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Characterising people with focal drug-resistant epilepsy: A retrospective cohort study

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ABSTRACT

Objectives: To describe the demographics, clinical characteristics, drug treatment outcomes, healthcare resource utilization, and injuries among people with focal drug-resistant epilepsy (F-DRE) analysed separately for six European countries.

Methods: We used electronic medical record data from six European (Belgium, Spain, Italy, France, UK and Germany) primary care/specialist care databases to identify antiseizure medication (ASM) treatment-naïve people (aged ≥ 18 years at F-DRE diagnosis). They were followed from their epilepsy diagnosis until death, the date of last record available, or study end. We used descriptive analyses to characterise the F-DRE cohort, and results were reported by country.

Results: One–thousand–seventy individuals with F-DRE were included (mean age 52.5 years; 55.4 % female). The median follow-up time from the first diagnosis to the end of the follow-up was 95.5 months across all countries. The frequency of F-DRE diagnosis in 2021 ranged from 8.8 % in Italy to 18.2 % in Germany. Psychiatric disorders were the most common comorbidity across all countries. Frequently reported psychiatric disorders were depression (26.7 %) and anxiety (11.8 %). The median time from epilepsy diagnosis to the first ASM failure ranged from 5.9 (4.2–10.2) months in France to 12.6 (5.8–20.4) months in Spain. Levetiracetam and lamotrigine were the most commonly used ASM monotherapies in all countries. Consultation with a general practitioner is sought more frequently after F-DRE diagnosis than after epilepsy diagnosis, except in the UK.

Significance: No one ASM is optimal for all people with F-DRE, and the risks and benefits of the ASM must be considered. Comorbidities must be an integral part of the management strategy and drive the choice of drugs.

1. Introduction

Epilepsy is a common chronic neurological brain disorder characterised by recurring unprovoked seizures. Some people experience epileptic seizures throughout their lifetime, while others achieve terminal remission without relapse [1,2]. Based on the part of the cortex initially affected (the focus), epileptic seizures are categorised as focal (originating in one hemisphere of the brain), generalised (simultaneously occurring in both hemispheres), and unknown [3,4].

People with epilepsy are more likely to have comorbid conditions than the general population, with anxiety, arthritis, dementia, depression, heart disease, migraine, and peptic ulcers up to eight times more common [5]. People with epilepsy also have an increased risk of injury and premature mortality compared with the general population and often experience social stigmatisation and poor quality of life [6,7].

Antiseizure medications (ASMs) are the mainstay of epilepsy treatment. A single ASM (monotherapy) should be used initially, with the selection of therapy based on the individual's age, sex, seizure type, epilepsy syndrome, comorbidities, concomitant medications, and the risks and benefits of the ASM [8,9]. As only around half of people with epilepsy achieve seizure freedom using the first appropriately selected ASM, a second ASM can be used, either as monotherapy or in

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combination; this, however, increases the risk of adverse effects and drug-drug interactions [8–12].

Most people with epilepsy have a good prognosis for seizure remission. Some, however, will continue to have seizures and, at some point, become drug-resistant. Drug-resistant epilepsy (DRE) is defined by the International League Against Epilepsy (ILAE) as the failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom [13].

There are few predictors or early markers of the transition to drug resistance in focal epilepsy [14]. People with an inadequate response to initial treatment with ASMs or who have had > 20 seizures before starting treatment are more likely to have refractory epilepsy [10]. Other risk factors for DRE include younger age at diagnosis, use of several ASMs, and neuropsychiatric disorders (mental retardation, psychiatric comorbidities, neurologic abnormalities) [15–18]. No significant reductions in DRE frequency have been noted in the last two decades, highlighting the continuing burden of unmet needs of people with DRE [6].

To improve the understanding of the burden of illness, demographic and clinical characteristics, and ASM treatment practices, we assessed cohorts of people with focal drug-resistant epilepsy (F-DRE) gathered from cohorts in six European countries.

2. Methods

2.1. Data source

Electronic medical record (EMR) data were retrieved from six primary care/specialist care databases in Europe, including the Longitudinal Patient Database (LPD) from Belgium, Spain, Italy, and France, the IQVIA Medical Research Data (IMRD) database from the United Kingdom (UK), and the Disease Analyser (DA) database from Germany (see Supplementary Material Table S1). All databases had their data mapped to the Observational Medical Outcomes Partnership (OMOP) standard data model [19].

2.2. Study design

This retrospective descriptive cohort study examined the demographics, clinical characteristics, ASM treatment patterns and response, healthcare resource utilisation (HCRU), and frequency of head trauma and fracture injury among people with F-DRE. The study aimed to identify people with F-DRE, i.e., those diagnosed with focal epilepsy and have not responded to at least two ASMs before the study period.

The study period, which differed between countries, spanned from July 2015 until May 2021 (UK), January 2022 (Belgium), February 2022 (Italy), March 2022 (Germany and France), and April 2022 (Spain).

The study population consisted of ASM treatment-naïve individuals who were followed from their first epilepsy diagnosis (i.e., non-specified epilepsy/focal epilepsy diagnosis; Index date 1) until the earliest of the following censoring events: (i) date of death; (ii) date of last available record in the database; or (iii) end of study period.

To be eligible for inclusion, people were required to have at least 180 days of follow-up after their first epilepsy diagnosis (Index date 1) and be ≥ 18 years of age at the time of F-DRE diagnosis, defined as the first date a participant was diagnosed with focal epilepsy resistant to 2 ASMs (i.e., Index date 2). Individuals with a history of generalised epilepsy or a record of ASM treatment before Index date 1 were excluded. An overview of the study design is shown in Fig. 1.

Individuals with F-DRE were identified from EMR data from six primary care/specialist care databases, based on these rules: the failure of two tolerated ASM treatments and the initiation of a third unique ASM, the latter recorded post epilepsy diagnosis and after at least three months from the 1st and 2nd ASM. The third treatment should have started between 1 July 2015 (i.e., the study initiation) and the end of the study. To account for titration, we used a minimum gap of 90 days between the start of the 1st and 2nd ASMs to assume the failure of the 1st

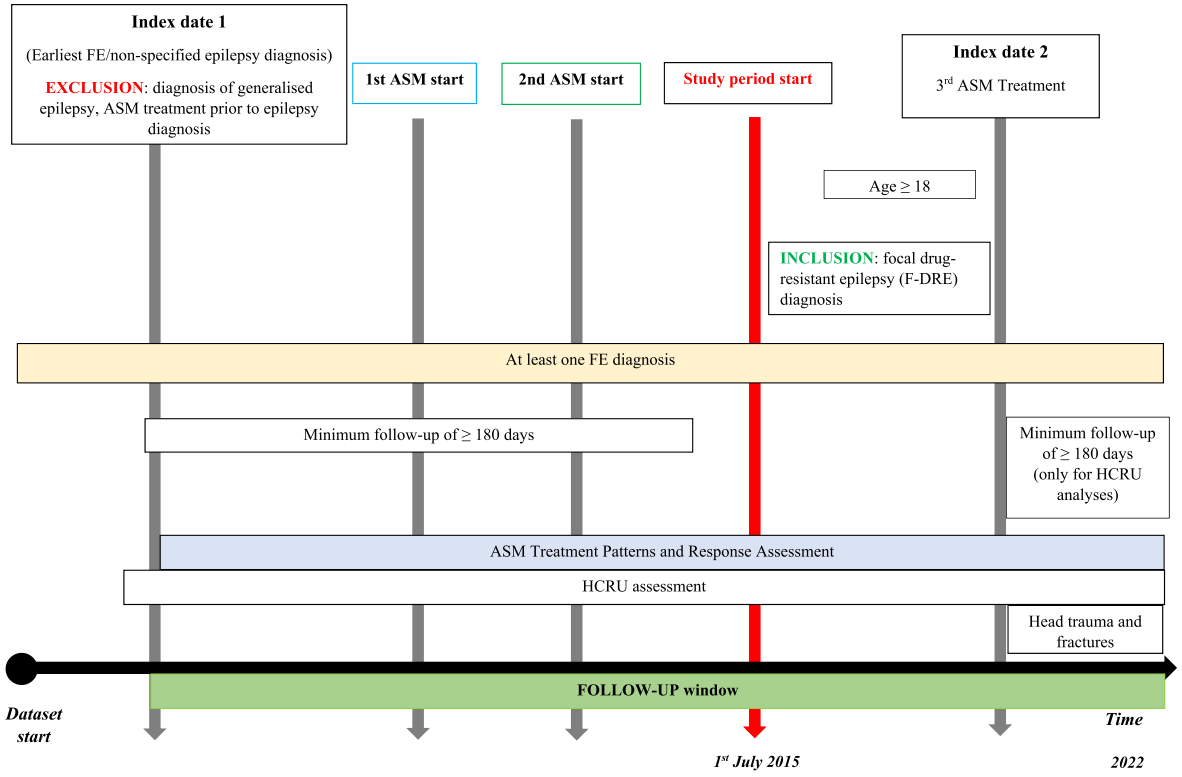

Fig. 1. Study design Abbreviations: ASM = Antiseizure medication; F-DRE = focal drug-resistant epilepsy; FE = Focal epilepsy; HCRU = Healthcare resource utilisation.

ASM. This gap was also applied to the 2nd and the 3rd ASMs.

We included individuals with non-specified epilepsy codes to identify an individual's initial epilepsy diagnosis. This allowed for ambiguity and differences in the specificity between clinician coding practices and the coding terminologies across databases.

2.3. Study objectives

The primary aim was to describe the demographics and clinical characteristics of people with F-DRE in different countries. The secondary objective was to describe ASM treatment patterns, including the sequence of ASMs received, on and after the first epilepsy diagnosis. Exploratory objectives were to describe ASM treatment response, the rate of HCRU (i.e., investigations, family physicians/general practitioner [GP] and specialist consultations, and the overall number of ASM products prescribed per case 1-year after epilepsy/F-DRE diagnosis), and the frequency of head traumas and fractures (recorded from F-DRE diagnosis until the end of follow-up).

2.4. Data

For each individual, data on age, sex, year of F-DRE diagnosis, comorbidities, GP referrals, consultations, laboratory investigations, ASM prescriptions, diagnostic test/procedures (in the 6 months before and after epilepsy diagnosis and the year following F-DRE diagnosis), seizure, head trauma, and fractures were extracted from the databases.

Comorbidities were identified using the ICD-10 coding system. They included psychiatric disorders (depression, anxiety, bipolar affective disorder, psychosis), intellectual disability, neurodevelopmental disorders (attention deficit hyperactive disorder, autism, other), cardiovascular disorders (type 2 diabetes, ischemic heart disease), cerebrovascular disorders (stroke), somatic autoimmune disorders (type I diabetes, systemic lupus erythematous, myasthenia gravis, coeliac disease, rheumatoid arthritis, multiple sclerosis), and other (migraine, dementia, malignancy). The list of comorbidities evaluated was considered relevant for this indication as supported by evidence [5,7].

2.5. Statistical analysis

Results were reported by country without formal comparison or pooled *meta*-analyses. All statistical analyses were performed on anonymised data using the R environment (v4.1.3).

Descriptive analyses were used to describe the F-DRE cohort. Categorical variables were reported as numbers and percentages, while continuous variables were reported as mean, standard deviation (SD), median, and first and third quartiles (Q1–Q3). Kaplan-Meier estimates were used for time-to-event analyses (i.e., time-to-ASM treatment failure, time to first 12-month seizure remission) to account for variable follow-up periods. Values ≤ 10 in France and ≤ 5 elsewhere were masked to maintain confidentiality and comply with data protection criteria.

2.5.1. ASM treatment patterns

ASM treatment patterns were evaluated using an algorithm based on prescription information. The assessment was based on continuous treatment episodes with each ASM and by combining and integrating these episodes to define ASM monotherapy and combination therapy regimens. Discontinuations occurred due to either the absence of further prescriptions or gaps between prescriptions exceeding the defined maximum (90 days). Reasons for discontinuation were unavailable for evaluation in this study. Treatment sequencing was determined for ASMs prescribed on or after Index date 1, considering only the first 3 ASM regimens. Consecutive prescriptions of the same ASM drug with a maximum gap of ≤ 30 days between the prescription's end date and the next start date were considered as a continuous treatment. Only ASM treatment episodes that lasted a minimum of 90 days were included in the analysis. Combination treatment was defined from treatment episodes overlapping at least 90 days OR the total duration of one of the treatment episodes. If the overlap period was short (<90 days) and not equal to the whole length of one of the treatment episodes, a switch was defined as a change from the previous treatment to a new therapy.

2.5.2. ASM treatment response

ASM treatment failure was explored using the treatment regimen from the ASM treatment pattern analysis, with regimen failure defined as the end date. We set a minimum interval of 90 days between the initiation of ASM, assuming the first ASM failure, to accommodate titration and prevent premature treatment discontinuations, such as those due to tolerance. Variables included the time (in months) from Index date 1 to 1st ASM regimen failure, Index date 1 to 2nd ASM regimen failure, treatment initiation to failure of 1st ASM regimen, treatment initiation to failure of 2nd ASM regimen, and Index date 1 to first seizure record.

The annualised frequency of seizures (i.e., the average number of seizures per individual, per year for interest) was reported as a categorical variable (≤one seizure per year, >one - five seizures per year, and > five seizures per year) and presented considering different periods of interest (i.e., from Index date 1 to the end of follow-up, Index date 1 to Index date 2, Index date 2 to the end of follow-up, the start of 1st ASM to the end of follow-up, the start of 1st ASM to start of 2nd ASM, and from the start of 2nd ASM to the end of follow-up).

Seizure freedom after epilepsy diagnosis was defined as the number and relative percentage of individuals who achieved at least one 12-month seizure-free period between Index date 1 and the end of follow-up. Only individuals with a minimum 12-month follow-up period were included in the analysis. Dates of recorded seizures were used to evaluate seizure freedom. The average seizure-free period after epilepsy diagnosis was defined as the number of days from Index date 1 until the first seizure record and using time-to-event analysis.

2.5.3. HCRU rate

Primary care referrals (to specialists), consultations (GP and/or specialists), investigations (by modality), and the number of ASM drugs prescribed were assessed for one year after Index date 1 and Index date 2. All HCRU variables (except the number of prescribed ASM drugs) were presented as an annualised rate per subject per year to maximise the sample size and avoid excluding people with < 1 year of observation in one or both periods of interest. The annualised rate of HCRU resource was estimated as the number of reported events divided by years of follow-up in the period of interest and summarised as a continuous variable across all individuals. A minimum follow-up time of six months after Index date 1 and Index date 2 was applied for annualised rate estimations, with individuals excluded from the analysis if this rule was not fulfilled in one or both periods. Only people with a full year of follow-up after each index date were considered in estimating the number of separate ASM drugs prescribed per subject.

2.5.4. Head trauma and fracture frequency

The frequency of head traumas and fractures was reported as the number of records per individual per year. This was estimated overall and stratified by pre-specified categories of the rate of seizures after Index date 2. These last were defined with a data-driven approach to recategorise seizure rates based on the observed distribution. Four categories were used based on the average number of seizures per subject per year from diagnosis until the end of follow-up for each subject: i) none, ii) 1–2 (low) iii) 3–5 (intermediate) iv) > 5 (high). People with a minimum of 6 months of follow-up time from Index date 2 were included in the analysis. The number of head trauma and fractures recorded were counted for each individual and divided by the respective follow-up time to obtain the number of events per case per year. The individual seizure rate was obtained as described above. For each seizure rate category and overall seizure rate, head trauma and fractures

frequency were reported as mean (SD), median (Q1–Q3), and min–max.

2.5.5. Missing values

Missing data and extreme values in study parameters were only imputed and replaced whilst calculating ASM treatment duration. Missing treatment durations were imputed with the subject- and drug-specific median duration of the intervals between consecutive prescriptions. The corresponding value was described as 'missing' in case of missing data. A 'missing' category was included in the categorical variables, and the number of units with missing values was reported for continuous variables.

3. Results

3.1. Demographics characteristics of people with F-DRE

Across all databases, 64,439 individuals were identified with at least one specific focal epilepsy diagnosis code at any point in their record (Fig. 2). After applying the inclusion and exclusion criteria, an ultimate cohort of 1,075 individuals with F-DRE were included. The individual distribution across countries is provided in Table 1. The highest numbers were from Germany (n = 632; 58.8 %) and France (n = 167; 15.5 %), while Belgium had the smallest number (n = 27; 2.5 %).

The demographics were similar across countries. For the overall study population, the mean age at F-DRE diagnosis (Index date 2) was 52.5 years, and the majority (54.1 %) were female (ranging from 51.6 % in Italy to 63.0 % in Belgium). When assessed by country, participants from the UK had the youngest mean ± SD age at F-DRE diagnosis (49.0 ± 16.5 years) versus Italy, which had the highest (54.4 ± 18.6 years).

The median (Q1–Q3) follow-up time from first diagnosis (Index date 1) to the end of follow-up ranged from 81.3 (53.3–107.0) months in France to 111.5 (61.3–120.5) months in Spain (Table 1), with a mean value of 95.5 months across all countries. The overall mean follow-up time from F-DRE diagnosis (Index date 2) until the end of follow-up was 31.5 months. The overall mean follow-up time from the first epilepsy diagnosis (Index date 1) to F-DRE diagnosis (Index date 2) was 64.0 months, with the most extended median (Q1–Q3) follow-up time of 59.6 (31.5–112.7) months in the UK, and the shortest in France (44.8 [26.0–65.5] months).

After omitting data from incomplete years of 2015 (all countries), 2021 (UK only), and 2022 (all other countries), the frequency of F-DRE diagnosis was relatively consistent across the study period for most countries (Table 1). There was, however, an increase in diagnosis of F-DRE in Germany from 10.4 % in 2016 to 18.2 % in 2021, and a decrease in the UK from 28 % in 2016 to 12.2 % in 2020.

3.2. ASM treatment patterns

Table 2 presents data on the most commonly received ASM treatments on and after the first epilepsy diagnosis, in people with F-DRE for each line of intervention by country.

Levetiracetam and lamotrigine were the most frequently used ASM in all countries (Belgium was excluded from the analysis due to masking) (Table 2).

For first-line treatment, levetiracetam was the most commonly used ASMs in France (n = 22; 13.2 %), Italy (n = 15; 16.5 %), and Germany (n = 146; 23.1 %), and was first equal with oxcarbazepine in Spain (7 each; 13.7 %). Lamotrigine was the second choice for first-line treatment in France (n = 20; 12.0 %), Germany (n = 83; 13.1 %), and Spain (n = 6; 11.8 %), while in Italy, this was carbamazepine and valproate (n = 9 each; 9.9 %). In the UK, the most commonly used regimens in the first two lines of treatment were lamotrigine (n = 31; 29.0 %) and carbamazepine (n = 19; 17.8 %).

Valproate continued to be used most often in Italy and in Germany, where it was the third most common first-line treatment (n = 59; 9.3 %). Valproate was also the third most common third-line treatment in the UK (n = 6; 5.6 %).

After the failure of monotherapy, combination treatment with ASMs

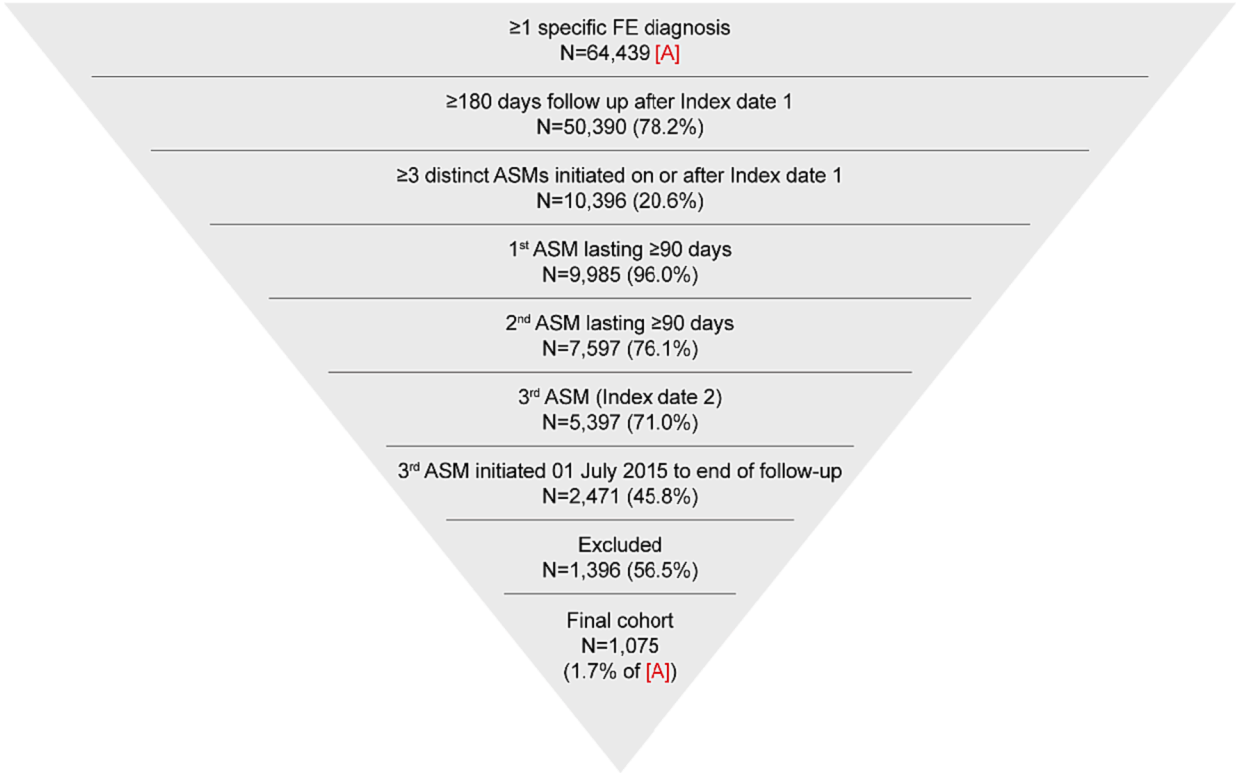

Fig. 2. Flow-chart for the identification of individuals with F-DRE. Abbreviations: ASM = Antiseizure medication; F-DRE = focal drug-resistant epilepsy; FE = Focal epilepsy. Index date 1 = Epilepsy diagnosis Index date 2 = F-DRE diagnosis.

Table 1
Demographics and clinical characteristics of individuals with F-DRE (all countries).

Demographics	Belgium	Spain	Italy	France	UK	Germany
	(n = 27)	**(n = 51)**	**(n = 91)**	**(n = 167)**	**(n = 107)**	**(n = 632)**
Age at Index date 2 (years)						
Mean (SD)	51.4 (15.7)	50.7 (19.1)	54.4 (18.6)	51.2 (15.5)	49.0 (16.5)	53.3 (18.8)
Min–Max	23–91	20–89	20–91	21–89	21–91	18–99
Sex, n (%)						
Male	10 (37.0)	22 (43.1)	33 (36.3)	62 (37.1)	46 (43.0)	295 (46.7)
Female	17 (63.0)	29 (56.9)	47 (51.6)	91 (54.5)	61 (57.0)	337 (53.3)
Missing	–	–	11 (12.1)	14 (8.4)	–	–
Time from Index date 1 to the end of follow-up (months)						
Mean (SD)	89.4 (28.6)	95.2 (31.9)	95.1 (30.1)	78.2 (31.0)	111.3 (65.9)	97.8 (60.0)
Median (Q1–Q3)	94.2 (59.4–114.4)	111.5 (61.3–120.5)	107.6 (68.6–121.2)	81.3 (53.3–107.0)	96.3 (62.1–144.0)	86.9 (51.8–129.4)
5th–95th percentile	46.1–120.6	38.4–121.4	40.5–123.1	24.9–119.3	29.7–255.0	23.5–209.2
Time from Index date 2 to the end of follow-up (months)						
Mean (SD)	34.5 (22.1)	39.0 (25.3)	38.0 (23.2)	30.8 (22.7)	29.5 (19.3)	30.4 (22.0)
Median (Q1–Q3)	31.4 (18.0–48.3)	39.9 (15.9–62.2)	35.2 (17.0–60.2)	27.3 (10.2–50.2)	26.9 (13.0–42.9)	24.4 (11.2–47.6)
5th–95th percentile	4.0–71.9	4.3–73.4	4.1–73.1	2.8–68.8	2.9–62.5	3.3–72.3
Interval between Index date 1 and Index date 2 (months)						
Mean (SD)	54.9 (27.4)	56.1 (27.4)	57.1 (25.6)	47.3 (25.7)	81.8 (62.1)	67.4 (55.9)
Median (Q1–Q3)	47.4 (30.0–73.2)	52.7 (41.8–70.6)	56.6 (39.4–71.4)	44.8 (26.0–65.5)	59.6 (31.5–112.7)	50.0 (25.1–95.2)
5th–95th percentile	17.1–100.4	14.5–106.0	15.8–106.0	12.4–95.2	17.3–220.6	11.3–175.5
Year of F-DRE diagnosis**, n (%)						
2015	*	*	9 (9.9)	12 (7.2)	*	29 (4.6)
2016	*	13 (25.5)	17 (18.7)	29 (17.4)	30 (28.0)	66 (10.4)
2017	*	8 (15.7)	20 (22.0)	35 (21.0)	19 (17.8)	87 (13.8)
2018	6 (22.2)	7 (13.7)	13 (14.3)	33 (19.8)	13 (12.2)	96 (15.2)
2019	*	6 (11.8)	12 (13.2)	19 (11.4)	19 (17.8)	110 (17.4)
2020	*	6 (11.8)	11 (12.1)	22 (13.2)	13 (12.2)	110 (17.4)
2021	*	8 (15.7)	8 (8.8)	16 (9.6)	*	115 (18.2)
2022	*	*	*	*	n/a	19 (3.0)

Abbreviations: F-DRE = focal drug-resistant epilepsy; LPD = Longitudinal Patient Database; Max = Maximum; Min = Minimum; n/a = Not applicable; Q1 = First quartile; Q3 = Third quartile; SD = Standard deviation; UK = United Kingdom.
Index date 1 = Epilepsy diagnosis.
Index date 2 = F-DRE diagnosis.
*Suppressed result due to small number of individuals: ≤10 for France and ≤ 5 for the remaining Countries.
**As the study period differed between countries, spanning from 1 July 2015 until May 2021 (UK), January 2022 (Belgium), February 2022 (Italy), March 2022 (Germany and France), and April 2022 (Spain), only half of 2015 and the first few months of 2021 (UK) and 2022 (all other countries) were included in the study period.

Table 2
Top three ASMs by treatment line in each country in individuals with F-DRE.

ASMs	**Spain (n = 51)**			**Italy (n = 91)**			**France (n = 167)**			**UK (n = 107)**			**Germany (n = 632)**		
	L1	**L2**	**L3**	**L1**	**L2**	**L3**	**L1**	**L2**	**L3**	**L1**	**L2**	**L3**	**L1**	**L2**	**L3**
Carbamazepine				2nd (9)	1st (7)		3rd (13)			2nd (19)					
Lacosamide								2nd (6)							
Lamotrigine	2nd (6)						2nd (20)			1st (31)	2nd (13)	1st (14)	2nd (83)	2nd (35)	2nd (26)
Levetiracetam	1st (7)			1st (15)			1st (22)	1st (9)		3rd (18)	1st (16)	2nd (10)	1st (146)	1st (50)	1st (36)
Oxcarbazepine	1st (7)														
Valproate				2nd (9)								3rd (6)	3rd (59)		
Lacosamide + levetiracetam														3rd (23)	3rd (24)
Lamotrigine + levetiracetam											3rd (11)	3rd (6)			

Abbreviations: ASMs = Anti-seizure medications; F-DRE = focal drug-resistant epilepsy; L = Line; UK = United Kingdom.
Notes: Due to the masking of small numbers, Belgium is not shown in the table, results are missing in some of the columns, and the number of individuals receiving other ASMs were excluded from the table. 1st, 2nd, and 3rd refer to the first, second, and third most common ASM therapy. The number of individuals receiving monotherapy or combination therapy is shown in parentheses.

was noted in Germany and the UK. Lacosamide with levetiracetam was the third most used ASM combination in Germany as second-line (n = 23; 3.6 %) and third-line (n = 24; 3.8 %) treatments, while lamotrigine and levetiracetam was the third most used ASM combination in the UK as second line (n = 11; 10.3 %) and third line (n = 6; 5.6 %) treatments.

3.3. ASM treatment response

Results from the exploratory analysis of ASM treatment failure showed that the median (Q1–Q3) time from epilepsy diagnosis (Index date 1) to the first ASM regimen failure ranged from 5.9 (4.2–10.2)

months in France to 12.6 (5.8–20.4) months in Spain, while the median (Q1-Q3) time from diagnosis (Index date 1) to the second ASM regimen ranged from 15.3 (10.9–24.48) months in France to a 33.2 (21.0–60.0) months in the UK (Table 3).

Overall, the median (Q1–Q3) time from the second ASM regimen initiation until failure had a shorter duration in Belgium, Spain, and the UK compared with the median time from the first ASM regimen initiation until failure, whereas the duration of the second ASM regimen was longer than the first ASM regimen in France but was of a similar length in Italy and Germany (Table 3).

For all countries, the median time from epilepsy diagnosis to the date of first seizure record was not reached, and there was a median of 0 seizures per individual per year between Index date 1 and the end of follow-up.

Most people across countries had at least one 12-month seizure-free period between epilepsy diagnosis and end of follow-up (Spain 94.1 %; France 99.4 %; all other countries 100.0 %).

3.4. Clinical characteristics of people with F-DRE

Clinical characteristics of participants are shown in Table 4. Psychiatric disorders, which ranged from 16.2 % in France to 59.3 % in Belgium, were the most common comorbidity across all countries (n = 359; 33.4 %) except for Spain, where cardiovascular and metabolic disorders had a similar prevalence (both 17.7 %).

Depression (n = 287; 26.7 %) and anxiety (n = 127; 11.8 %) were the most frequently reported psychiatric disorders overall, despite low values (≤5) masking the frequency of anxiety reported in Spain and Italy. In Italian (28.6 % vs ≤ 5.5 %) and German participants (32.8 % vs 13.0 %), depressive disorder was more common than anxiety, whereas depression and anxiety were represented more uniformly in Belgium, France, and the UK. Bipolar affective disorder and psychosis were also higher in German participants than in all other countries.

Intellectual disability (n = 86; 13.61 %) and neurodevelopmental disorders (n = 151; 23.9 %) were more common in German participants, with low numbers reported in all other countries except in Belgium, where none were diagnosed with intellectual disability. In Germany, a total of 6 (1.0 %) participants had autism, whilst 147 (23.3 %) had 'other' neurodevelopmental disorders.

Cardiovascular and metabolic disorders (most commonly type 2 diabetes) were reported in all included countries, ranging from ≤ 10 individuals in France to 22.2 % (n = 6) in Belgium. Specifically, type 2 diabetes was reported as a comorbidity in 13.7 % (n = 7) of participants in Spain, 8.8 % (n = 8) in Italy, 7.5 % (n = 8) in the UK, and 7.0 % (n = 44) in Germany.

Cerebrovascular disorders, such as stroke, were reported in 149 (23.6 %) individuals in Germany.

Somatic autoimmune disorders were more common in Italy (n = 7; 7.69 %) and Germany (n = 17; 2.69 %), with numbers masked in all other countries.

Migraine, dementia, and malignancy were other reported comorbidities. Malignancy was the most common of these comorbidities across the countries, ranging from 7.2 % (n = 12) in France to 15.7 % (n = 8) in Spain, with numbers masked in Belgium. Migraine was reported in 8.4 % (n = 9) in the UK and 6.0 % (n = 38) in Germany, while dementia was reported in 7.4 % (n = 47) of the German study population.

3.5. HCRU and frequencies of head trauma and fractures

There were generally more GP or specialist consultations post Index date 2 (i.e., F-DRE diagnosis) than post Index date 1 (i.e., epilepsy diagnosis) in most countries, except in France, where specialist consultations were less frequent post Index date 2 than post Index date 1, in Belgium where the mean (SD) number of GP consultations were similar, and in the UK where the mean (SD) number of GP referrals (to any specialist type) were comparable (Supplementary Table S2). Participants from Spain had the most GP/Specialist consultations in the 1-year post Index date 1 and 2 compared with people in other countries; GP/Specialist consultations were also high in Italy and Germany.

For most countries, a median of two ASMs were prescribed in the first-year post-Index date 1 and post-Index date 2, except for Spain and the UK where a median of 1 ASM post-Index date 2 was reported.

Hepatic and renal function tests were the most common investigations (Supplementary Table S3). In Belgium and Germany, people underwent blood screens (i.e., hepatic function, renal function) mainly after epilepsy diagnosis (Index date 1). In contrast, these investigations were mostly after F-DRE diagnosis (Index date 2) in Italy, Spain, and the UK. France had the lowest number of individuals having any blood screens.

Reports of head trauma following F-DRE diagnosis were poorly reported across all countries, but fractures were more common, particularly amongst people in Italy (21.4 %) and Spain (15.2 %) (Supplementary Table S4).

4. Discussion

With over 1,000 participants across six European countries, this study sought to generate evidence to describe people diagnosed with F-DRE. It provides a snapshot of the epilepsy treatments, including ASM regimens used in different countries and their commonalities, comorbidities, and HCRU outcomes.

Similar demographics were seen across the six participating countries. In the overall study cohort, the mean age at F-DRE diagnosis aligned with previously available evidence [18,20,21]. In particular, a study of US veterans with DRE reported a mean age of 58.3. At the same time a retrospective analysis of an Italian population found a mean age of 53 years for people with F-DRE [20,21]. The Italian study also reported a similar sex distribution, with 57 % females. In our study, the prevalence of females was reported for the whole cohort; within the Italian subgroup, the female proportion was 51.6 % [20].

We report that the prevalence of F-DRE in 2021 ranged from 8.8 % in Italy and 18.2 % in Germany. This is comparable to the prevalence of 13.7 % for DRE, highlighted by a systematic review of community-based populations, indicating the reliability of the data in our source databases [18]. Another study underlined the significant heterogeneity in DRE prevalence among studies, reflecting the high variation in the different cohorts in our study.

For most people with F-DRE, epilepsy was not an isolated diagnosis, and at least one comorbidity was found. Comorbidities have been frequently described in people with epilepsy as factors that strongly

Table 3
Median (Q1–Q3) time interval in months to ASM treatment failure in individuals with F-DRE (all countries).

	Belgium	Spain	Italy	France	UK	Germany
Index date 1 to 1st ASM regimen failure	10.5 (3.9–20.5)	12.6 (5.8–20.4)	12.2 (5.7–24.1)	5.9 (4.2–10.2)	12.0 (7.3–25.1)	10.4 (5.9–26.6)
Index date 1 to 2nd ASM regimen failure	19.2 (10.9–24.1)	26.7 (16.8–43.8)	25.8 (15.3–37.6)	15.3 (10.9–24.5)	33.2 (21.0–59.6)	21.8 (13.8–47.5)
1st ASM regimen: initiation to failure	6.6 (3.6–9.4)	10.0 (5.3–19.3)	6.9 (4.2–19.0)	5.1 (3.7–7.8)	10.3 (5.6–19.9)	5.5 (3.4–9.3)
2nd ASM regimen: initiation to failure	4.8 (3.8–7.1)	8.5 (4.6–14.4)	6.5 (4.5–15.2)	5.9 (3.9–10.6)	9.6 (5.1–23.2)	5.6 (3.7–9.9)

Abbreviations: ASM = Anti-seizure medications; F-DRE = focal drug-resistant epilepsy; Q1 = First quartile; Q3 = Third quartile; UK = United Kingdom.
Notes: These results may be affected by immortal time bias (due to the way the Index date is defined) and possible underreporting of seizure events.

Table 4
Presence of comorbidities in individuals with F-DRE (all countries).

Comorbidity, n (%)	Belgium (n = 27)	Spain (n = 51)	Italy (n = 91)	France (n = 167)	UK (n = 107)	Germany (n = 632)
Psychiatric disorders						
Any	16 (59.3)	9 (17.7)	31 (34.1)	27 (16.2)	30 (28.0)	246 (38.9)
Depression	10 (37.0)	7 (13.7)	26 (28.6)	15 (9.0)	22 (20.6)	207 (32.8)
Anxiety	10 (37.0)	*	*	17 (10.2)	18 (16.8)	82 (13.0)
Bipolar affective disorder	*	0 (0)	*	*	*	7 (1.1)
Psychosis	*	0 (0)	*	*	0 (0)	28 (4.4)
Intellectual disability						
Yes	0 (0)	*	*	*	*	86 (13.6)
No	27 (100.0)	45–50 (*)	85–90	161–166	100–105	546 (86.4)
Neurodevelopmental disorders						
Any	*	*	*	*	*	151 (23.9)
ADHD	*	*	*	*	*	*
Autism	*	*	*	*	*	6 (1.0)
Other	*	*	*	*	*	147 (23.3)
Cardiovascular and Metabolic Disorders						
Any	6 (22.2)	9 (17.7)	12 (13.2)	*	11 (10.3)	67 (10.6)
Type 2 diabetes	*	7 (13.7)	8 (8.8)	*	8 (7.5)	44 (7.0)
Ischemic heart disease	*	*	6 (6.6)	*	*	38 (6.0)
Cerebrovascular disorders						
Stroke	*	*	*	*	*	149 (23.6)
Somatic autoimmune disorders						
Any	*	*	7 (7.7)	*	*	17 (2.7)
Type 1 diabetes	*	*	*	*	*	*
SLE	*	*	0 (0)	*	*	0 (0)
Myasthenia gravis	*	*	0 (0)	*	*	0 (0)
Coeliac disease	*	*	*	*	*	0 (0)
RA	*	*	*	*	*	6 (1.0)
Multiple sclerosis	*	*	*	*	*	8 (1.3)
Other						
Dementia	*	*	*	*	*	47 (7.4)
Malignancy	*	8 (15.7)	12 (13.2)	12 (7.2)	9 (8.4)	73 (11.6)
Migraine	*	*	*	*	9 (8.4)	38 (6.0)

Abbreviations: ADHD = Attention deficit hyperactive disorder; F-DRE = focal drug-resistant epilepsy; n = Number; RA = Rheumatoid arthritis; SD = Standard deviation; SLE = Systemic lupus erythematous; UK = United Kingdom.
[†]Index date 2 = F-DRE diagnosis.
*Suppressed result due to small number of individuals: ≤10 relative to France and ≤ 5 for the remaining Countries.

correlate with DRE. Neurological issues are among the predictors of DRE [18]. Psychiatric comorbidities were the most common, with depression and anxiety predominant. These disorders had a similar prevalence everywhere except for Germany and Italy, where depression was more prevalent than anxiety.

Our results support the evidence showing a high comorbidity burden in people with epilepsy, with highly prevalent anxiety and mood disorders, with figures for each condition reported in at least a fifth of our cohort, which may still be underestimated [22]. In comparison, the prevalence of anxiety and depression in the global population is much lower (<5%) [23,24].

Almost a quarter of the German participants had cerebrovascular diseases, whereas low values may obscure an exact estimate of stroke frequency in other countries. German participants also had higher levels of intellectual disability, neurodevelopmental disorders, and dementia. This could be partly due to differences in the population and the variations in healthcare practices across different countries. Some individuals with learning disabilities, dementia or stroke do not typically seek consultation from epilepsy specialists. It is already recognised that epilepsy is highly prevalent in people with intellectual disabilities, especially where these are more severe [25]. At the same time, age-related and ageing-related epileptogenic conditions, such as stroke and dementia, are also associated with seizures [26].

Somatic comorbidities seem less common than psychiatric disorders, but some, such as type 2 diabetes and malignancy, were also observed among participants. Indeed, epilepsy is associated with a higher risk of diabetes, somatic autoimmune disorders, and malignancy, predominantly primary brain tumours and brain metastases [27–30]. All these comorbidities negatively influence the quality of life of people with epilepsy and represent an increased mortality risk [21].

The bidirectional interaction between epilepsy and comorbidities has several implications. Early identification and treatment of comorbidities that might develop in people with epilepsy may improve clinical outcomes and reduce disease burden by enhancing quality of life and reducing need for HCRU [5,7]. Ideally, comorbidities should be an integral part of medical management and drive the choice of ASMs [31]. Treatment of comorbidities should consider the risk of seizures, whilst epilepsy treatment may also worsen existing comorbidities. Pharmacokinetic interactions between ASMs and other drugs may also interfere with optimal dosing [32,33].

Significant variability in ASM regimens used in the different lines of treatment was seen across national boundaries. Lamotrigine and levetiracetam were the most common monotherapies given as first-line treatments across different countries, with carbamazepine still used in such role in Italy and the UK. This was in line with approved treatment guidelines [8,9,34–36]. Levetiracetam is a main first-line treatment in a US study [21]. In our study, levetiracetam appears not commonly used in the UK as the first option. We cannot explain such a result. This may be down to physician preferences, which may be influenced by the results of the SANAD II study conducted in the UK, not supporting levetiracetam as a first-line treatment for focal epilepsy [37].

Valproate continued to be used in first-line treatment in Italy and Germany despite the increased risk of teratogenicity and child neurodevelopmental disorders after prenatal exposure [38]. In contrast, it is only used as a third-line treatment in the UK and is not reported to be used in the first three lines in Spain and France. These data support the evidence reporting a decreased drug use in France, Scotland, and Serbia in the last 20 years [39–41].

The median time of ASM failure was variable across the countries, and we cannot describe a common pattern. ASM retention is also a well-recognised measure of effectiveness as a combination of efficacy and tolerability [42]. This has formed the basis of the outcome measures in studies such as SANAD and remains a measure of pragmatic studies of the comparative effectiveness of ASMs [43–45].

In the countries analysed, we found that the start of treatment followed the diagnosis with variable delay. We defined the first index date as the first record of a diagnosis found in the database. One of the study objectives was a description of the treatment patterns, and some delay between diagnosis and treatment initiation was possible.

ASM treatment outcomes were generally less favourable amongst people in the French cohort and best amongst people in the UK; however, this evaluation is deduced only by treatment duration. The longer (33.2 months) treatment duration reported in the UK compared to France (15.3 months) may indicate continued use in the UK, early switching in France, or both alternatives. Results were broadly comparable across countries; more than 94 % of participants had at least one 12-month seizure-free period between epilepsy diagnosis and the end of follow-up.

Specialist and GP consultations were uncommon across most countries for epilepsy and DRE diagnosis. There were generally more consultations post-F-DRE diagnosis than post-epilepsy diagnosis. People with F-DRE in Spain had the most GP consultations across both periods compared with those in other countries. Germany and Spain had a similar number of specialist consultations, whereas in France it was slightly less. Specialist consultations were not available for Belgium, Italy, and the UK. Seeking specialist consultation is likely to be implemented overall. It has been reported that full care is associated with lower mortality [21].

The most common laboratory investigations were hepatic and renal function tests, and in Belgium and Germany, these tests were conducted mainly after epilepsy diagnosis, while in Italy, Spain, and the UK, they were mainly after F-DRE diagnosis. Even though blood screenings are not mandatory for diagnosing epilepsy and DRE, they are indicated for a better definition of the clinical situation, particularly adverse effects [46]. There is still poor information on tests performed on people with F-DRE. Our findings confirm the need for comprehensive information for treatment management.

Across all countries, records of head trauma following F-DRE diagnosis were rare, but fractures were more commonly observed in the Spanish and Italian study populations.

Management of F-DRE represents a substantial economic burden on healthcare systems. The socioeconomic consequences of DRE are also prevalent in developing countries and adversely affect personal finances, education, employment, and marital prospects [47].

4.1. Limitations

A critical study limitation was the complexity of identifying people with F-DRE from EMR databases. The case definition relied on combining diagnostic codes with ASM treatment and seizure records to determine F-DRE, which could have missed actual F-DRE cases or erroneously identified others.

The low number of recorded seizures was due to the nature of the data collected in the databases. When recording seizures in GP/primary care practice, it is expected that this may be under-recorded where seizures are mild and/or occurring in a home/hospital setting. In contrast, hospital data more accurately reports seizure numbers, head trauma, and fractures. In some cases, seizure freedom may result from an incomplete recording since seizures that do not require a consultation with a GP/specialist are likely underreported in the databases. Hospital data, including the treatments and surgeries conducted in the hospital setting, are not recorded in primary care databases. As such, the first epilepsy diagnosis would be only subsequently reported if given in a hospital setting, resulting in a delayed recording.

Similarly, diagnostic tests and procedures (video electroencephalography, electroencephalography, electrocardiography, blood pressure monitoring, MRI brain scan, CT scan, tilt test, polysomnography) performed when individuals are referred to the hospital or specialised centres are not reported in primary care databases and were available for the analysis. The primary care database mainly reports blood test results.

Results showing time from first regimen initiation to treatment failure should be interpreted cautiously, as treatment discontinuation was used as a proxy for regimen failure. The treatment discontinuation rate may be overestimated due to misinterpreting prescription gaps longer than 90 days.

We did not control HCRU for comorbidities with a comprehensive and validated comorbidity scales (Elixhauser/Charlson) to assess whether epilepsy per se leads to increased HCRU or whether it is the comorbidity driving such changes. Thus, an evaluation of the overall health state of the individual was not performed. Comorbidities were evaluated only at a one-time point, i.e., before or on F-DRE diagnosis. Assessing HCRU following a diagnosis of F-DRE may yield limited meaningful results, primarily due to the small sample sizes in most countries. Where data is available, the specialist responsible for HCRU assessment is typically a neurologist, given the nature of the condition.

An analysis on pooled results was not planned and performed due to the heterogeneity of the information available across the six countries, given the different healthcare systems. The aim of our work was to report and highlight the existing differences among the countries and to look at the range of different outcomes. A pooled analysis would have led to a loss of information on the details of each area. Results refer to data collected and cannot be generalized to the entire population of each country.

5. Conclusion

We attempted to understand better the burden of illness and treatment patterns of people with F-DRE. Our results show no one-size-fits-all approach in the appropriate selection of ASM, and the drug's potential risks and possible benefits must be individually considered. Identifying and considering comorbidities must be an integral part of the management and should influence ASM choice. Our findings may generate valuable information on actual treatment practices and features of people with F-DRE at the primary and specialist care levels, which may support future treatment recommendations and improvements in clinical care.

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7. Declaration of financial/other relationships

JWS or his department has received grants from Esai, and UCB Pharma. He has received personal compensation for serving on the Advisory Boards or Speaker's Bureau for UCB, and Angelini.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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