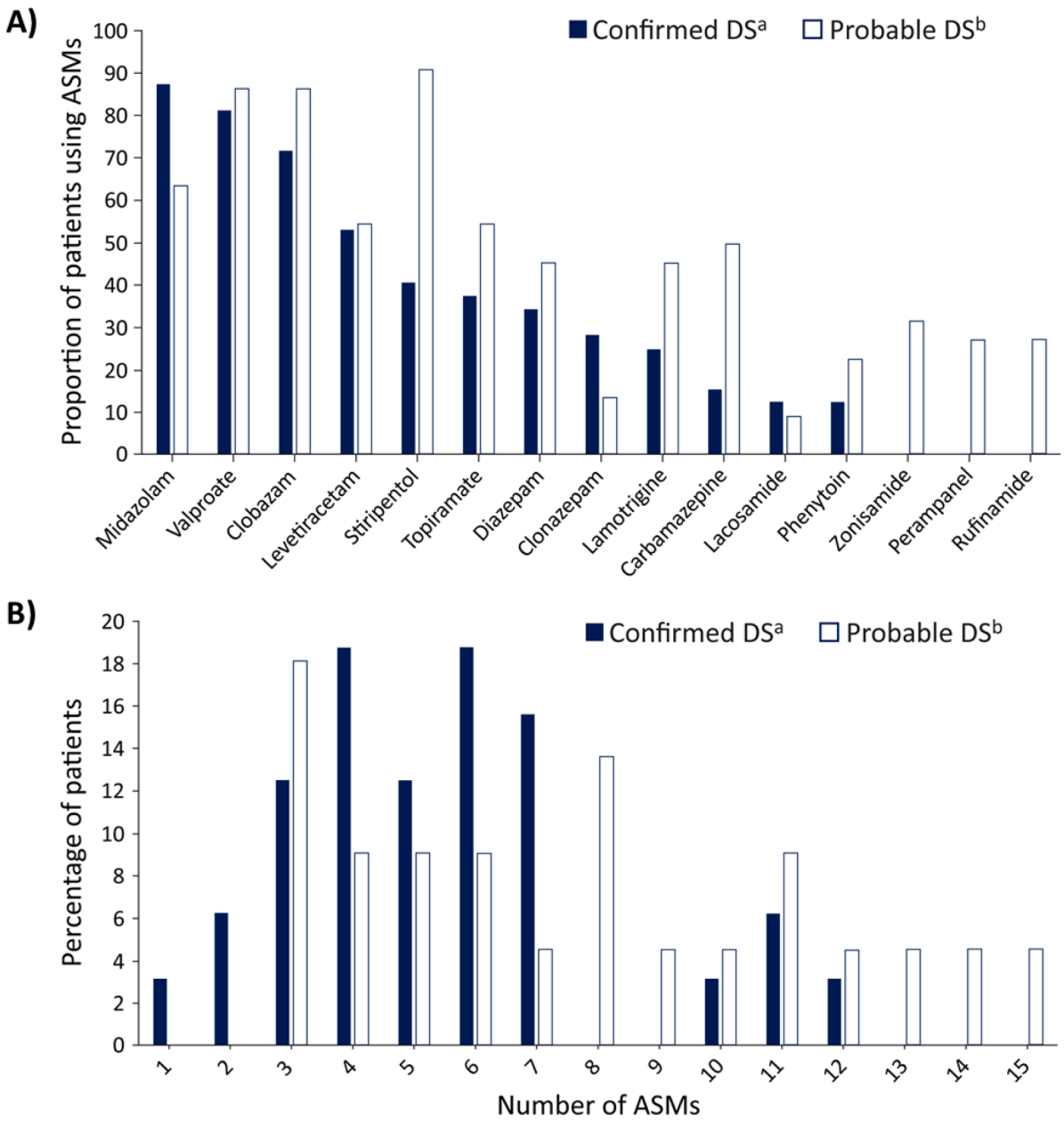

Fig 1. A) ASM usage during the follow-up period (confirmed[a] + probable[b]), and B) Number of ASMs prescribed over the follow-up period (confirmed[a] + probable[b]). ASM, antiseizure medication; DS, Dravet syndrome; ICD, International Classification of Diseases. [a]Diagnosis confirmed by the Read Code for DS: F25G.11 or F25G.00. [b]DS considered probable based on ICD-10/Read Code for epilepsy and at least one prescription of stiripentol or potassium bromide within a year of diagnosis.

4. Discussion

This is the first study to use large-scale healthcare data to determine UK prevalence and HCRU for patients with DS. Period prevalence for confirmed and probable DS in 2017 was low, but was higher in patients aged <18 years. Inclusion of patients who were lost to follow-up would have increased the period prevalence estimate but this could not be done because it was unknown how many of these patients were alive during 2017. Patients with DS (confirmed and probable) were prescribed multiple ASMs and had high HCRU; few deaths were reported.

The greater prevalence of DS in patients aged <18 versus ≥18 years may partially be explained by the impact of childhood mortality on adult prevalence [2]. Other reasons may include misdiagnosis or miscoding of DS [7]; diagnosis is challenging in adults that may no longer display the typical myoclonic seizures, particularly when their paediatric seizure history is missing [13]. Also, patients may have been diagnosed with refractory epilepsy before DS was widely recognized and routine genetic testing introduced.

In the confirmed DS group, the median age at diagnosis of epilepsy (1 year) and DS (5.5 years) differs. This likely reflects the delay in DS diagnosis after seizure onset in the affected child that may result from the evolving DS phenotype and diagnosis or coding delays [14].

Average number of ASMs used (confirmed, 5.5; probable, 7.6) is higher than reported in UK patients with epilepsy [15], and reflects the drug-resistant nature of DS. As all probable DS cases were recorded before 2014, data for the confirmed DS cohort may be more reflective of current treatment patterns. ASM use reported in a given year (one on average, not more than two) is in line with National Institute for Health and Care Excellence guidelines for management of epilepsies [16]. Stiripentol was the most frequently prescribed ASM for patients with probable DS. This is expected because, until recently, stiripentol was the only ASM specifically indicated for DS in Europe [17]. and is indicated

Table 1
Healthcare resource utilization by identification criteria[a,b] and age group during follow-up[c].

A) Primary care	Confirmed DS[a]		Probable DS[b]	
	<12 years ($n = 18$)	≥12 years ($n = 14$)	<12 years ($n = 17$)	≥12 years ($n = 16$)
Number of primary care consultations, PPY				
All (nurse/GP)	6.50 (4.55)	7.50 (6.47)	9.59 (5.99)	9.13 (10.78)
GP consultations	4.78 (3.57)	5.21 (4.87)	7.59 (5.98)	7.88 (9.88)
GP home visits	0.83 (1.58)	0.71 (0.99)	0.29 (1.21)	0.38 (1.26)
GP phone call	0.06 (0.24)	0.36 (0.84)	0.53 (0.72)	0.38 (0.62)
Nurse consultations	0.78 (1.22)	1.00 (1.71)	0.82 (0.88)	0.19 (0.40)
Nurse home visits	0	0	0	0
Nurse phone call	0.06 (0.24)	0.07 (0.27)	0.06 (0.24)	0
B) Secondary care	**Confirmed DS[a]**		**Probable DS[b]**	
	<12 years ($n = 10$)	≥12 years ($n = 7$)	<12 years ($n = 12$)	≥12 years ($n = 10$)
Number of hospital outpatient visits, PPY				
All causes	8.3 (7.39)	6.43 (6.32)	7.58 (3.90)	5.6 (4.38)
Number of hospital admissions, PPY				
All causes	1.00 (1.25)	0.86 (1.46)	4.00 (3.81)	1.70 (2.75)
Epilepsy related	0.90 (1.10)	0.71 (1.11)	3.33 (3.55)	1.70 (2.75)
Hospital admissions LOS, days				
	$n = 34$	$n = 16$	$n = 297$	$n = 61$
All causes	1.00 (1.67)	0.63 (1.54)	1.28 (2.35)	2.16 (4.52)
	$n = 29$	$n = 14$	$n = 249$	$n = 60$
Epilepsy related	1.14 (1.77)	0.71 (1.64)	1.16 (2.21)	2.15 (4.55)
Emergency department visits resulting in hospital admissions, PPY				
All causes	0.90 (1.60)	0.29 (0.76)	2.33 (2.50)	1.60 (2.55)

Data are mean (SD).
DS, Dravet syndrome; GP, general practitioner; ICD, International Classification of Diseases; LOS, length of stay; PPY, per patient-year; SD, standard deviation.
[a]Diagnosis confirmed by the Read Code for DS: F25G.11 or F25G.00.
[b]DS considered probable based on ICD-10/Read Code for epilepsy and at least one prescription of stiripentol or potassium bromide within a year of diagnosis.
[c]Data shown by age at resource utilization, resulting in some patients being included in both groups.

as an adjunctive therapy with clobazam and valproate [17]. Furthermore, we would expect that patients treated with stiripentol have DS and that they are using at least three ASMs. However, a greater proportion of patients with probable DS than confirmed DS were prescribed sodium channel blockers, such as lamotrigine and carbamazepine, that are contraindicated for DS [9]. This may be explained by a diagnosis of a severe epilepsy other than DS; however, as DS was not formally diagnosed in these patients, another likely explanation is that contraindications for DS were not considered when ASMs were prescribed to these patients.

HCRU in primary and secondary care was high. Compared with confirmed and probable DS, UK patients with epilepsy had lower HCRU in secondary care (mean number per year: hospital admissions, 0.22; outpatient visits, 0.72; emergency visits, 0.31) [18]. The number of hospital admissions in patients with probable DS <12 years was particularly high; this may reflect more severe seizures in younger patients due to natural DS progression [1], misdiagnosis for focal epilepsy and therefore incorrectly prescribed ASMs (such as carbamazepine) that can exacerbate seizures in children with DS, and the time taken to achieve the right ASM regime [4]. In contrast to patients with probable DS, patients with confirmed DS were indexed using the DS diagnosis date, not the epilepsy onset date (Fig. S1; therefore, some hospital admissions in patients with confirmed DS aged <12 years were potentially missed.

Limitations of this study include potential miscoding, misdiagnosis, and lack of sensitivity in the probable DS algorithm. While our algorithm may have missed some patients, its specificity for DS is evidenced by the lack of cases of probable DS identified following the introduction of Read Codes in 2013–14 (SMEI and DS). However, we would note that a greater prevalence of DS was reported when a similar, but slightly broader probable DS algorithm was used in a German population [19]. Additionally, the potassium bromide product code used in the probable DS algorithm potentially identified patients with other severe epilepsies that manifest in the first year of life. Further limitations are that secondary care data (e.g. letters) are not fully captured, only a subset of patients in the CPRD database are eligible for HES linkage, lack of access to patient level data to confirm DS diagnosis, and there were insufficient patient-years of follow-up and reported deaths to accurately assess mortality. Altogether, these limitations likely contributed to the low DS prevalence reported and limited our estimation of mortality rate in this population, which is known to be high (15.8/1000 person-years) [2].

5. Conclusion

Despite some limitations, this study provides valuable information on the UK burden of illness in patients with DS and highlights the high HCRU and ASM usage. UK prevalence of DS recorded in primary care was low. Most patients with DS were aged <18 years.

Declaration of Competing Interest

WOP has received consultancy fees from GW Pharmaceuticals companies, now part of Jazz Pharmaceuticals, Inc., and Arvelle Therapeutics. He has been a principal investigator for GW Research Ltd, now part of Jazz Pharmaceuticals, Inc. FG is an employee of Syneos Health. MM was an employee of Syneos Health at the time of study completion. RH owns shares in GW Pharmaceuticals plc, now part of Jazz Pharmaceuticals, Inc., and is a current employee of GW Pharma Ltd, now part of Jazz Pharmaceuticals, Inc. RC has provided consultancy and speaker services, and has participated in events and studies, for GW Pharmaceuticals companies, now part of Jazz Pharmaceuticals, Inc., Eisai, Neopharm Group, and Zogenix, and has shares in the Rize Medical Cannabis and Life Sciences UCITS ETF. All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship.

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Data statement

Data were obtained from CPRD after going through their process for obtaining access, which includes ethics approval. The data were analyzed by Syneos on behalf of GW Pharmaceuticals, now part of Jazz Pharmaceuticals, Inc., to answer this particular research question. While the same data cut could be obtained from CPRD, the current data are confidential.

Author contributions

All authors contributed to the study concept, design, and interpretation of the data. FG analyzed the data.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2022.05.018.

References

[1] Dravet C. The core Dravet syndrome phenotype. Epilepsia 2011;52(Suppl. 2):3–9.
[2] Cooper MS, Mcintosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, et al. Mortality in Dravet syndrome. Epilepsy Res 2016;128:43–7.
[3] Lagae L, Brambilla I, Mingorance A, Gibson E, Battersby A. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol 2018;60(1):63–72.
[4] Ziobro J, Eschbach K, Sullivan JE, Knupp KG. Current treatment strategies and future treatment options for Dravet syndrome. Curr Treat Options Neurol 2018;20 (12):52.
[5] The Medicines and Healthcare products Regulatory Agency (MHRA). Clinical practice research datalink [Internet]. 2021 [cited 2021]. Available from: https://www.cprd.com/.
[6] Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015; 44(3):827–36.
[7] Chin RFM, Pickrell WO, Guelfucci F, Martin M, Holland R. Prevalence, healthcare resource utilization and mortality of Lennox-Gastaut syndrome: retrospective linkage cohort study. Seizure 2021;91:159–66.
[8] Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. Int J Epidemiol 2019; 48(6):1740. –1740g.
[9] Cross JH, Caraballo RH, Nabbout R, Vigevano F, Guerrini R, Lagae L. Dravet syndrome: treatment options and management of prolonged seizures. Epilepsia 2019;60(Suppl. 3):S39–48.
[10] Chiron C, Dulac O. The pharmacologic treatment of Dravet syndrome. Epilepsia 2011;52:72–5. Suppl2.
[11] Padmanabhan S, Carty L, Cameron E, Ghosh RE, Williams R, Strongman H. Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. Eur J Epidemiol 2019;34(1):91–9.
[12] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370(9596):1453–7.
[13] Selvarajah A, Zulfiqar-Ali Q, Marques P, Rong M, Andrade DM. A systematic review of adults with Dravet syndrome. Seizure 2021;87:39–45.
[14] Silvennoinen K, Puvirajasinghe C, Hudgell K, Sidhu MK, Martins Custodio H, et al. Late diagnoses of Dravet syndrome: how many individuals are we missing? Epilepsia Open 2021;6:770–6.
[15] Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78(20):1548–54.
[16] National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management [Internet]. NICE; 2020 [cited 2020]. Available from: https://www.nice.org.uk/guidance/cg137/resources/epilepsies-diagnosis-and-management-pdf-35109515407813.
[17] Frampton JE. Stiripentol: a review in Dravet syndrome. Drugs 2019;79(16): 1785–96.
[18] Myland M, Buysse B, Tsong W, Power GS, Nordli D, Chin RF. Seizure frequency, healthcare resource utilisation and mortality in childhood epilepsy: a retrospective cohort study using the THIN database. Arch Dis Child 2019;104(11):1070–6.
[19] Schubert-Bast S, Kay L, Simon A, Wyatt G, Holland R, Rosenow F, et al. Epidemiology, healthcare resource use, and mortality in patients with probable Dravet syndrome: a population-based study on German health insurance data. Epilepsy Behav 2022;126:108442.