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Research Submissions

Clinical Characteristics and Treatment Patterns Among Patients Diagnosed With Cluster Headache in U.S. Healthcare Claims Data

Casey K. Choong, MPH; Janet H. Ford, MPH; Allen W. Nyhuis, MS; Shivang G. Joshi, MD, MPH, RPh; Rebecca L. Robinson, MS; Sheena K. Aurora, MD; James M. Martinez, MD

Objective.—To characterize demographics, clinical characteristics, and treatment patterns of patients with cluster headache (CH).

Background.—CH is an uncommon trigeminal autonomic cephalalgia with limited evidence-based treatment options. Patients suffer from extremely painful unilateral headache attacks and autonomic symptoms with episodic and chronic cycles.

Design/Methods.—This retrospective analysis used insurance claims from Truven Health Analytics MarketScan® research databases from 2009 to 2014. Two cohorts were compared: CH patients (with ≥2 CH claims) were propensity score matched with 4 non-headache controls, all with continuous enrollment for 12 months before and after the date of first CH claim or matched period among controls.

Results.—CH patients (N = 7589) were mainly male (57.4%) and 35-64 years old (73.2%), with significantly more claims for comorbid conditions vs controls (N = 30,341), including depressive disorders (19.8% vs 10.0%), sleep disturbances (19.7% vs 9.1%), anxiety disorders (19.2% vs 8.7%), and tobacco use disorders (12.8% vs 5.3%), with 2.5 times greater odds of suicidal ideation (all $P < .0001$). Odds of drug dependence were 3-fold greater among CH patients (OR = 2.8 [95% CI 2.3-3.4, $P < .0001$]). CH patients reported significantly greater use of prescription medications compared with controls; 25% of CH patients had >12 unique prescription drug claims. Most commonly prescribed drug classes for CH patients included: opiate agonists (41%), corticosteroids (34%), 5HT-1 agonists (32%), antidepressants (31%), NSAIDs (29%), anticonvulsants (28%), calcium antagonists (27%), and benzodiazepines (22%). Only 30.4% of CH patients received recognized CH treatments without opioids during the 12-month post-index period. These patients were less likely to visit emergency departments or need hospitalizations (26.8%) as compared to CH patients with no pharmacy claims for recognized CH treatments or opioids (33.6%; $P < .0001$).

Conclusions.—The burden of CH is associated with significant co-morbidity, including substance use disorders and suicidal ideation, and treatment patterns indicating low use of recognized CH treatments.

Key words: cluster headache, clinical characteristics, claims database, matched case–control study, treatment patterns

From the Eli Lilly and Company, Indianapolis, IN, USA (C.K. Choong, J.H. Ford, A.W. Nyhuis, R.L. Robinson, S.K. Aurora, and J.M. Martinez); Community Neuroscience Services, Westborough, and MCPHS University, Worcester, MA, USA (S.G. Joshi).

Address all correspondence to C. K. Choong, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA, email: choong@lilly.com

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Abbreviations: CH cluster headache, OR odds ratio, CI confidence interval, 5HT-1 agonist 5-hydroxytryptamine-1 agonist, ICD-9-CM International Classification of Diseases, Ninth Revision, clinical modification codes, NSAIDs nonsteroidal anti-inflammatory drugs, SMD standardized mean differences, U.S. United States

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Cluster headache (CH), an uncommon trigeminal autonomic cephalalgia, is characterized by excruciating unilateral pain (orbital, supraorbital, and/or temporal) with attacks occurring every other day to multiple times per day for weeks or months during active cluster periods (or "cycles"), followed by periods of remission.[1] A meta-analysis of 15 population-based epidemiology studies found that CH is a relatively uncommon pain condition with an estimated lifetime prevalence of 124 per 100,000.[2] Men are 3 times more prone to CH and onset is typically between 20 and 40 years of age.[1] The pain associated with CH can be excruciating and has been described as the most severe pain known to humans.[3] Accordingly, the disease has substantial negative impact on social function and quality of life.[4] A U.S. CH survey reported that nearly 20% of afflicted patients lost a job because of their headaches, and 8% were unemployed or on work-related disability as a result of their condition.[5] Furthermore, 55% of sufferers report having suicidal ideation.[5]

Despite the fact that CH is clinically well-defined, its epidemiology in the U.S. is largely unknown, in part due to rarity of the condition.[6-8] A significant drop in incidence of CH between the 1979-1981 and 1989-1990 periods was observed in the Olmsted County (Minnesota) population, although the reason for the decline remains unclear.[6] Clinical practice and treatment patterns in real world settings also remain ill-defined. Treatments are generally aimed at treating individual attacks ("acute" or "abortive" treatments) and reducing overall attack frequency during active cluster cycles ("preventive" or "prophylactic" treatments). Several published guidelines provide recommendations for acute and preventive treatments,[9-12] although few treatments are specifically approved for such use. Commonly recommended acute treatments include high-flow oxygen and triptans (subcutaneous or intranasal), while commonly recommended preventive treatments include verapamil (often used in high doses), lithium, and certain anticonvulsants.[9-12] Additionally, corticosteroids are often used as "transitional" treatment at the start of active cluster cycles.[9,10]

The paucity of epidemiologic data, coupled with the personal burden and limited therapeutic choices for CH, suggests the need to address the following research questions in order to improve care and management: what is the burden of illness in the U.S., what proportion of patients are receiving recognized treatments, and what is the remaining unmet need for those suffering from this neurological disease. The primary aim of this observational study was to analyze demographics, clinical characteristics, and treatment data using a U.S.-based administrative healthcare claims database and to compare the findings in patients diagnosed with CH to a non-headache control group.

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METHODS

Study Design and Data Sources.—This observational retrospective database study extracted and analyzed claims data from the Truven Health Analytics Market Scan® research databases from January 1, 2009, through December 31, 2014. The patient population consists of commercially insured employees and covered dependents, early retirees with supplemental Medicare coverage, and a select sample of Medicaid recipients. These data include de-identified

administrative claims capturing patient-level data on age, gender, geographic region, and healthcare resource utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services. The Truven Health Analytics Market Scan® research databases link paid claims and encounter data, capturing when services occurred, and diagnosis codes via the International Classification of Diseases, Ninth Revision (ICD-9); Healthcare Common Procedure Coding System; and Current Procedural Terminology codes. Given the millions of unique patient lives captured in the database, it is suitable for research for uncommon diseases. Institutional review board approval was not required due to the de-identified nature of this existing data source, and methods to protect both patients and healthcare sites.

Patient Selection.—Two patient cohorts were identified: CH and control. The CH cohort included patients with at least 2 medical diagnoses for CH (ICD-9 medical codes: 339.00, including episodic 339.01 or chronic 339.02) between January 1, 2010 and December 31, 2013, with continuous enrollment both 12 months before ("pre-period") and after ("post-period") the index date allowing for a single gap of $\leq$45 days between re-enrollment during the full "study period." The index event date was equal to the date of the first CH diagnosis. Patients with CH claims during the pre-period were excluded. The control cohort included patients who had no claim for CH using ICD-9 codes listed above or any other headache diagnosis (339.xx, 346.xx, and 377.xx) from January 1, 2009 to December 31, 2014. The index date for controls was determined during the matching process described in the next section such that controls also had 12-month pre- and post-periods centered on the index date. Patients in both cohorts had to be at least 18 years of age at their index date.

Outcome Measures.—*Comorbid Conditions and Long-Term Drug Use.*—Medical condition claims, stratified by organ system, for CH and control patients during the post-period were summarized. In addition, long-term drug use (ie, high-risk agents [methadone, opiate], anticoagulants, aspirin, corticosteroids, and nonsteroidal anti-inflammatory drugs [NSAIDs]) was compared between the two cohorts.

Definition of Suicide-Related Claims.—Suicide-related claims during the study period (12-month pre- and post-index) were explored based on the framework of groupings recommended by the Centers for Disease Control and Prevention including any hospital admission associated with a diagnosis of self-inflicted injury (ICD-9 codes E950-E959).[13] Codes associated with suicidal ideation, poisoning, and open wound claims were also explored (ICD-9 codes: V6284, 960-989, and 870-897, respectively).

Overall Medication Use for Cluster Headache.—The overall numbers and proportions of patients with claims for 14 major classes of common medications used to achieve analgesia were computed post-period for the CH cohort vs controls. The classes of drugs were categorized by "therapeutic class" as defined in the RED BOOK, a classification system that groups National Drug Codes into therapeutic classes.[14]

Recognized Treatments and Overall Emergency Department and Hospital Utilization.—Pharmacy claims and procedural claims recorded within 7 days following a diagnosis of CH were evaluated using published evidence-based guidelines available during the study period.[9,10] One of the limitations of pharmacy claims data is that the diagnosis associated with each medication is not available. To address this issue, only pharmacy claims occurring 7 days post-CH diagnoses were analyzed. This assumption would exclude some medications prescribed for other health conditions. Specifically, drugs identified for our study were based on treatments that have been researched for CH per the guidelines[9,10] and clinical judgment. Over-the-counter drugs were not captured in claims, intravenous drugs were excluded, and methysergide (a prescription drug formerly used for prophylaxis of CH and migraine headaches[9]) was excluded as it is no longer recommended due to its association with retroperitoneal/retropulmonary fibrosis.[10]

Accordingly, recognized acute, preventive, and transitional treatments for CH in this analysis included: oxygen, sumatriptan (subcutaneous, intranasal), lidocaine, zolmitriptan (intranasal, oral), dihydroergotamine, ergotamine, octreotide, somatostatin, verapamil, prednisone, topiramate,

methylprednisolone, gabapentin, valproate, fluticasone, occipital nerve block, lithium, dexamethasone, triamcinolone, baclofen, hydrocortisone, betamethasone, budesonide, prednisolone, fludrocortisone, capsaicin, civamide, melatonin, mifepristone, and pizotifen.[9,10]

The relationship between patient claims for a recognized treatment within the post-period and healthcare resource utilization (rates of emergency department visits or hospital admissions) was assessed. Patients with CH were divided into 3 cohorts for comparison based on recorded prescription claims: (1) recognized treatment excluding opioids, (2) recognized treatment plus opioids or opioids only, and (3) no recognized treatment or opioids or unknown.

Statistical Analysis.—Twenty control patients who met all the inclusion criteria stated above were randomly assigned for each CH patient as a pool of potential control patients. Then a propensity score matching technique was applied to adjust for the differences in covariates and to reduce the impact of selection bias. Propensity scores were calculated with logistic regression using demographic factors (ie, age and sex) and factors that might influence clinical characteristics of CH patients (ie, index year, geographic region, health plan type, and comorbidity index). Subsequently, CH patients were matched with 4 control patients by propensity score greedy algorithm.[15] The greedy matching algorithm[15] performed up to 7 passes to find matches for each CH patient. It searched for control patients with propensity scores within a tolerance of 1×10^{-7} and progressively lessened the tolerance by 1 digit until reaching a value of 1×10^{-1}. Some of the CH patients might not have had 4 matched controls. The use of *P* values to determine the degree of match can be too dependent on sample size, and Austin[16] recommends using standardized mean differences (SMDs) to interpret the degree of match. For propensity score balance assessment, both the *P* values from comparing each of the covariates between the 2 groups and SMDs were used. The goal was to have all *P* values not be statistically significant ($P \geq .05$) and have all SMDs <0.1. No blocking factor was accounted for in estimating the difference between CH and control patients due to the large sample size in this study.

Summary descriptive analyses are presented for the CH and control cohorts. Continuous variables were summarized as the number of patients, mean, standard deviation, and median statistics. Pairwise comparisons (paired t-test or the Wilcoxon rank-sum test, as appropriate) were performe to measure group differences. Categorical variables were summarized as the frequency and percentage of patients in each category. Chi-square tests were conducted comparing categorical variables. The 95% confidence intervals (CIs) for the odds ratio (OR) statistic were estimated using the Mantel–Haenszel method. For all statistical tests, a 2-sided 5% significance level was utilized, and CIs were 2-sided at 95%. All analyses were performed using SAS® version 9.2 (Copyright © 2002-2008 by SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics.—There were a total of 110,086,514 medically insured patients in the Truven Health Analytics Market Scan® research databases during the study period. Approximately half of these patients (n = 57,140,548) were adult patients (>18 years old) with at least 2 years of continuous enrollment. Of these patients, 65,016 were identified to have one diagnosis code for CH (ICD-9 diagnosis codes 339.00, 339.01, or 339.02) from January 1, 2010 to December 31, 2013. One-third of these patients (n = 21,222) had at least one additional diagnosis code for CH during the postperiod, thus excluding 43,794 patients. An additional 682 subjects were removed because they had CH diagnoses in the pre-period (n = 20,540). Subsequently, 926 patients were excluded due to criteria requiring patients to be ≥18 years of age at index. Fewer than half of the remaining patients (n = 7596) met the inclusion criteria of 12 months of continuous enrollment pre- and post-index date. After propensity score matching an additional 7 patients were excluded as they had no control match, resulting in a study population of 7589 CH patients. Subsequently, 30,341 propensity score matched non-headache controls were identified. Note that a few

Table 1.—Demographic Characteristics After Propensity Score Matching

	Characteristics	Cluster Headache (N = 7589)	Control (N = 30,341)	*P* value
Gender, n (%)	Male	4356 (57.4)	17,605 (58.0)	.3240
	Female	3233 (42.6)	12,736 (42.0)	
Age at index, years	Mean ± SD	46.97 ± 13.4	46.73 ± 13.18	.2625
	Median	47	47	
Age group, n (%)	18-24	390 (5.0)	1569 (5.2)	
	25-34	1047 (13.8)	4169 (13.7)	
	35-44	1750 (23.1)	7112 (23.4)	
	45-54	2197 (29.0)	8919 (29.4)	
	55-64	1599 (21.1)	6331 (20.9)	
	65+	606 (8.0)	2241 (7.4)	
Charlson comorbidity index	Mean ± SD	0.74 ± 1.42	0.71 ± 1.41*	.0124
	Median	0	0	
Region, n (%)	North Central	1781 (23.4)	7090 (23.3)	.9791
	Northeast	1062 (14.0)	4177 (13.8)	
	South	2518 (33.2)	10,155 (33.5)	
	West	1461 (19.3)	5831 (19.2)	
	Unknown	767 (10.1)	3088 (10.2)	
Insurance coverage, n (%)	Commercial	6351 (83.7)	25,522 (84.1)	.3820
	Medicaid	618 (8.1)	2485 (8.2)	
	Medicare Supplement	620 (8.2)	2334 (7.7)	

SD = standard deviation.
*N = 30,198.

CH patients had fewer than 4 matching control patients due to statistical criteria of matching.

CH patients were mainly male (57.4%), between 35 and 64 years of age (73.2%), and resided in North Central and Southern regions of the U.S. (56.6%) (Table 1). Approximately 84% of CH patients were covered by commercial insurance. Propensity score matching was considered successful, given that the only statistically significant difference between the CH and control cohorts was the mean Charlson comorbidity index, 0.74 vs 0.71 ($P = .0124$; Table 1). For propensity score greedy matched samples, all P values were >.05, which met the goal. As all SMDs were <0.1; this suggests that the fit of the matched samples was considered acceptable.

Cluster Headache: Concomitant Diseases and Long-Term Drug Use.—Patients with CH were at increased risk of other diseases identified during the post-period (Table 2). Specifically, depressive disorders, sleep disturbance, and anxiety disorders were approximately 2 times more common in the CH cohort than in controls, 19%-20% vs 9%-10%, respectively (all $P < .0001$). The percentage of patients with claims for tobacco use disorders (a subset of substance use disorder) was nearly 3 times greater in the CH cohort than in controls, 13% vs 5%, respectively ($P < .0001$). Additionally, 39.3% of the CH cohort had at least one claim for migraine; controls with headache conditions were excluded.

The CH cohort also was more likely than controls to suffer from diseases originating from the nervous system (eg, cerebral degeneration, abnormal movement disorders, and epilepsy) and the respiratory system (eg, asthma) ($P < .0001$) (Table 2). Among metabolic diseases, hypercholesterolemia was more common in CH patients (10.5% vs 9.0%, respectively; $P < .0001$), while significantly fewer CH patients had claims related to diabetes mellitus compared with controls (10% vs 16%, respectively; $P < .0001$). Circulatory system comorbidities, except for myocardial infarction, were statistically significantly more prevalent in CH patients vs controls ($P < .0001$), and the odds of

Table 2.—Medical Conditions Reported in the Insurance Claims During the 12-month Post-index Period

	Cluster Headache		Control				
	n	%	n	%	OR	95% CI	*P* value
Mental							
Depressive disorder	1499	19.8	3028	10.0	2.22	2.07-2.38	<.0001
Sleep disturbance	1492	19.7	2748	9.1	2.46	2.29-2.63	<.0001
Anxiety disorder	1459	19.2	2637	8.7	2.50	2.33-2.68	<.0001
Substance abuse condition	1159	15.3	2005	6.6	2.55	2.36-2.75	<.0001
Tobacco use	970	12.8	1604	5.3	2.63	2.41-2.86	<.0001
Any drug dependence[†]	161	2.1	233	0.8	2.80	2.29-3.43	<.0001
Unspecified illicit drug use[‡]	116	1.5	166	0.6	2.82	2.22-3.58	<.0001
Opioid dependence[§]	114	1.5	136	0.5	3.39	2.64-4.35	<.0001
Nervous system							
Epilepsy	209	2.8	271	0.9	3.14	2.62-3.77	<.0001
Other cerebral degeneration	120	1.6	163	0.5	2.97	2.35-3.77	<.0001
Abnormal movement disorder	273	3.6	248	0.8	4.53	3.81-5.39	<.0001
Eye disorder	81	1.1	0	0.0	NA	NA	<.0001
Circulatory system							
Hypertension	2133	28.1	6715	22.1	1.38	1.30-1.46	<.0001
Obstructive sleep apnea	749	9.9	1628	5.4	1.93	1.76-2.11	<.0001
Stroke	414	5.5	688	2.3	2.49	2.20-2.82	<.0001
Myocardial infarction	67	0.9	210	0.7	1.28	0.97-1.68	.0809
Blood							
Anemia	452	6.0	1312	4.3	1.40	1.26-1.56	<.0001
Iron deficiency anemia	195	2.6	498	1.6	1.58	1.34-1.87	<.0001
Digestive system							
Peptic ulcer	39	0.5	89	0.3	1.76	1.20-2.56	.0030
Hematemesis	26	0.3	42	0.1	2.48	1.52-4.05	.0002
Metabolic							
Pure hypercholesterolemia	795	10.5	2719	9.0	1.19	1.09-1.29	<.0001
Diabetes mellitus	780	10.3	4893	16.1	0.60	0.55-0.65	<.0001
Neoplasms							
Intracranial neoplasm	40	0.5	41	0.1	3.92	2.53-6.06	<.0001
Pituitary tumor	4	0.1	10	<0.1	1.60	0.50-5.10	.4231
Nasopharyngeal carcinoma	1	<0.1	4	<0.1	1.00	0.11-8.94	.9996
Respiratory system							
Chronic obstructive pulmonary disease	781	10.3	2072	6.8	1.57	1.44-1.71	<.0001
Asthma	695	9.2	2124	7.0	1.34	1.22-1.46	<.0001
Injury							
Intracranial trauma	16	0.2	21	0.1	3.05	1.59-5.85	.0004

Table 2.—*Continued*

	Cluster Headache		Control				
	n	%	n	%	OR	95% CI	*P* value
Musculoskeletal system							
Cervical disc displacement	267	3.5	297	1.0	3.69	3.12-4.36	<.0001
Long-term (current) drug use							
Long-term or current use of other medications¶	1199	15.8	2657	8.8	1.96	1.82-2.10	<.0001
Long-term use of anticoagulants	145	1.9	419	1.4	1.39	1.15-1.68	.0006
Long-term use of aspirin	136	1.8	276	0.9	1.99	1.62-2.44	<.0001
Long-term use of corticosteroids	54	0.7	68	0.2	3.19	2.23-4.56	<.0001
Long-term use of NSAIDs	18	0.2	34	0.1	2.12	1.20-3.75	.0084

CI = confidence interval; NA = not available; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio.
†Drug dependence defined as an emotional ± physical state resulting from the interaction between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug on a continuous or periodic basis to experience its psychic effects, and sometimes to avoid the discomfort of its absence.
‡Unspecified illicit drug use defined as addiction to non-opioid medications alone or in combination with any other drug dependence and nondependent other mixed or unspecified drug use.
§Opioid dependence defined as addiction to opioid medications either alone or in combination with any other drug dependence and nondependent opioid use.
¶Including long-term use of methadone or other opiate analgesics.

Table 3.—Suicide-Related Claims Among Patients With Cluster Headache vs Controls: Entire Analysis Period

		Cluster Headache		Control				
	ICD-9-CM	n	%	n	%	OR	95% CI	*P* value
Self-inflicted injury	E950–E959	15	0.2	17	0.1	3.53	1.76-7.08	.0001
Undetermined injury	E980–E988	20	0.3	54	0.2	1.48	0.89-2.48	.1308
Suicidal ideation	V6284	89	1.2	144	0.5	2.49	1.91-3.25	<.0001
Poisoning	960-989	150	2.0	190	0.6	3.20	2.58-3.97	<.0001
Open wound	870-897	573	7.6	1718	5.7	1.36	1.23-1.50	<.0001

CI = confidence interval; ICD-9-CM = International Classification of Diseases, Ninth Revision, clinical modification codes; OR = odds ratio.

stroke (OR = 2.5; 95% CI 2.2-2.8) and obstructive sleep apnea (OR = 1.9; 95% CI 1.8-2.1) were significantly greater in CH patients ($P < .0001$).

Approximately 16% of the CH cohort had a diagnosis of long-term or current use of other medication (ICD-9 code V5869), which includes the use of methadone or an opiate analgesic for pain control, vs 9% of controls ($P < .0001$) (Table 2). Overall, the odds of any drug dependence were nearly 3 times greater in the CH cohort (OR = 2.8; 95% CI 2.3-3.4; $P < .0001$). There was also a 2-3 times greater chance of opioid use and illicit drug use ($P < .0001$) in the CH cohort.

Suicide-Related Claims.—CH patients had a 2-3 times greater chance of self-inflicted injury and suicidal ideation claims than controls ($P \leq .0001$) during the pre- and post-period (Table 3). There were also higher rates of poisoning and open wound claims for CH patients vs controls ($P < .0001$), which may be related to suicide attempts.

Overall Medication Use for Cluster Headache.—The CH cohort had significantly higher usage of prescription drugs in all captured drug classes during the post-period vs controls ($P < .0001$) (Fig. 1a). The most common drug claims among CH patients included: opiate agonists (41%), corticosteroids (34%), 5-hydroxytryptamine-1 (5HT-1) agonists (32%), antidepressants (31%), NSAIDs (29%), anticonvulsants (28%), calcium antagonists (27%), and benzodiazepines (22%). The CH cohort was twice as likely to be treated with high-risk medications defined as opiate agonists, benzodiazepines, and anxiolytic/sedative/hypnotics, than controls. Far fewer control patients were prescribed a vascular 5HT-1 agonist compared with CH patients (<1% vs 32%; $P < .0001$).

As shown in Figure 1b, approximately 79% of CH patients and 72% of controls had at least one prescription drug claim during the post-period. Approximately 25% of the CH cohort had a categorical frequency of >12 unique prescription drug claims vs 9% of controls ($P < .0001$). Accordingly, the CH cohort used a significantly larger variety of medications (8.46 ± 8.19 [mean ± standard deviation] unique prescription claims) compared with controls (4.76 ± 5.59 unique prescription claim) ($P < .0001$).

Use of Recognized Treatments and Emergency Department or Hospital Utilization Among the CH Cohort.—Recognized pharmacy claims and procedural claims for CH recorded in the database within 7 days following a diagnosis of CH were summarized (Table 4). In regards to acute treatments, 16% of CH patients had a claim for oxygen inhalation, 11% for sumatriptan oral, 7% for sumatriptan subcutaneous injection, and the remaining acute prescription claims had percentages <5%. In regards to preventive treatments, 16% had a prescription claim for verapamil, 13% for prednisone, 8% for topiramate, and the remaining preventive prescription claims had percentages <5%. Opioid treatment was prescribed to >20% of CH patients.

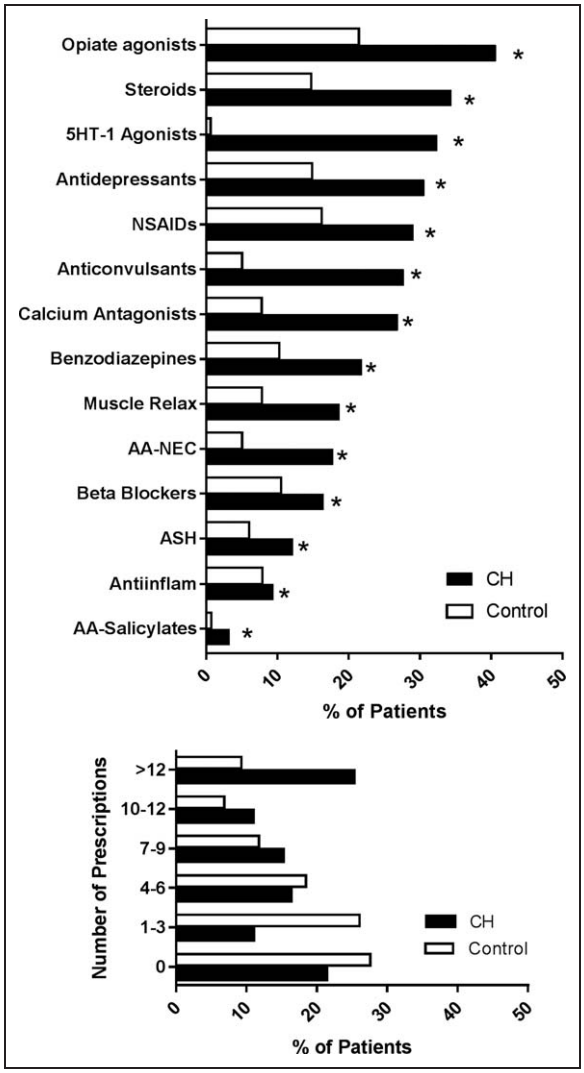

Fig. 1.—(a) Proportions of patients prescribed classes of drugs during the 12-month post-index period; for patients with cluster headache vs non-headache controls: chi-square test *$P < .0001$; 5HT-1 agonist = 5-hydroxytryptamine-1 agonist; AA-NEC = analgesics/antipyretics-not elsewhere classified (NEC); AA-Salicylates = analgesics/antipyretics-salicylates; Antiinflam = anti-inflammatory agents and combinations; ASH = anxiolytic/sedative/hypnotic NEC; CH = cluster headache; Muscle Relax = skeletal central muscle relaxer; NSAIDs = nonsteroidal anti-inflammatory drugs. (b) Number of unique prescription drug claims during the 12-month post-index period. CH = cluster headache.

Fewer than 3% were prescribed interventional treatment (ie, occipital nerve block) following diagnosis. Very few (<2%) invasive surgical treatments (eg, gamma-knife radiosurgery, trigeminal ganglio-rhizolysis/rhizotomy, deep brain stimulation, stimulation of the sphenopalatine ganglion) were claimed in the post-period (data not shown).

Overall, observed treatment patterns in the post-period showed that 30.4% of the CH cohort was prescribed recognized treatments without opioids: acute, preventive, or both (Table 5). More than 24% of CH patients had no claims for recognized treatment or opioids or had an unknown treatment not listed in Table 4. CH patients with at least one claim for a recognized treatment and no opioid claims were less likely to visit the emergency department or be admitted to the hospital (26.8%) vs CH patients who were prescribed an opioid (53.3%, $P < .0001$) (Table 5). Among the 24% of CH patients who either did not have any pharmacy claims or did not receive a recognized treatment or an opioid (ie, 21% had no pharmacy claims plus 3% had non-recognized medication claims or unknown interventions), 33.6% had at least one claim for an emergency department visit or hospital admission. Claims for emergency department and hospital admissions were also high among controls with opioid prescription claims (36.3%) compared to those without (15.1%, $P < .0001$).

DISCUSSION

The key findings of this large, geographically diverse cohort study utilizing U.S.-based administrative healthcare claims showed that CH patients had significantly higher rates of comorbid conditions, including mental health disorders; a 2.5-times greater risk of suicidal ideation; and a ~3-times greater risk of drug dependence, opioid dependence, and unspecified illicit drug use compared with controls. Opioid drugs were the most frequently prescribed class given to CH patients and fewer than one-third of patients were prescribed a recognized treatment without opioids based on relevant guidelines during the study period.[9,10] Of importance, CH patients who were not treated with a recognized treatment visited the emergency department or were admitted to the hospital more frequently than patients who received a recognized treatment, without opioids; however, opioid use in the CH and control cohorts produced the greatest utilization in each group. This study expands the

Table 4.—Recognized Pharmacy Prescriptions for Cluster Headache and Opioid Therapy in the 7-Day Period Post-index/Diagnosis

Acute Therapy†	n (%)	Transition/Preventive Therapy†	n (%)	Opioid Therapy	n (%)
Oxygen	1229 (16.2)	Verapamil	1238 (16.3)	Strong	1563 (20.6)
Sumatriptan (oral)	831 (11.0)	Prednisone	972 (12.8)	Weak‡	288 (3.8)
Sumatriptan (SC)	517 (6.8)	Topiramate	630 (8.3)		
Sumatriptan (IN)	246 (3.2)	Methylprednisolone	336 (4.4)		
Lidocaine	91 (1.2)	Gabapentin	287 (3.8)		
Zolmitriptan (IN)	82 (1.1)	Valproate	271 (3.6)		
Zolmitriptan (oral)	58 (0.8)	Fluticasone	271 (3.6)		
Dihydroergotamine	55 (0.7)	Occipital nerve block	213 (2.8)		
Ergotamine	25 (0.3)	Lithium	141 (1.9)		
Octreotide	1 (<0.1)	Dexamethasone	86 (1.1)		
Somatostatin	0 (0.0)	Triamcinolone	57 (0.8)		
		Baclofen	43 (0.6)		
		Hydrocortisone	34 (0.5)		
		Betamethasone	31 (0.4)		
		Budesonide	31 (0.4)		
		Prednisolone	16 (0.2)		
		Fludrocortisone	3 (<0.1)		
		Capsaicin	0 (0.0)		
		Civamide	0 (0.0)		
		Melatonin	0 (0.0)		
		Pizotifen	0 (0.0)		
		Mifepristone	0 (0.0)		

AAN = American Academy of Neurology; AHS = American Headache Society; EFNS = European Federation of Neurological Societies; IN = intranasal; SC = subcutaneously.
†Acute and preventive medications recommended by AAN/AHS and EFNS at time of study.[9,10]
‡Weak opioids include drugs with propoxyphene, tramadol, or nalbuphine.

awareness of personal burden caused by CH and suggests the need for increased adherence to current evidence-based treatment guidelines,[12] and the need for additional and better treatment options for this uncommon, severely painful neurological condition.

Comorbid conditions, especially mental health disorders, were commonly reported in CH patients during the study period. The most commonly noted comorbidities, other than migraine, in the CH cohort were hypertension (28%), depression (~20%), sleep disturbance (~20%), anxiety (~19%), and substance abuse conditions (~15%), which were reported at higher rates when compared with controls during the post-period. Our depression data align with Rozen et al,[5] but our estimate was 2-fold lower than that reported by Donnet et al.[17] Diagnoses of sleep apnea, abnormal movement disorders including restless leg syndrome, and asthma also were found to be significantly more common among CH patients than controls in our study; observed rates among CH patients were mostly consistent with a previous survey study of patient self-reported diagnosis.[5] The chances of selected cardiovascular-related diseases (ie, hypertension and stroke) were significantly higher (OR = 1.4-2.5) in our CH patients vs controls, which is contrary to previous survey findings of relatively low incidences of cardiovascular disease (≤3%) in CH patients.[5,18] The clinical characteristics of CH could not be determined in our study; thus the association between cardiovascular-related disease and CH remains unclear. Interestingly, we also observed that diabetes mellitus

Table 5.—Treatment Patterns and Emergency Department/In-Patient Admissions for Cluster Headache Based on Prescription Claims for Recognized Treatments vs Opioids in the Post-period

	Treatment Patterns		Emergency Department/ In-Patient Admission	
	N	%	n	%
Cluster Headache Patients With Recognized Treatment Claims[†] Without Opioids				
Acute	529	7.0	150	28.4
Preventive	847	11.2	230	27.2
Acute + Preventive	924	12.2	236	25.5
Total	2300	30.4	616	26.8[‡,§]
Cluster Headache Patients With Opioid Claims ± Recognized Treatment Claims[†]				
Acute + Preventive + Opioids	1486	19.6	819	55.1
Preventive + Opioids	1278	16.8	699	54.7
Opioids	423	5.6	202	47.8
Acute + Opioids	270	3.6	122	45.2
Total	3457	45.6	1842	53.3[‡]
Cluster Headache Patients With No Recognized Treatment or Opioid Claims or Unknown	1832	24.1	616	33.6[§]

AAN = American Academy of Neurology; AHS = American Headache Society; EFNS = European Federation of Neurological Societies.

[†]Acute and preventive medications recommended by AAN/AHS and EFNS at time of study.[9,10]

‡$P < .0001$; difference in emergency department/in-patient admission rates between patients with cluster headache with recognized treatment prescription and no opioid prescription claims and patients with opioid treatment claims with or without recognized treatment claims.

§$P < .0001$; difference in emergency department/in-patient admission rates between patients with cluster headache with recognized treatment and no opioid prescription claims and patients with cluster headache without recognized treatment and no opioid prescription claims.

occurred at a significantly lower rate (10.3%) in CH patients vs controls (16.1%; $P < .0001$). A similar finding has been reported among patients with migraine, wherein there was a negative relationship with diabetes mellitus.[19,20] Although it is difficult to make causal inference in a retrospective database study, it is possible that CH patients live a highly regulated lifestyle in an effort to avoid triggers and prevent CH attacks. Overall, our study provides further evidence that the burden of living with CH is high.

In our study, the chances of tobacco use were 2.6 times greater among CH patients than controls. CH patients also were found to have significantly higher risk of chronic obstructive pulmonary disease vs controls (OR = 1.6; 95% CI 1.4-1.7; $P < .0001$), which may be linked to smoking. This is consistent with other findings that have found smoking to be frequent and extensive in CH patients.[5,21] Approximately 90% of CH patients have a reported prolonged history of tobacco use.[22] The link between smoking and CH is likely a coping strategy to reduce the severe pain. Nicotine has been shown to decrease pain sensitivity among smokers[23] and to attenuate emotional distress associated with pain.[24] However, smoking may have minimal positive benefit for CH patients as emerging data reveal that cigarette smokers may, in fact, prolong the active phase of an attack episode compared to nonsmokers (mean 15.1 vs 5.7 weeks; $P < .001$)[22] and lead to higher pain intensity and poorer pain-related functioning.[25]

Our claims study also found an increased risk of substance abuse in CH patients vs controls (OR:

2.6; 95% CI 2.4-2.8; $P < .0001$); nearly 2% of CH patients had a claim of unspecified illicit drug use. The reason addictive behaviors are more common in CH patients than controls is unclear. However, further analysis on individual types of drug dependence (ICD-9-clinical modification codes [ICD-9-CM]: 304) revealed that only drugs with known analgesic properties were being abused (eg, cannabis, sedatives, hypnotics, anxiolytics, opioid), suggesting that a subpopulation of CH patients in our study were self-medicating with unapproved, sometimes illegal treatments. Despite the variable therapeutic benefit of cannabis and hallucinogens in selected patients,[26] these agents are not recommended due to the lack of blinded studies. Given the limited effective drugs to treat the brutally painful headache, CH patients may use narcotics to take the edge off the pain, thus reflecting the desperation of this patient population.

Among CH patients in our study, the chances of having a claim for self-inflicted injury were 3.5 times greater when compared with the non-headache control cohort. These findings are consistent with other epidemiological studies. In a U.S. survey study, over 50% of responders with CH admitted to having suicidal thoughts and 2% had suicide attempts.[5] Documented suicidal thoughts/tendencies in recent survey studies considerably outnumbered the cases of suicidal behaviors captured in our study (25% to 55% vs 11%, respectively),[5,27] thus suggesting that suicide-related behavior may frequently go undetected in insurance claims. Use of administrative codes to identify suicide-related attempts is recognized to have high specificity, but very low sensitivity.[28] Physicians and patients likely under-report suicide-related behavior because of the stigma associated with it. State death certification and cause-of-death codes (available in ICD-10 CM) were not evaluated in this study; thus, suicide deaths among CH patients were not identified. Furthermore, patients committing suicide were likely missed as they did not maintain enrollment in an insurance plan over the study period.

During the 12-month post-period, more than three-quarters of our CH patients had at least one prescription drug claim, and one-quarter of these patients reported >12 unique prescription drug claims. Opiate agonists and corticosteroids were each prescribed to more than one-third of the CH cohort and 5HT-1 agonists, antidepressants, NSAIDs, anticonvulsants, and calcium antagonists were each prescribed to more than one-fourth of the CH cohort. Surprisingly, only one-third of CH patients were prescribed recognized treatments without opioids in the post-period.[9,10] We believe this is the first U.S. study to systematically examine the extent to which a specific treatment is received by CH patients, and if the treatment is consistent with recognized therapies reported in the literature.

In the 7-day post-CH diagnosis period, sumatriptan (all routes) was the most prescribed drug for acute CH attacks in our claims study, prednisone was the most prescribed drug for short-term preventive/transition therapy, and verapamil was the most prescribed drug for prevention. High-flow oxygen claims for abortive/acute treatment were only found in <20% of CH patients. Despite the fact that high-flow oxygen is considered one of the most effective, safe, and well-tolerated treatments for CH,[12,29] a survey study reported that one-third of patients had not tried this approach.[30] Barriers to oxygen use among patients with CH are in need of further research.

Our study also found that analgesic medications were prescribed more often for CH patients vs controls. Because of the rapid onset of pain intensity associated with CH, only fast-acting medications are considered helpful. Although opioids and NSAIDs have questionable effectiveness and are not recommended in current guidelines,[12] >40% of CH patients had a prescription claim for at least one opioid and nearly one-third of patients were prescribed NSAIDs within 12 months post-CH diagnosis. It is unclear whether use of opioids and NSAIDs was for other comorbid pain conditions. Owing to the excruciating nature of the pain associated with CH, it is possible that the extensive use of opioid analgesics was obligatory; however, their use could also serve as a means for suicide-related claims in an at-risk patient population. Considering NSAIDs are among the most common over-the-counter medications used to treat headache, the

number of patients who used NSAIDs to treat their CH is likely underestimated. While the severity of CH warrants that patients have access to effective analgesics, overuse or misuse of NSAIDs may lead to other health complications such as GI-related complications (eg, ulcers).[31] Overall, our study indicated that an appreciable percentage of patients (70%) may not receive the most effective treatments based on substantial overuse of opioids and NSAIDs and underutilization of nonpharmacological treatment (eg, oxygen). Finally, it is unknown if patients were experiencing a CH attack during the 12-month post-period, which may explain some of the treatment underutilization.

Overall, CH patients had higher emergency department visits and hospitalizations for any reason vs controls. However, data analyzed in our study did not include information that permits assessment of whether the patient prescribed a recognized treatment received adequate relief. Presumptively, CH patients experiencing no relief were more likely to be admitted to the emergency department or hospital. An important finding from our study is that CH patients who had claims for acute and/or preventive recognized treatments without opioids utilized emergency department and hospital services the least. Opioid use in both the CH and control cohorts, regardless of other treatments received, increased utilization of these health services. Admittedly, emergency department or hospital admission of patients with opioid prescription claims may be associated with other comorbid conditions, generally poorer health, mismanagement of other pain conditions, or prescription drug abuse. Notably, recent research has indicated that compliance with protocols for the management of chronic pain conditions leads to a reduction in the use of emergency health services and decreased use of medications with abuse potential.[32] Further research should be directed toward investigating reasons for emergency department or hospital admission in the CH population, informing practices to ensure adequate pain management, and preventing overuse of these health services.

There are several limitations that need to be considered when interpreting the findings presented herein. First, diagnostic codes in claims data for CH may be viewed as a symptom vs a diagnosis or may involve misdiagnosis or underdiagnosis. The diagnosis of CH could not be validated in the Truven Health Analytics Market Scan® research databases due to lack of details related to clinical information. For example, two-thirds of patients only had one diagnosis claim for CH and therefore were not included in this analysis, which may indicate that this code is being used as a screen-out for other conditions or that some physicians are not using the code consistently. Also, the medical codes for the chronic and episodic forms are underutilized, and it is unknown if patients were experiencing a CH attack or were in remission during the study. A longitudinal analysis could not be performed due to the retrospective nature of the study, thus suggesting the possibility that initial diagnoses of CH could potentially change to an alternate diagnosis. Although the possibility of having misdiagnosed patients with migraine in the CH cohort cannot be ruled out, it is noteworthy to point out that most CH patients (>60%) did not have a migraine diagnosis 12 months prior to their diagnosis of CH. The study cautiously used 2 CH claims as part of the inclusion criteria to enhance the specificity. A recent study of the validity of CH diagnoses in an electronic health record data repository showed a relatively modest positive predictive value when one ICD-9 code was used relative to a headache expert's clinical impression.[33] This possibility does not diminish the significance of the finding that only a low proportion of patients in the CH cohort received CH-recommended treatments, because these patients were presumably receiving treatments based on their diagnosis (accurate or inaccurate) of CH. Future study is needed to develop algorithms for identifying CH using health claims data. Second, the study population may not be representative of the CH population as a whole. Thus, characteristics of CH and its treatment patterns in the general population may be different from the population studied in claims data. For example, CH is widely recognized to predominantly afflict males.[1] However, the study analyses presented herein showed a relatively low male-to-

female (M/F) gender ratio of 1.35. in comparison to an overall ratio of 4.3 (range: 1.3-14.0) derived from pooled data of survey-based epidemiological studies on CH.[2] However, 2 other studies have suggested that the gender ratio (M/F) has significantly decreased over recent years, with a trend toward decreasing male preponderance, especially for diagnoses occurring after 1970.[34,35] Admittedly, the database used in this study might not provide an ideal representation of the gender ratio of CH for several reasons. There were more females than males in the database during the study period (52.2% female vs 47.8% male). Also, it is generally accepted that females are more likely to utilize medical care than males,[36] which may explain the reduced overall number of male patients identified in this study. Another possible explanation that may also have affected the ratio is the source of the patients who are insured employees and dependents and geographical distribution of this sample, which was predominantly from southern regions of the U.S. Also, the ICD-9 diagnosis code for CH was not available prior to 2008; thus, patients with CH prior to this date could not be included in this study. Last, specific variables of interest for the patient population are underreported in claims, including use of over-the-counter analgesics and events related to suicidal behaviors, tobacco use, substance abuse, and illicit drug use.

CONCLUSION

In summary, patients diagnosed with CH in this large medical insurance claims database had a significantly higher comorbidity burden, including mental health and substance use disorders and suicidal behaviors, compared to non-headache controls. All pain-related medications in these analyses were used at significantly higher rates among CH patients. Opioid use and overall drug dependence in this population were particularly problematic due to the comorbidity profile and signals of suicide risk. Treatment patterns for acute or preventive management of CH did not appear to adhere to recognized treatments that were relevant during the study period for more than two-thirds of CH patients. More importantly, this analysis suggested that when recognized treatments were used in CH patients, there were reductions in hospitalization and ER visits. Overall, our findings emphasize the heavy burden of illness among CH patients, and suggest the need for increased awareness of evidence-based treatment recommendations[12] and to identify new established treatments for this severely painful neurological disease.

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Casey K. Choong, Janet H. Ford, Rebecca L. Robinson, Sheena K. Aurora, James M. Martinez

(b) Acquisition of Data

Casey K. Choong, Allen W. Nyhuis

(c) Analysis and Interpretation of Data

Casey K. Choong, Janet H. Ford, Allen W. Nyhuis, Rebecca L. Robinson, Shivang G. Joshi, Sheena K. Aurora, James M. Martinez

Category 2

(a) Drafting the Manuscript

Casey K. Choong, Janet H. Ford, Rebecca L. Robinson

(b) Revising It for Intellectual Content

Casey K. Choong, Janet H. Ford, Rebecca L. Robinson, Shivang G. Joshi, Allen W. Nyhuis, Sheena K. Aurora, James M. Martinez

Category 3

(a) Final Approval of the Completed Manuscript

Casey K. Choong, Janet H. Ford, Allen W. Nyhuis, Rebecca L. Robinson, Shivang G. Joshi, Sheena K. Aurora, James M. Martinez

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