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Research Article

Burden of Episodic and Chronic Migraine in Patients Who Had Failed Multiple Preventive Treatments From France, Spain, and the United Kingdom

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Objectives: Migraine affects more than 80 million people in Western Europe. The present study evaluated disability and health-related quality of life (HRQoL) among patients with episodic migraine (EM) and chronic migraine (CM) who had failed multiple preventive treatments.
Materials and Methods: This study was an analysis of cross-sectional, web-based survey data from adult patients with migraine (EM and CM) from the United Kingdom, France, and Spain who had self-reported failure of two or more preventive treatments. Patient characteristics and patient-reported HRQoL, migraine-related disability, healthcare resource use (HCRU), and burden of migraine were evaluated by classification (CM and EM) and country (EM only).
Results: In this sample of 316 patients (United Kingdom, $n = 106$; Spain, $n = 105$; France, $n = 105$), 76 (24.1%) patients had CM, the mean (standard deviation [SD]) age was 39.5 (12.3) years, and 164 (51.9%) patients were female. Those patients with CM reported greater migraine-related disability based on Migraine Disability Assessment (MIDAS) scores versus those with EM (mean [SD]: 43.8 [44.7] vs. 23.2 [28.3]), as well as greater pain-related impact on daily activities and higher HCRU. Among patients with EM, MIDAS scores indicated disability was severe in Spain (mean [SD]: 31.6 [31.1]) and France (24.3 [31.1]) and moderate in the United Kingdom (13.8 [17.9]), while HRQoL was similar across countries. Regarding the burden of EM, higher levels of pain and symptom-related interference with many aspects of life, including occupational functioning, were reported in the United Kingdom and Spain versus France.
Conclusions: Migraine is associated with substantial disability and decreased HRQoL among patients who have failed previous preventive therapies. Although migraine burden varied by country, the results suggest high unmet needs in all countries. Appropriate treatment could reduce migraine-related burden and HCRU among patients with difficult-to-treat migraine.

Keywords: burden of disease; migraine; real-world evidence

1. Introduction

Migraine affects more than one billion individuals globally [1], including more than 80 million in Western Europe [1], and carries significant disability, ranking as the second leading cause of years lived with disability worldwide [2]. Migraine is a complex neurological disease with a significant negative impact on almost all aspects of a patient's life [1, 3–9].

Migraine negatively affects patients' health-related quality of life (HRQoL), including their ability to perform day-to-day activities and their mental and emotional well-being [10–12]. Patients have also reported that migraine affects their professional lives, social lives, and relationships [4]. Migraine is associated with increased healthcare resource use (HCRU), including visits to healthcare providers (HCPs) and the emergency room (ER) [12], which are associated with substantial healthcare costs. As of 2012, the estimated total annual cost of migraine across Europe was €111 billion, including both direct and indirect costs [13]. Migraine is also associated with an increased risk of sleep disorders, mood disorders, and cardiovascular disease, and the presence of such comorbidities may be associated with more frequent and severe migraine attacks, greater headache-related disability, and an increased risk of migraine progression [14–18].

The burden of migraine generally increases with increasing frequency of headache days [11, 12], and the estimated annual prevalence of progression from episodic migraine (EM; <15 headache days/month) to chronic migraine (CM; ≥ 15 headache days/month, including ≥ 8 days with migraine, for >3 months) [19] is approximately 2.5% [20]. Individuals with CM typically experience a greater impact on their daily activities and poorer HRQoL and incur greater HCRU and direct medical costs [7] compared with those experiencing EM.

Migraine preventive treatments are used to reduce the frequency, severity, and duration of attacks among those with significant headache burden [21]. Preventive treatment is generally considered for patients with attacks that impair quality of life on two or more days per month that are not prevented by optimal acute therapy [22]. The updated 2022 European Headache Federation (EHF) guidelines recommend that monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway (erenumab, fremanezumab, or galcanezumab) be considered as first-line treatment options in patients requiring migraine preventive treatment [23]. However, in clinical practice, patients generally do not receive CGRP pathway–targeting mAbs until after multiple prior migraine preventive treatment failures.

The World Health Organization has identified further elucidation of the impact and burden of migraine as an urgent public health priority [24]. The large, survey-based epidemiological studies evaluating the burden of migraine employ varied methodologies, which make comparisons between studies difficult. These studies do not routinely evaluate differences in the HRQoL impact and burden of migraine among patients who have failed multiple prior treatments by migraine classification (i.e., EM vs. CM) or country [4, 11, 12, 25–28]. Given the disconnect between the current EHF guidelines and typical use in clinical practice for CGRP pathway–targeting mAbs [23], a comprehensive understanding of the ongoing burden and impact of migraine in patients across multiple European countries would be valuable to inform decisions around migraine preventive treatment options for HCPs and decision-makers. Thus, this study evaluated migraine characteristics and patient-reported HRQoL and migraine-related disability among EM and CM patients who had failed two or more migraine preventive treatments in a real-world setting in the United Kingdom, France, and Spain.

2. Materials and Methods

2.1. Study Design. This study was an analysis of cross-sectional, web-based survey data from migraine patients (EM and CM) from the United Kingdom, France, and Spain. Patients were recruited from verified online consumer panels: Lightspeed Health, a market research operations company specializing in healthcare audiences, and EMI Research Solutions, a sample agency with access to a wide variety of audiences. This retrospective database study combined with a cross-sectional direct-to-patient web survey did not require ethical regulatory submission. The investigated databases had been approved by local regulatory authorities and comply with patients' data requirements. Patients were included in the study if they were ≥ 18 years of age; resided in the United Kingdom, France, or Spain; were able to read and write the local language; reported a confirmed CM or EM diagnosis from a HCP; reported that they were currently taking a migraine preventive treatment; self-reported failure of two or more prior migraine preventive treatments from different classes; and provided informed consent to participate.

After providing informed consent, patients were asked to complete an approximately 25-min questionnaire administered in their local languages; translation to English was provided by GlobaLexicon, London, United Kingdom. This web-based survey was created by the Kantar Health (New York, NY, United States) programming team using Sawtooth software (Sawtooth Software Inc.; Provo, UT, United States) for web-based survey programming.

2.2. Demographics. The following demographic and health characteristic data were collected: migraine classification, migraine diagnosis history, prescription medication usage, age, sex, marital status, employment status, level of education, annual household income category, location (e.g., urban or rural), insurance type, height, and weight. Data on comorbidities were collected and used to calculate the Charlson Comorbidity Index (CCI) score [29]. An additional description of the CCI has been presented in the Supporting Information section.

2.3. Variables. Patient-reported HRQoL, migraine-related disability, HCRU, and burden of migraine were evaluated in this study. Descriptions of the assessments of HRQoL (assessed using EuroQol 5-Dimension 5-Level [EQ-5D-5L]) [30], migraine-related disability (assessed using Migraine Disability Assessment [MIDAS]) [31], and migraine-related burden (a 38-item questionnaire covering diagnosis and treatment history, HCRU, and migraine-related impacts and perceptions) are presented in the Supporting Information section.

2.4. Statistical Analyses. No power analyses were conducted; the population sample size was based on the number of patients who could be recruited. Descriptive statistics calculated the means, standard deviations (SDs), and medians for continuous variables and counts and percentages of patients

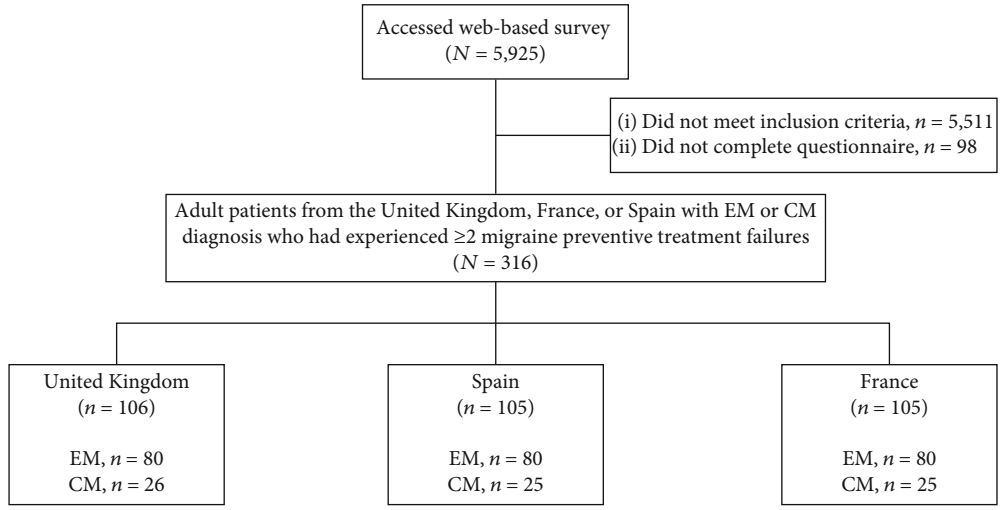


Figure 1: Study population. CM, chronic migraine; EM, episodic migraine.

in each category for categorical variables. Stratified analyses were conducted by migraine classification (based on headache days in the past month; EM [4–14 headache days] or CM [≥15 headache days]) and by country among patients with EM. Due to sample size limitations of the CM cohort, country-level differences in CM burden could not be analyzed.

3. Results

3.1. Migraine Patient Demographics. The total sample size for this study was 316 patients (EM, $n = 240$; CM, $n = 76$); 106 patients (EM, $n = 80$; CM, $n = 26$) were from the United Kingdom, and 105 (EM, $n = 80$; CM, $n = 25$) each were from France and Spain (Figure 1). Demographic characteristics for the EM and CM cohorts of the overall study population are summarized in Table 1(a), and demographics for patients with EM by country are summarized in Table 1(b). A lower proportion of patients with EM than with CM were women (48% [116/240] vs. CM, 63% [48/76]), and a higher proportion of patients with EM were employed full-time (70.4% [169/240] vs. CM, 56.6% [43/76]).

Compared with France and Spain, a lower proportion of patients with EM were women in the United Kingdom (35% [28/80] vs. Spain, 51% [41/80] and France, 59% [47/80]). The mean (SD) age was lower in the United Kingdom (38.93 [9.89] years) and Spain (37.94 [11.32] years) than in France (41.14 [15.04] years), and a higher proportion of patients were employed full-time in the United Kingdom (87.5% [70/80]) and Spain (70.0% [56/80]) versus France (53.8% [43/80]).

Comorbidity data are displayed in Table S1A by migraine classification, and among patients with EM by country in Table S1B. The EM cohort more frequently endorsed having ≥3 comorbidities on the CCI compared with the CM cohort (22.9% vs. 18.4%). A greater proportion of patients in the United Kingdom endorsed having ≥3 comorbidities (28.8% [23/80]) compared with France (22.5% [18/80]) and Spain (17.5% [14/80]).

3.2. Migraine Classification and Treatment History. The mean (SD) average number of days per month with headache was 6.5 (3.3) days for patients with EM and 19.2 (4.2) days for patients with CM. Compared with patients with EM, patients with CM were younger on average when they first experienced migraine (mean [SD]: CM, 20.8 [11.8] years; EM, 23.1 [11.1] years) and were diagnosed with migraine (CM, 24.2 [11.7] years; EM, 24.8 [10.2] years).

Among patients with EM, those in Spain reported being younger upon first experiencing and being diagnosed with migraine (mean [SD]: 21.0 [10.9] and 22.5 [10.0] years, respectively) compared with the United Kingdom (23.4 [9.5] and 25.6 [10.2] years, respectively) and France (24.8 [12.5] and 26.5 [10.4] years, respectively). The mean (SD) number of days per month with headaches was similar across the three countries (Spain, 6.6 [3.4]; France, 6.3 [3.3]; United Kingdom, 6.5 [3.3]).

Daily oral preventive prescription medication use was reported by a greater proportion of patients with CM (98.7% [75/76]) compared with EM (93.8% [225/240]) (Table S2A). Compared with their peers with CM, a greater proportion of patients with EM reported treatment via injections (EM, 31.3% [75/240] vs. CM, 25.0% [19/76]), nerve blocks (EM, 25.4% [61/240] vs. CM, 23.7% [18/76]), external stimulators (EM, 24.6% [59/240] vs. CM, 15.8% [12/76]), implanted stimulators (EM, 15.8% [38/240] vs. CM, 9.2% [7/76]), and past other forms of surgery (EM, 11.3% [27/240] vs. CM, 5.3% [4/76]).

The proportion of patients with EM who reported prior or current daily oral preventive prescription medication use was comparable across countries (United Kingdom, 97.5% [78/80]; France, 95.0% [76/80]; Spain, 88.8% [71/80]) (Table S2B). However, a greater proportion of patients in the United Kingdom compared with Spain and France endorsed treatment via injections (United Kingdom, 50.0% [40/80]; Spain, 26.3% [21/80]; France, 17.5% [14/80]), nerve blocks (United Kingdom, 41.3% [33/80]; Spain, 25.0% [20/80]; France, 10.0% [8/80]), external stimulators (United Kingdom, 41.3% [33/80]; Spain, 12.5% [10/80];

Table 1: Demographic and migraine characteristics by migraine classification (a) and among EM patients by country (b).

(a)

	CM ($n = 76$)	EM ($n = 240$)	Entire study sample ($N = 316$)
Number of days per month you have headaches (SD)	19.20 (4.22)	6.48 (3.33)	9.54 (6.50)
Age first experienced migraine (year) (SD)	20.80 (11.82)	23.06 (11.12)	22.52 (11.31)
Age when diagnosed with migraine (year) (SD)	24.15 (11.67)	24.77 (10.24)	24.62 (10.59)
Sex, *n* (%)			
Male	28 (36.8)	124 (51.7)	152 (48.1)
Female	48 (63.2)	116 (48.3)	164 (51.9)
Age (year) (SD)	40.20 (12.13)	39.33 (12.30)	39.54 (12.25)
Marital status, *n* (%)			
Single, never married	13 (17.1)	39 (16.3)	52 (16.5)
Living with partner	16 (21.1)	45 (18.8)	61 (19.3)
Married	42 (55.3)	138 (57.5)	180 (57.0)
Divorced	3 (3.9)	10 (4.2)	13 (4.1)
Separated	1 (1.3)	5 (2.1)	6 (1.9)
Widowed	0 (0.0)	2 (0.8)	2 (0.6)
Prefer not to answer	1 (1.3)	1 (0.4)	2 (0.6)
Current work situation, *n* (%)			
Employed full-time	43 (56.6)	169 (70.4)	212 (67.1)
Employed part-time	13 (17.1)	21 (8.8)	34 (10.8)
Homemaker	4 (5.3)	9 (3.8)	13 (4.1)
Retired	3 (3.9)	16 (6.7)	19 (6.0)
Student	3 (3.9)	14 (5.8)	17 (5.4)
Long-term or short-term disability	6 (7.9)	5 (2.1)	11 (3.5)
Not employed and looking for work	3 (3.9)	4 (1.7)	7 (2.2)
Not employed and not looking for work	1 (1.3)	2 (0.8)	3 (0.9)
Education, *n* (%)			
High school graduate or less	14 (18.4)	31 (12.9)	45 (14.2)
Some college	8 (10.5)	17 (7.1)	25 (7.9)
Graduated college (3- or 4-year degree)	15 (19.7)	86 (35.8)	101 (32.0)
Postgraduate work or graduate degree	26 (34.2)	83 (34.6)	109 (34.5)
Other education beyond high school (business, nursing, technical, etc.)	13 (17.1)	22 (9.2)	35 (11.1)
Prefer not to answer	0 (0.0)	1 (0.4)	1 (0.3)
Income (France and Spain)[a], *n* (%)			
< €15,000	9 (18.0)	25 (15.6)	34 (16.2)
€15,000–€27,999	13 (26.0)	43 (26.9)	56 (26.7)
€28,000–€54,999	15 (30.0)	64 (40.0)	79 (37.6)
€55,000–€74,999	4 (8.0)	20 (12.5)	24 (11.4)
≥ €75,000	6 (12.0)	6 (3.8)	12 (5.7)
Income (United Kingdom), *n* (%)			
< £15,000	2 (7.7)	5 (6.3)	7 (6.6)
£15,000–£27,999	8 (30.8)	11 (13.8)	19 (17.9)
£28,000–£54,999	10 (38.5)	23 (28.8)	33 (31.1)
£55,000–£74,999	3 (11.5)	30 (37.5)	33 (31.1)
≥ £75,000	3 (11.5)	11 (13.8)	14 (13.2)

Table 1: Continued.

	CM ($n = 76$)	EM ($n = 240$)	Entire study sample ($N = 316$)
Location where you live, *n* (%)			
Major metropolitan area (population, > 500,000)	20 (26.3)	93 (38.8)	113 (35.8)
Urban area (population, 100,000–500,000)	18 (23.7)	57 (23.8)	75 (23.7)
Suburb of a large city (population, > 100,000)	12 (15.8)	29 (12.1)	41 (13.0)
Small city (population, 30,000–100,000)	11 (14.5)	31 (12.9)	42 (13.3)
Rural or small town (population, < 30,000)	15 (19.7)	30 (12.5)	45 (14.2)
Health insurance, *n* (%)			
Public, without additional private insurance	21 (27.6)	72 (30.0)	93 (29.4)
Public, along with additional private insurance	23 (30.3)	69 (28.8)	92 (29.1)
Private insurance	13 (17.1)	67 (27.9)	80 (25.3)
Aid entitlement and additional private insurance	4 (5.3)	15 (6.3)	19 (6.0)
Other	5 (6.6)	6 (2.5)	11 (3.5)
None of the above	10 (13.2)	11 (4.6)	21 (6.6)
Height (m) (SD)	1.65 (0.22)	1.72 (0.29)	1.70 (0.28)
Weight (kg) (SD)	65.38 (17.89)	68.56 (19.65)	67.78 (19.25)

[a]Do not know or prefer not to answer: CM, 3 (6.0%); EM, 2 (1.3%); total, 5 (2.4%).

(b)

	United Kingdom ($n = 80$)	Spain ($n = 80$)	France ($N = 80$)
Number of days per month you have headaches (SD)	6.54 (3.34)	6.61 (3.41)	6.29 (3.28)
Age first experienced migraine (year) (SD)	23.39 (9.54)	21.00 (10.90)	24.80 (12.52)
Age when diagnosed with migraine (year) (SD)	25.55 (10.15)	22.45 (9.95)	26.46 (10.35)
Sex, *n* (%)			
Male	52 (65.0)	39 (48.8)	33 (41.3)
Female	28 (35.0)	41 (51.3)	47 (58.8)
Age (year) (SD)	38.93 (9.89)	37.94 (11.32)	41.14 (15.04)
Marital status, *n* (%)			
Single, never married	11 (13.8)	10 (12.5)	18 (22.5)
Living with partner	7 (8.8)	23 (28.8)	15 (18.8)
Married	59 (73.8)	40 (50.0)	39 (48.8)
Divorced	1 (1.3)	4 (5.0)	5 (6.3)
Separated	2 (2.5)	1 (1.3)	2 (2.5)
Widowed	0 (0.0)	1 (1.3)	1 (1.3)
Prefer not to answer	0 (0.0)	1 (1.3)	0 (0.0)
Current work situation, *n* (%)			
Employed full-time	70 (87.5)	56 (70.0)	43 (53.8)
Employed part-time	5 (6.3)	7 (8.8)	9 (11.3)
Homemaker	0 (0.0)	1 (1.3)	8 (10.0)
Retired	1 (1.3)	4 (5.0)	11 (13.8)
Student	2 (2.5)	7 (8.8)	5 (6.3)
Long-term or short-term disability	1 (1.3)	1 (1.3)	3 (3.8)
Not employed and looking for work	1 (1.3)	2 (2.5)	1 (1.3)
Not employed and not looking for work	0 (0.0)	2 (2.5)	0 (0.0)

Table 1: Continued.

	United Kingdom ($n = 80$)	Spain ($n = 80$)	France ($N = 80$)
Education, *n* (%)			
High school graduate or less	8 (10.0)	4 (5.0)	19 (23.8)
Some college	5 (6.3)	9 (11.3)	3 (3.8)
Graduated college (3- or 4-year degree)	24 (30.0)	37 (46.3)	25 (31.3)
Postgraduate work or graduate degree	38 (47.5)	20 (25.0)	25 (31.3)
Other education beyond high school (business, nursing, technical, etc.)	4 (5.0)	10 (12.5)	8 (10.0)
Prefer not to answer	1 (1.3)	0 (0.0)	0 (0.0)
Income[b], *n* (%)			
< €15,000	5 (6.3)	13 (16.3)	12 (15.0)
€15,000–€27,999	11 (13.8)	27 (33.8)	16 (20.0)
€28,000–€54,999	23 (28.8)	31 (38.8)	33 (41.3)
€55,000–€74,999	30 (37.5)	6 (7.5)	14 (17.5)
≥ €75,000	11 (13.8)	2 (2.5)	4 (5.0)
Location where you live, *n* (%)			
Major metropolitan area (population, > 500,000)	40 (50.0)	30 (37.5)	23 (28.8)
Urban area (population, 100,000–500,000)	10 (12.5)	28 (35.0)	19 (23.8)
Suburb of a large city (population, > 100,000)	13 (16.3)	8 (10.0)	8 (10.0)
Small city (population, 30,000 100,000)	12 (15.0)	7 (8.8)	12 (15.0)
Rural or small town (population, < 30,000)	5 (6.3)	7 (8.8)	18 (22.5)
Health insurance, *n* (%)			
Public, without additional private insurance	27 (33.8)	36 (45.0)	9 (11.3)
Public, along with additional private insurance	14 (17.5)	21 (26.3)	34 (42.5)
Private insurance	24 (30.0)	21 (26.3)	22 (27.5)
Aid entitlement and additional private insurance	4 (5.0)	1 (1.3)	10 (12.5)
Other	2 (2.5)	0 (0.0)	4 (5.0)
None of the above	9 (11.3)	1 (1.3)	1 (1.3)
Height (m) (SD)	1.82 (0.39)	1.66 (0.21)	1.67 (0.19)
Weight (kg) (SD)	65.23 (22.34)	72.55 (18.19)	66.96 (18.36)

Abbreviations: CM, chronic migraine; EM, episodic migraine; SD, standard deviation.
[b]Do not know or prefer not to answer: United Kingdom, 0 (0.0%); Spain, 1 (1.3%); France, 1 (1.3%).

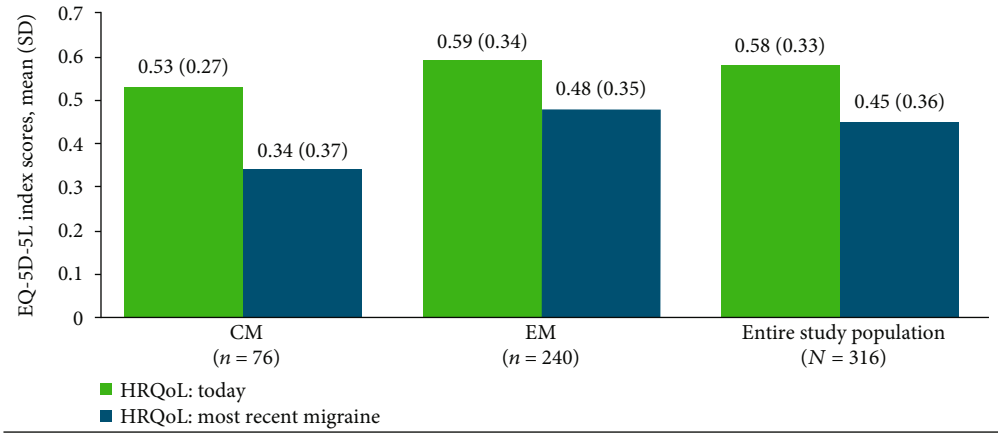
France, 20.0% [16/80]), implanted stimulators (United Kingdom, 35.0% [28/80]; Spain, 3.8% [3/80]; France, 8.8% [7/80]), and past other forms of surgery (United Kingdom, 21.3% [17/80]; Spain, 7.5% [6/80]; France, 5.0% [4/80]).

3.3. HRQoL. When asked about their health "today," patients' responses on the EQ-5D-5L index and visual analog scale (VAS) scores were similar across the EM and CM groups. However, when asked about their health during their most recent migraine attack, patients in the CM cohort reported lower scores relative to the EM cohort on the total index score (mean [SD]: CM, 0.34 [0.37]; EM, 0.48 [0.35]) and VAS score (mean [SD]: CM, 43.5 [26.1]; EM, 58.2 [25.1]; Figure 2(a)).

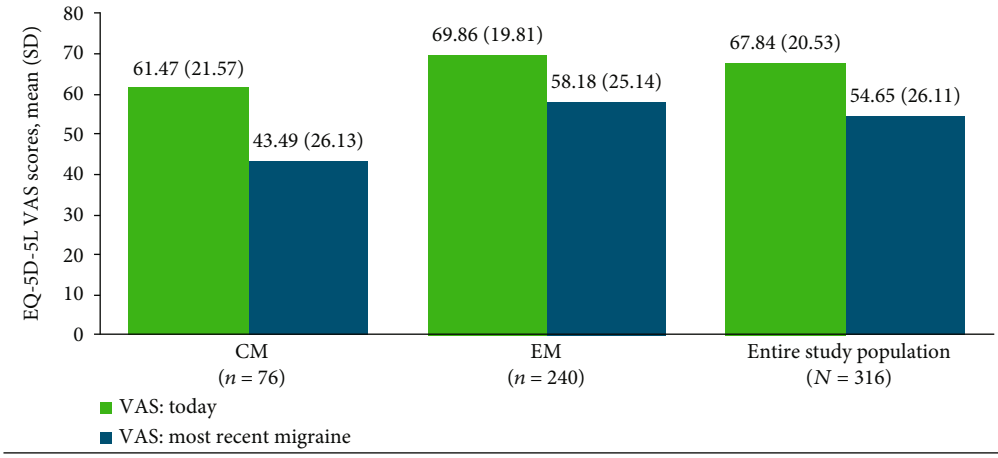
When patients with EM were asked about their health "today," EQ-5D-5L index scores were higher in Spain (mean [SD]: 0.70 [0.26]) than in the United Kingdom (0.54 [0.40]) or France (0.53 [0.32]); however, EQ-5D-5L index scores for their most recent migraine were similar across countries (mean [SD]: United Kingdom, 0.49 [0.42]; Spain, 0.51 [0.31]; France, 0.45 [0.30]). EQ-5D-5L VAS scores tended to be higher in the United Kingdom (for both patients' health "today" and during their most recent migraine) than in Spain or France (see Figure 2(b)).

3.4. Migraine-Related Disability. MIDAS scores are presented stratified by migraine classification in Figure 3(a) and among EM patients by country in Figure 3(b). Overall, patients with CM endorsed greater migraine disability, as assessed by MIDAS, compared with EM (mean [SD]: CM, 43.8 [44.7]; EM, 23.2 [28.3]). MIDAS scores were highest in Spain (mean [SD]: 31.6 (31.1)], followed by France (24.3 [31.1]), then the United Kingdom (13.8 [17.9]).

3.5. All-Cause and Migraine-Related HCRU. HCRU is presented by migraine classification in Table 2(a) and among patients with EM by country in Table 2(b). Migraine-specific HCRU was higher among patients with CM compared with those with EM; patients with CM reported a mean (SD) of 3.40 (3.15) primary care provider visits for migraine in the past 12 months, whereas those with EM reported an average of 2.79 (3.67) visits during the same



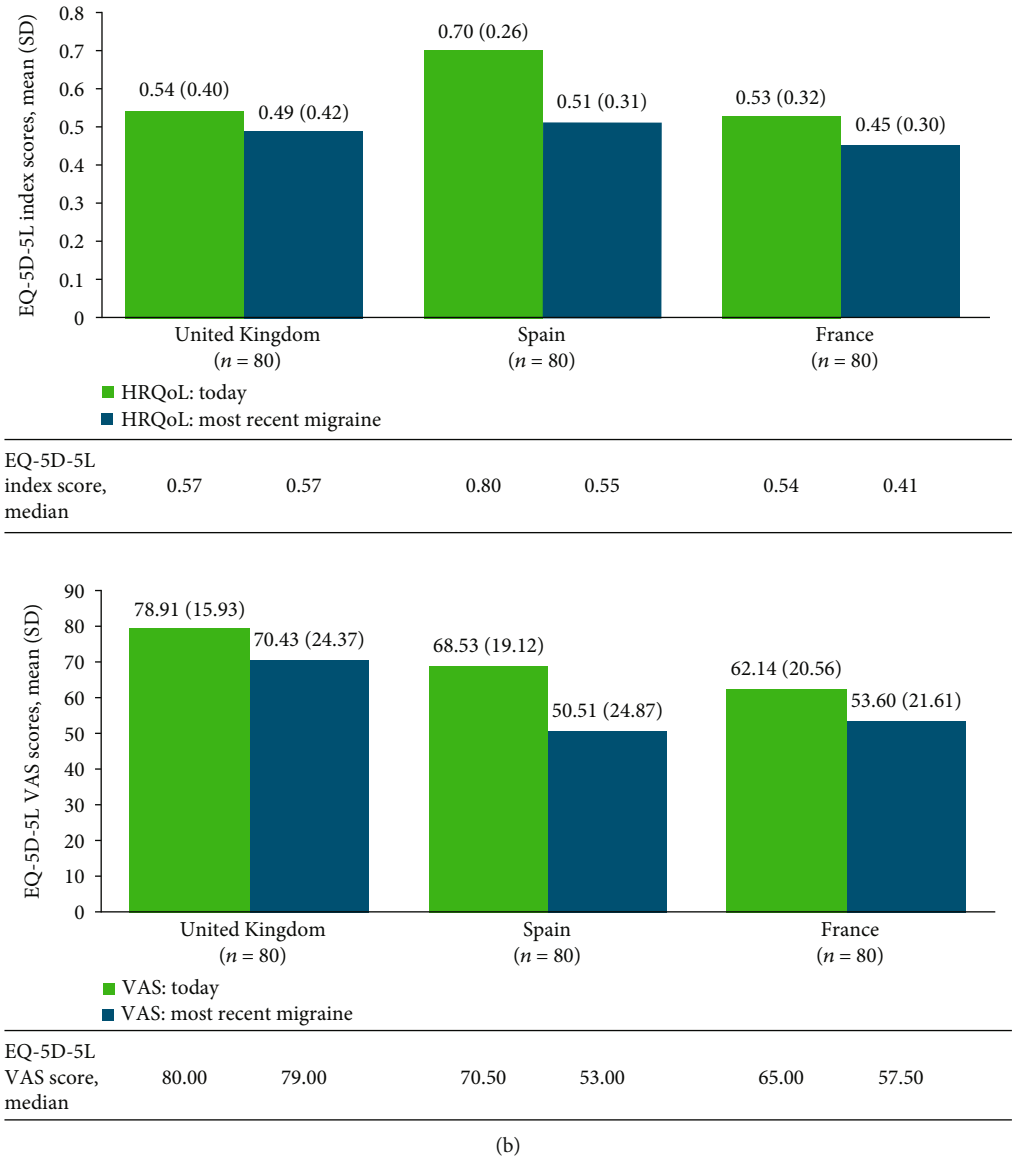
EQ-5D-5L index score, median	0.56	0.35	0.68	0.52	0.64	0.48



EQ-5D-5L VAS score, median	70.00	40.00	72.00	60.00	71.00	59.50

(a)

Figure 2: Continued.



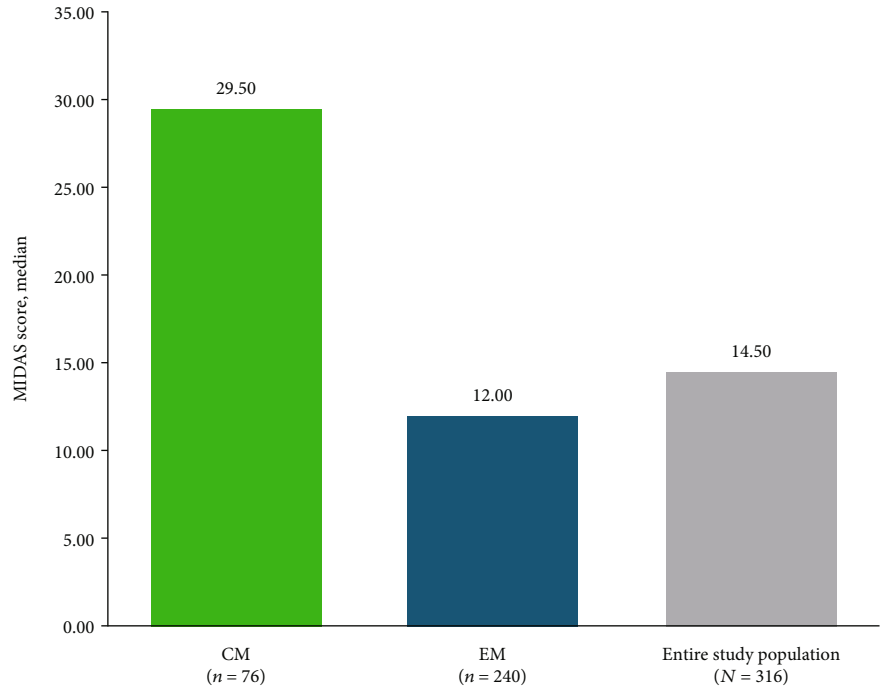
(b)

FIGURE 2: HRQoL by migraine classification (a) and among EM patients by country (b) as measured by EQ-5D-5L index and VAS scores. CM, chronic migraine; EM, episodic migraine; EQ-5D-5L, EuroQol 5-Dimension 5-Level; HRQoL, health-related quality of life; SD, standard deviation; VAS, visual analog scale.

period. Further, patients with CM reported a mean (SD) of 2.53 (1.89) headache specialist visits for migraine in the past 12 months compared with an average (SD) of 2.44 (2.27) such visits reported by patients with EM during the same period. Migraine-related ER and urgent care center visits during the past 12 months were also higher among patients with CM (mean [SD]: 2.41 [7.24] and 3.17 [6.73], respectively) compared with EM (1.56 [2.04] and 1.94 [2.96], respectively).

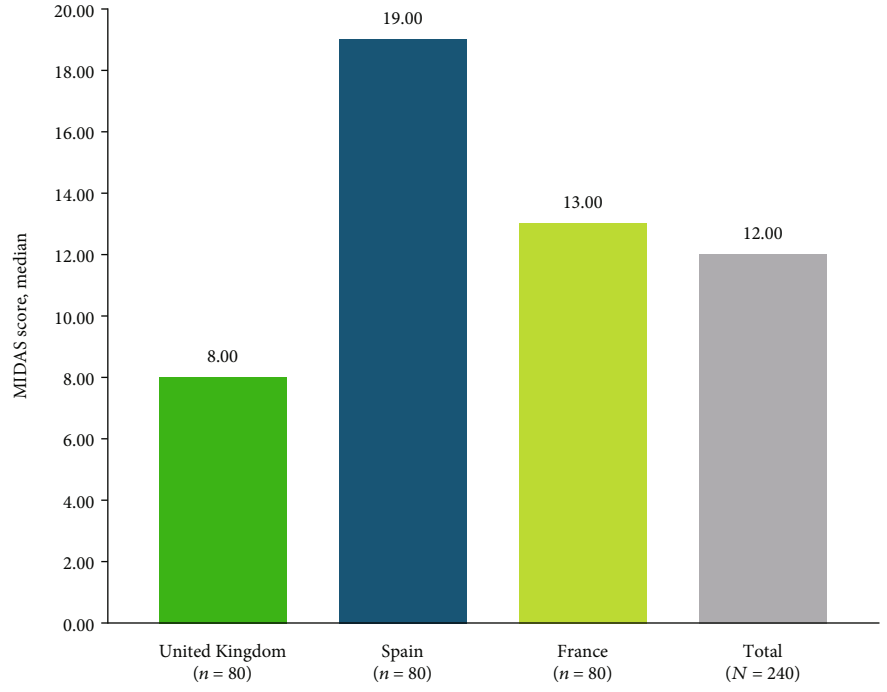
The mean (SD) number of migraine-related primary care provider visits in the past 12 months was higher in Spain (3.31 [3.86]) and France (2.89 [3.86]) when compared with the United Kingdom (2.05 [3.08]). Migraine-related visits to specialists (general neurologist, headache specialist, or pain specialist) were higher in the United Kingdom and Spain when compared with France (Table 2(b)). The mean (SD) number of migraine-specific ER visits in the past 12 months was highest in the United Kingdom (1.94 [2.51]), followed by Spain (1.51 [2.06]) and France (1.00 [0.45]). The mean (SD) number of migraine-related urgent care visits in the past 12 months was highest in Spain (2.74 [4.06]), followed by the United Kingdom (1.68 [2.10]) and France (0.96 [0.36]).

3.6. Migraine-Related Burden Questionnaire. Patients with CM reported higher levels of pain on an 11-point numerical rating scale (0 = *no pain* to 10 = *worst pain imaginable*); 25.0% (19/76) of patients with CM and 14.6% (35/240) of those with EM endorsed a "10" (Figure S1A). Patients with CM reported higher instances ("all the time") compared with those with EM of their pain and symptoms interfering with many aspects of their life, including their



MIDAS score, mean (SD)	43.75 (44.65)	23.24 (28.25)	28.17 (34.02)

(a)



MIDAS score, mean (SD)	13.84 (17.85)	31.61 (31.07)	24.26 (31.12)	23.24 (28.25)

(b)

FIGURE 3: Migraine-related disability by migraine classification (a) and among EM patients by country (b) as measured by Migraine Disability Assessment scores. CM, chronic migraine; EM, episodic migraine; MIDAS, Migraine Disability Assessment; SD, standard deviation.

Table 2: All-cause and migraine-related HCRU by migraine classification (a) and among EM patients by country (b).

(a)

Number of healthcare provider visits in the past 12 months, mean (SD)	CM ($n = 76$)	EM ($n = 240$)	Entire study sample ($N = 316$)
Visit for any reason			
Primary care, family medicine, or internist	5.92 (6.31)	4.41 (6.05)	4.78 (6.14)
General neurologist	1.33 (1.97)	1.80 (3.51)	1.68 (3.21)
Headache specialist	2.04 (3.90)	2.06 (3.09)	2.06 (3.30)
Pain specialist	1.01 (2.51)	1.12 (2.73)	1.09 (2.68)
Emergency room at a hospital	1.97 (5.88)	1.34 (3.03)	1.49 (3.91)
Urgent care center	1.34 (4.20)	1.25 (2.61)	1.28 (3.06)
Community/pharmacy walk-in or convenient care center	3.75 (10.06)	2.64 (6.67)	2.91 (7.62)
Other type of doctor/specialist	1.11 (1.98)	1.12 (2.28)	1.11 (2.21)
Visit for migraine			
Primary care, family medicine, or internist[a]	3.40 (3.15)	2.79 (3.67)	2.95 (3.55)
General neurologist[b]	2.03 (1.91)	1.94 (1.76)	1.96 (1.79)
Headache specialist[c]	2.53 (1.89)	2.44 (2.27)	2.46 (2.18)
Pain specialist[d]	1.48 (1.24)	1.71 (1.59)	1.65 (1.51)
Emergency room at a hospital[e]	2.41 (7.24)	1.56 (2.04)	1.81 (4.26)
Urgent care center[a,b]	3.17 (6.73)	1.94 (2.96)	2.18 (3.98)
Community/pharmacy walk-in or convenient care center[g]	6.13 (11.63)	2.53 (3.19)	3.32 (6.27)
Other types of doctor/specialist[h]	1.45 (1.30)	1.21 (1.34)	1.26 (1.33)

[a]CM, $n = 67$; EM, $n = 194$; total, $n = 261$.
[b]CM, $n = 34$; EM, $n = 126$; total, $n = 160$.
[c]CM, $n = 38$; EM, $n = 137$; total, $n = 175$.
[d]CM, $n = 29$; EM, $n = 85$; total, $n = 114$.
[e]CM, $n = 41$; EM, $n = 99$; total, $n = 140$.
[f]CM, $n = 23$; EM, $n = 94$; total, $n = 117$.
[g]CM, $n = 32$; EM, $n = 113$; total, $n = 145$.
[h]CM, $n = 22$; EM, $n = 86$; total, $n = 108$.

(b)

Number of healthcare provider visits in the past 12 months, mean (SD)	United Kingdom ($n = 80$)	Spain ($n = 80$)	France ($N = 80$)
Visit for any reason			
Primary care, family medicine, or internist	2.30 (3.72)	5.79 (6.77)	5.15 (6.65)
General neurologist	2.10 (3.50)	2.03 (3.44)	1.26 (3.56)
Headache specialist	2.04 (2.57)	2.91 (4.03)	1.24 (2.16)
Pain specialist	1.13 (2.29)	1.40 (3.82)	0.84 (1.61)
Emergency room at a hospital	1.63 (3.74)	1.70 (3.26)	0.70 (1.59)
Urgent care center	1.05 (2.23)	2.04 (3.52)	0.68 (1.47)
Community/pharmacy walk-in or convenient care center	1.85 (4.89)	5.00 (9.87)	1.06 (2.15)
Other type of doctor/specialist	1.08 (1.86)	1.50 (3.01)	0.78 (1.71)
Visit for migraine			
Primary care, family medicine, or internist[i]	2.05 (3.08)	3.31 (3.86)	2.89 (3.86)
General neurologist[a,f]	2.02 (1.95)	2.11 (1.66)	1.62 (1.65)
Headache specialist[k]	2.34 (1.97)	3.02 (2.85)	1.70 (1.31)
Pain specialist[l]	1.78 (2.03)	1.77 (1.38)	1.52 (1.16)
Emergency room at a hospital[m]	1.94 (2.51)	1.51 (2.06)	1.00 (0.45)
Urgent care center[n]	1.68 (2.10)	2.74 (4.06)	0.96 (0.36)
Community/pharmacy walk-in or convenient care center[o]	1.91 (1.84)	3.60 (4.13)	1.39 (1.77)
Other types of doctor/specialist[p]	1.29 (1.36)	1.44 (1.52)	0.61 (0.61)

Abbreviations: CM, chronic migraine; EM, episodic migraine; HCRU, healthcare resource use; SD, standard deviation.
[i]United Kingdom, $n = 56$; Spain, $n = 68$; France, $n = 70$.
[j]United Kingdom, $n = 45$; Spain, $n = 47$; France, $n = 34$.
[k]United Kingdom, $n = 53$; Spain, $n = 51$; France, $n = 33$.
[l]United Kingdom, $n = 32$; Spain, $n = 30$; France, $n = 23$.
[m]United Kingdom, $n = 35$; Spain, $n = 43$; France, $n = 21$.
[n]United Kingdom, $n = 31$; Spain, $n = 39$; France, $n = 24$.
[o]United Kingdom, $n = 35$; Spain, $n = 50$; France, $n = 28$.
[p]United Kingdom, $n = 34$; Spain, $n = 34$; France, $n = 18$.

mood and abilities to drive and exercise or play sports (see Figure 4(a)). Patients with CM also more frequently reported feeling that others had a negative view of their migraine attacks than those with EM (Table S3). A higher proportion of patients with CM compared with those with EM endorsed consequences associated with their migraine headaches, such as having problems with family members, coworkers, or supervisors or altering their work hours or plans (Figure S4A).

Further, only 23.7% (18/76) of patients with CM reported they work or function normally during migraine attacks, compared with 31.3% (75/240) with EM (Figure S2). A higher proportion of patients with CM when compared with patients with EM (6.6% [5/76] vs. 3.3% [8/240]) endorsed that their current employer is not at all understanding when they have migraines or severe headaches (Figure S3). A greater proportion of patients with CM reported wanting to hide or minimize their migraine headaches from others compared with patients with EM (Table S3).

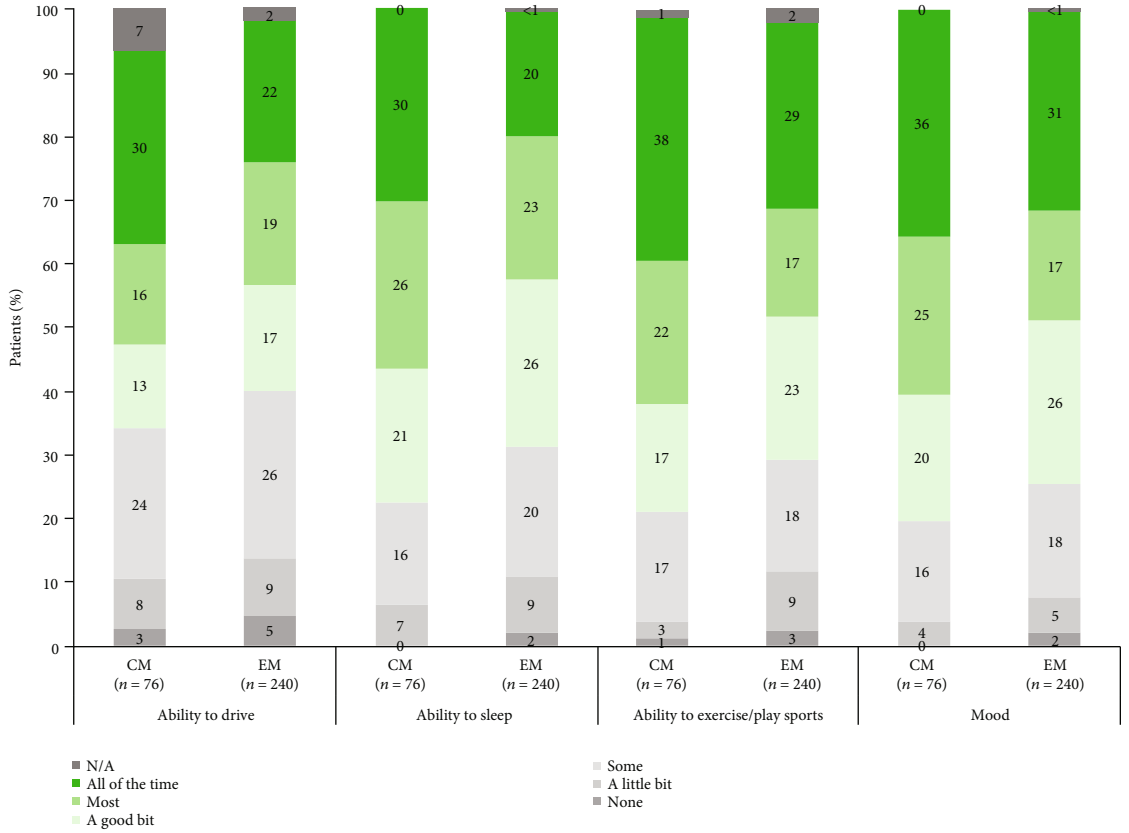
Among patients with EM, a higher proportion reported the maximum pain rating (10 on the numerical rating scale) for their headaches in the United Kingdom (18.8% [15/80]) and Spain (18.8% [15/80]) than in France (6.3% [5/80]; Figure S1B). Additionally, for patients in the United Kingdom and Spain, pain and symptoms tended to interfere with more aspects of their lives (Figure 4(b)). Also, compared with France, a higher percentage of patients in the United Kingdom and Spain reported that their migraine interfered with their work and social life (Figure S4B).

4. Discussion

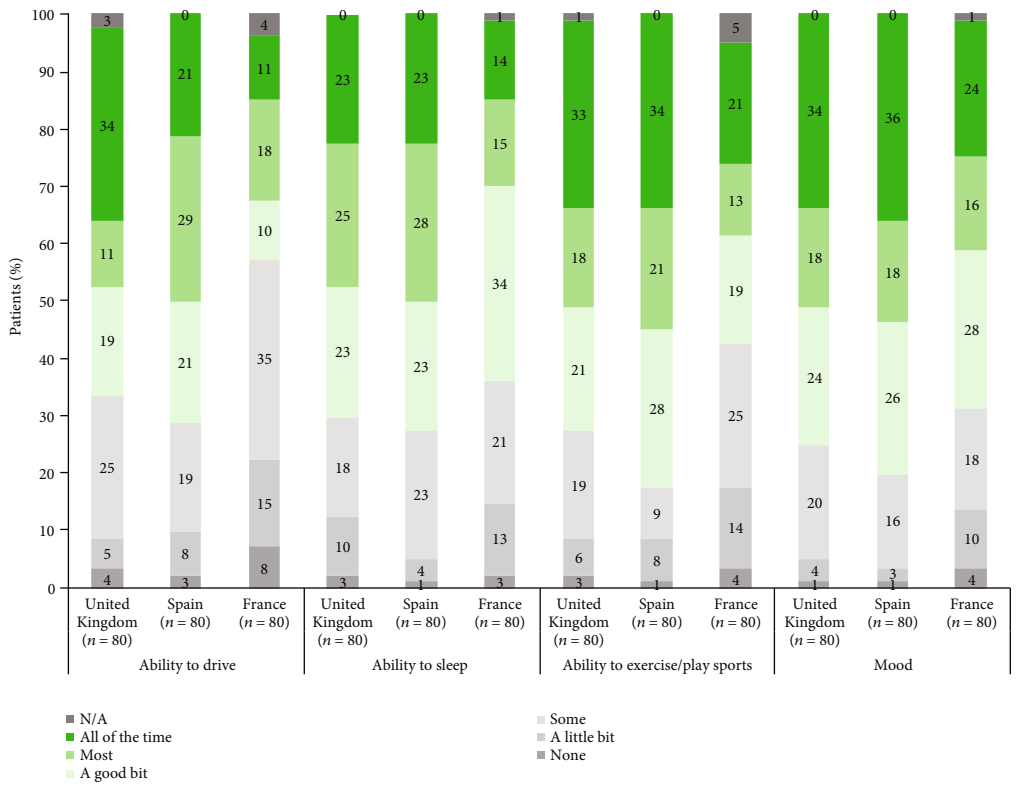
Findings from this study add to the literature by further elucidating the impact and burden associated with migraine among patients who have failed multiple prior migraine preventive treatments and providing information on differences in that burden by migraine classification and country. Several important differences were found between patients with EM and CM and across the three included countries. Only 57% of CM patients were employed full-time, compared with 70% of EM patients, which was in line with results of prior studies showing lower rates of full-time employment among CM versus EM patients [32, 33]. However, in the current study, the proportion of patients with part-time employment was almost twice as high in the CM cohort (17%) compared with the EM cohort (9%), while the proportion of CM and EM patients who were employed part-time were generally comparable in prior studies [32, 33]. There was little difference in the proportion of patients who were married or living with a partner between the CM and EM cohorts in the current study. In a recent study evaluating the social impact of migraine on patients, those with CM were more than twice as likely compared to EM patients to report that headaches impacted their romantic relationships; nevertheless, in line with the current study, the proportion of patients with CM and EM in a relationship or living together was comparable [34]. Surprisingly, the comorbidity burden was higher among patients with EM than among those with CM, which is contrary to the literature suggesting that the burden increases in parallel with the number of monthly headache days [11]. Although all patients included in this study had self-reported failure of two or more prior migraine preventive treatments from different classes, the types of prior preventive treatments used varied by migraine classification and country. The variations in the types of prior preventive treatment used across the three countries may have been related to regional availability or preferences.

Consistent with extant data [3], CM patients reported greater migraine-related disability compared with those with EM, as assessed by the MIDAS. In the present study, patient-reported HRQoL was relatively comparable for both CM and EM patients when asked about their health "today"; however, HRQoL was lower among those with CM compared with EM when asked about their health during their most recent migraine attack. Given that CM patients spend much more of their lives in a state of migraine attack, this difference in HRQoL during attacks is particularly concerning for the overall quality of life of patients with CM. HCRU was higher among those with CM compared with EM, which is consistent with data from previous studies [35]. Regarding migraine-related burden, those with CM reported higher levels of pain and greater pain- and symptom-related interference with many aspects of their life compared with those with EM. Those areas included their mood; abilities to drive, exercise, and sleep; and relationships with their families, coworkers, and employers.

Overall, the current study population had similar proportions of male and female patients; migraine and cross-country comparisons revealed that a higher proportion of patients with EM in the United Kingdom were male, whereas a higher proportion were female in Spain and France. These demographics differ from available survey data from Europe indicating that migraine is substantially more common in women than in men [11, 12]. This finding suggests the need for a cautious interpretation of the generalizability of study results because it may be an artifact of this unique study design or of cultural differences. Additionally, a higher proportion of patients with EM in the United Kingdom were employed full-time and had higher levels of education compared with those in Spain or France; this finding may be reflective of labor market statistics, which show a higher rate of employment in the United Kingdom, followed by France, then Spain [36]. The comorbidity burden was also higher in the United Kingdom compared with France and Spain. Migraine-related disability scores were highest in Spain, and scores in Spain and France were consistent with severe levels of disability; scores in the United Kingdom were consistent with moderate levels of disability. Although disability levels varied between studied countries, the level of disability was consistently high, which underscores the high unmet need in patients with migraine. Further, HRQoL was observed to be higher in Spain when patients with EM were asked to rate their health "today," but similar across the three countries when they were asked to rate it during their most recent migraine. Findings from previous European



(a)



(b)

FIGURE 4: Aspects of life most interfered with by migraine pain and symptoms by classification (a) and among EM patients by country (b). CM, chronic migraine; EM, episodic migraine; N/A, not available.

surveys of patients with EM reported markedly higher HRQoL scores (mean EQ-5D-5L index scores for patients with EM ranged from 0.70 to 0.74) [11, 12] compared with those observed among patients with EM in the present study (mean EQ-5D-5L utility index scores during their most recent migraine and "today," respectively: Spain, 0.51 and 0.70; United Kingdom, 0.49 and 0.54; France, 0.45 and 0.53), indicating that quality of life among this sample was more severely impaired. Similarly, EQ-5D-5L VAS scores in patients with CM in this study were lower compared with the results from the previous European survey (mean score of 43.5 during their most recent migraine vs. 52.3) [11]. These across-study differences may be due to differences in comorbidity profiles and prior migraine preventive treatment histories in the study populations. Thus, this discrepancy suggests that the HRQoL burden may be worse for this population of patients with difficult-to-treat EM and highlights the need for efficacious therapeutics in patients in whom previous treatments proved ineffective.

Migraine-specific HCRU among patients with EM varied by country. Patients with EM in Spain and France reported greater numbers of HCP visits, including migraine-related visits and visits for any reason, compared with the United Kingdom; however, migraine-related ER visits were highest in the United Kingdom, while migraine-related urgent care visits were highest in Spain. This finding is in agreement with the International Burden of Migraine Study (IBMS), demonstrating that the average number of primary care physicians and ER visits over a 3-month period among EM patients was greatest in Spain; however, both primary care physicians and ER visits were greater in the United Kingdom compared with France [37]. Given that disability scores were lowest for the United Kingdom, the higher rates of ER visits in the United Kingdom may suggest that the impact of migraine is understated by patients. Further research is needed to better understand patient needs and care-seeking behaviors by country.

Further, the humanistic burden of EM in patients who fail preventive treatments may be greater in some European countries relative to others. Patients from France reported lower symptom-related interference with many aspects of daily life and reported the highest proportion of patients living outside urban areas. This may suggest that aspects of urbanized life (air pollution, noise pollution, lifestyle, etc.) may contribute to a higher impact of migraine symptoms on daily activity. Previous studies have shown an association between air pollution exposure and risk for migraine [38, 39]. Further studies are required to verify the noted observations and explore possible causal relationships.

This study had a few limitations. The cross-sectional nature of the data does not allow for causal inferences to be drawn, and the self-report nature of this study may have resulted in recall bias. Further, along with validated instruments such as the EQ-5D-5L and MIDAS, this study also utilized nonpsychometrically validated survey items to collect data on migraine-related burden, which may limit the reliability and replicability of some of these findings. MIDAS was used as the only measure of migraine-related disability in the current study. Recall bias may impact MIDAS scores as it has been shown that patients with CM and medication overuse headaches have a tendency to round scores up to multiples of five or 10 on individual questions more often than patients with EM due to the higher frequency of headache days in the 3-month period assessed on the MIDAS [40]. Despite this potential limitation, patient responses to other questions around HRQoL during the most recent migraine attack and levels of pain and pain- and symptom-related interference with various aspects of life in the current study support the greater burden of migraine for patients with CM compared with those with EM. Data for this study were obtained using responses from a web-based survey of invited consumers recruited from online consumer panels. Such web-based surveys may be associated with inherited limitations, including self-selection bias around the choice to participate in the online consumer panels and exclusion of patients with a lack of internet access or poor computer literacy. Nevertheless, web-based instruments offer a number of advantages, including that they are often inexpensive, quicker to execute, and may offer more reliable data due to the reduced potential for data entry errors compared with researcher-administered surveys [41]. The included patients were from only three countries in Western Europe and may not be representative of the overall migraine patient population. The generalizability of these findings may also be limited because the sample was constituted by patients' self-reports, and they were from only three countries in Western Europe. Deviations in demographics (fewer female patients in both the CM and EM subgroups) and baseline characteristics (greater comorbidity burden in patients with EM vs. CM) when compared with epidemiological statistics [11, 12, 35] also limit the generalizability of study findings. This may be a consequence of the study design, wherein recruitment specifically targeted a specific sample of the migraine population (patients who had self-reported failure of two or more migraine preventive treatments). Further, the noted differences in patient characteristics, including sex distribution, age, frequency of comorbidities, prior treatments used, and employment status across countries and between patients with EM and CM, may have contributed to the differences observed in the impact and burden of migraine across the three countries and between the two migraine classification cohorts. Those migraine classification cohorts (CM and EM) were defined based on the number of headache days in the month prior to the study and did not reflect potential progression or reversion between CM and EM prior to or during the study. Additionally, due to sample size limitations of the CM cohort, results by country were combined; thus, country-level differences in CM burden were not analyzed.

The strength of this study rests on its use of a single methodology across a multinational sample and psychometrically validated measures of HRQoL and migraine-related disability, allowing for cross-country comparisons of impact and burden of migraine among patients who had self-reported failure of two or more prior migraine preventive treatments, a subpopulation that is challenging to treat and has been less well studied. Additionally, this study analyzed real-world data instead of data from controlled clinical trials,

which may have afforded a more representative view of clinical characteristics, treatment patterns, and patient-reported outcomes of migraine patients who have self-reported failure of at least two prior preventive migraine treatments. To the authors' knowledge, this is a first-of-its-kind analysis assessing the broader impact of migraine beyond validated questionnaires in these specific CM and EM populations; the current study also describes the impact of migraine on daily activities, including social, recreational, family, and work activities.

5. Conclusion

Overall, this study further illuminates the significant impact and real-world burden associated with migraine among patients who have self-reported failure of at least two prior preventive migraine treatments. Findings also highlight unmet patient needs among those with difficult-to-treat migraine, which differ by migraine classification and country. Although patients in this population were receiving current preventive treatment for their migraine, they still reported a substantial disease-related burden. Study findings suggest that addressing these unmet needs with efficacious treatments could reduce the burden and costs associated with migraine in this patient group with difficult-to-treat migraine. Further, this study adds novel real-world data regarding the less well-studied local country impact of migraine on patients' social, occupational, and emotional functioning and well-being, factors important to patients but not always considered by prescribers or payers. This study can guide HCPs and policy makers to consider local factors in treatment choices as well as promote more effective interventions that are tailored to the needs of the target migraine population.

Nomenclature

CCI	Charlson Comorbidity Index
CM	chronic migraine
EM	episodic migraine
EQ-5D-5L	EuroQol 5-Dimension 5-Level
ER	emergency room
HCP	healthcare provider
HCRU	healthcare resource use
HIV/AIDS	human immunodeficiency virus/acquired immunodeficiency syndrome
HRQoL	health-related quality of life
MIDAS	Migraine Disability Assessment
SD	standard deviation
VAS	visual analog scale

Data Availability Statement

Anonymized data that support the findings of this study can be obtained by request from any qualified investigator.

Conflicts of Interest

S.D.-I. has received personal fees from Allergan, Almirall, Bial, Chiesi, Fundació Universitat-Empresa de València, Kern Pharma, Lilly, Lundbeck, MSD, Novartis, and Teva Pharmaceuticals. S.S.-L. declares no conflicts of interest. M.T.D. is an employee of Teva Pharmaceuticals. J.M.C. was an employee of Teva Pharmaceuticals. L.L. is an employee of Kantar, which received funding from Teva Pharma to conduct this study. P.J.G. has received grants and personal fees from Amgen and Eli Lilly and Company; a grant from Kallyope; personal fees for consulting from Aeon Biopharma, Abbvie, Aurene, CoolTech LLC, Dr Reddy's, Eli-Lilly and Company, Epalex, Linpharma, Lundbeck, Pfizer, PureTech Health LLC, Satsuma, Shiratronics, Teva Pharmaceuticals, Tremeau, and Vial, and personal fees for advice through Gerson Lehrman Group, Guidepoint, SAI Med Partners, Vector Metric, and fees for educational materials from CME Outfitters and WebMD, and publishing royalties or fees from Massachusetts Medical Society, Oxford University Press, UptoDate and Wolters Kluwer, and a patent magnetic stimulation for headache assigned to eNeura without fee.

Author Contributions

Samuel Díaz-Insa: conceptualisation (equal), writing—review and editing (equal). Sonia Santos-Lasaosa: conceptualization (equal), writing—review and editing (equal). Maurice T. Driessen: conceptualisation (equal), writing—review and editing (equal). Joshua M. Cohen: conceptualisation (equal), writing—review and editing (equal). Lulu Lee: methodology (lead), data curation (lead), formal analysis (lead), writing—review and editing (equal). Peter J. Goadsby: conceptualisation (equal), writing–review and editing (equal).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. *(Supporting Information)* Table S1. Comorbidity by migraine classification (A) and among EM patients by country (B). Table S2. Previous and current medication usage by migraine classification (A) and among EM patients by country (B). Table S3. Frequency of how respondents feel others view their migraine headaches by migraine classification (A) and among EM patients by country (B). Figure S1. Headache pain by classification (A) and among EM patients by country (B). Figure S2. Effect of migraine on patient functioning by classification (A) and among EM patients by country (B). Figure S3. Employers' understanding when a patient has migraine or severe headaches by classification (A) and among EM patients by country (B). Figure S4. Consequences associated with migraine headaches by classification (A) and among EM patients by country (B).

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