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ORIGINAL RESEARCH

Inpatient Constipation Among Migraine Patients Prescribed Anti-calcitonin Gene-Related Peptide Monoclonal Antibodies and Standard of Care Antiepileptic Drugs: A Retrospective Cohort Study in a United States Electronic Health Record Database

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ABSTRACT

Introduction: Erenumab, an anti-calcitonin gene-related peptide (CGRP) receptor monoclonal antibody (mAb), was approved by the US Food and Drug Administration in May 2018. Constipation with serious complications was added to the Warning and Precautions section in the erenumab Prescribing Information in October 2019 after events were observed during post-marketing surveillance. We aimed to assess and compare the risk of inpatient constipation, and, separately, inpatient constipation with serious complications, among patients with migraine treated with CGRP mAbs and standard of care antiepileptic drugs (AEDs).

Methods: Within Optum's Electronic Health Record Research Database, patients with migraine who initiated erenumab, other CGRP mAbs, and AEDs were identified from May 2018 through March 2020. Erenumab initiators were propensity score-matched separately to initiators of other CGRP mAbs and AEDs. Incident inpatient constipation events, and serious complications, were identified using multiple risk windows for outcome assessment (30-, 60-, 90-day risk windows, and all available follow-up). Odds ratios (ORs) were calculated comparing inpatient constipation risk among matched erenumab initiators relative to comparators.

Results: We identified 17,902 erenumab, 13,404 other CGRP mAb, and 49,497 AED initiators who met study criteria. Among matched initiators, the risk of inpatient constipation was 0.46% (95% confidence interval (CI) 0.35–0.60) for erenumab and 0.44% (95% CI 0.33–0.58) for other CGRP mAbs within the 90-day risk window, with a corresponding OR of 1.06 (95% CI 0.72–1.55). Among matched erenumab and AED initiators, inpatient constipation risk was 0.53% (95% CI 0.42–0.66) and 0.76% (95% CI 0.62–0.92), respectively, and the OR was 0.69

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(95% CI 0.51–0.94). Few serious complications were observed.
Conclusion: Patients initiating erenumab had similar risk of inpatient constipation within 90 days of treatment initiation versus patients initiating other CGRP mAbs, and lower risk versus patients initiating AEDs. These findings provide context to events observed during post-marketing surveillance.

Keywords: Migraine; Constipation; CGRP; Monoclonal antibodies; Antiepileptic drugs; Electronic health record

Key Summary Points

Why carry out this study?

Erenumab, an anti-calcitonin gene-related peptide (CGRP) receptor monoclonal antibody (mAb), was approved by the US Food and Drug Administration in May 2018. Constipation with serious complications was added to the Warning and Precautions section in the erenumab Prescribing Information in October 2019 after events were observed during post-marketing surveillance.

We aimed to assess and compare the risk of inpatient constipation, and, separately, inpatient constipation with serious complications, among patients with migraine treated with CGRP mAbs and standard of care antiepileptic drugs (AEDs).

What was learned from this study?

Patients initiating erenumab had similar risk of inpatient constipation within 90 days of treatment initiation versus patients initiating other CGRP mAbs, and lower risk versus patients initiating AEDs.

Findings from this study provide context to events observed in the post-marketing setting.

INTRODUCTION

Migraine is a neurological disorder characterized by recurrent headache attacks of moderate to severe pain. In 2018, the prevalence of migraine or severe headache was 21.0% in women and 10.7% in men in the USA [1]. Treatment options include medications for acute episodes (e.g., triptans) and preventive medications to reduce the frequency of migraines. Medications including antiepileptics, beta blockers, calcium channel blockers, antidepressants, and botulinum toxins are prescribed for prevention, but have primary indications for other conditions such as epilepsy, depression, and hypertension [2].

Therapies targeting the calcitonin gene-related peptide (CGRP) pathway have been developed for both acute and preventive treatment of migraine. One class, known as gepants, consists of oral, non-peptide, small molecule, CGRP receptor antagonists. The other class of medications is the anti-CGRP pathway monoclonal antibodies (referred to hereafter as CGRP mAbs) which were developed specifically for the prevention of migraine and are administered by injection or infusion. Four CGRP mAbs have been approved by the US Food and Drug Administration (FDA): erenumab-aooe (Aimovig®, Amgen Inc., Thousand Oaks, CA) on 17 May 2018, fremanezumab-vfrm (Ajovy®, Teva Pharmaceuticals USA, Parsippany, NJ) on 14 September 2018, galcanezumab-gnlm (Emgality®, Eli Lilly and Company, Indianapolis, IN) on 27 September 2018, and eptinezumab-jjmr (Vyepti®, Lundbeck Seattle BioPharmaceuticals Inc., Bothell, WA) on 21 February 2020. Erenumab is a mAb that targets the CGRP receptor, whereas fremanezumab, galcanezumab, and eptinezumab are mAbs that target the CGRP ligand.

Among patients included in three placebo-controlled clinical studies of erenumab [3–5], the incidence of constipation was 1% with placebo, 1% with 70 mg erenumab, and 3% with 140 mg erenumab during the 12-week double-blinded treatment phase, as described in the Adverse Reactions section of the Prescribing Information upon FDA approval [6]. In the post-

marketing setting, constipation with serious complications was reported following the use of erenumab and was added to the Prescribing Information for erenumab in October 2019 [6].

The purpose of this retrospective observational study was to estimate and compare the risk of inpatient constipation (constipation recorded during an inpatient stay or emergency department (ED) visit) among patients with migraine following initiation of treatment with a preventive migraine medication. Multiple risk windows for assessment of inpatient constipation were evaluated, with the 90 days following treatment initiation specified a priori as the primary window of interest. Additionally, the risk of serious complications within 30 days following inpatient constipation was assessed. The medications examined included erenumab, other CGRP mAbs, and standard of care antiepileptic drugs (AEDs). We hypothesized that the risk of inpatient constipation among initiators of erenumab would be similar to the risk among initiators of other CGRP mAbs and initiators of AEDs.

METHODS

Data Source

In this retrospective cohort study, the study population was drawn from Optum's Electronic Health Record (EHR) Research Database, a de-identified patient-level database that integrates multiple electronic medical record (EMR) data systems with medical claims, prescription, and practice management data. The database incorporates relevant clinical data on patients from both ambulatory and inpatient settings, including medical records, laboratory results, and drug prescription and administration data, as recorded during routine clinical practice.

For 2019, data relating to 32 million patients with at least one medical encounter were available. The data are collected from more than 92,000 providers and 195 hospitals representing 50 EMR-based provider/hospital networks across the USA. The population captured in Optum's EHR Research Database is geographically diverse and not specific to health insurance so that patients with commercial health insurance are present along with patients with coverage through Medicare, Medicaid, and even patients with no health insurance.

The database is certified as de-identified by an independent statistical expert following Health Insurance Portability and Accountability Act statistical de-identification rules; the study protocol was exempt from institutional review board review.

Study Population

Patients with a prescription order for erenumab, other CGRP mAbs (fremanezumab, galcanezumab, eptinezumab), and AEDs (carbamazepine, gabapentin, topiramate, valproate sodium/valproic acid/divalproex sodium, zonisamide) between 17 May 2018 and 31 March 2020 were identified using National Drug Codes (NDCs). To restrict to new users, only the first prescription order per patient and per medication was identified during the study period and assessed for the following criteria:

- At least 18 years of age on the prescription order date
- At least two diagnosis codes for migraine (International Classification of Diseases, 10th revision (ICD-10) code G43.*) on two different days, or at least one diagnosis code for migraine and one prescription order for an acute migraine treatment (triptan or ergot), in the 12 months prior to and including the prescription order date (to ensure cohort members were patients with migraine, especially those initiating AEDs, which have other indications)
- At least two outpatient visits prior to the prescription order date, including one visit at least 12 months prior to the prescription order date (to establish a 12-month baseline period for assessment of clinical covariates)
- No prescription order for any CGRP mAb during the prior 12 months
- For the AED cohort only, no prescription order for any of the five antiepileptic medications during the 12 months prior to the prescription order date

The index date was set as the date of the earliest prescription order that met all the aforementioned criteria. Because it was expected that patients would have started a CGRP mAb after attempting treatment with an AED, the AED cohort was selected from the remaining population of migraine preventive treatment users after the erenumab and other CGRP mAb cohorts were formed.

Ascertainment of Covariates

The baseline period for covariate assessment was the 12 months prior to and including the index date. Demographic variables were extracted directly from the EHR database. Clinical variables were assessed with ICD-10 diagnosis codes, NDCs, and procedure codes derived from the structured data tables in the database. They included comorbidities related to migraine, preventive migraine treatments, drugs that may cause or treat constipation, gastrointestinal disorders, conditions related to constipation, and constipation history. Personal and family history of constipation and enemas used for constipation treatment (gastrografin, glycerin/Fleet) were identified using semi-structured data (i.e., data derived from natural language processing of clinical notes) within the EHR database.

Propensity Score Modeling and Matching

Two separate logistic regression models were used to estimate propensity scores (PSs) predicting initiation of erenumab compared to initiation of (1) other CGRP mAbs and (2) AEDs. PSs were estimated on the basis of a priori potential confounders and risk factors for constipation. The variables included in the PS model are listed in Tables 1 and 2.

Each erenumab initiator was matched on the basis of PS to one initiator in each comparator cohort (1:1). Initiators were matched without replacement, using a greedy matching algorithm with a variable caliper that allowed for a maximum PS difference of 0.1 [7, 8].

Identification of Outcomes

Inpatient constipation was identified on the basis of ICD-10 diagnosis codes for constipation (K59.00–K59.09) that were recorded during an ED or inpatient stay. Inpatient constipation was assessed starting on the day after the index date through the earliest occurrence of switching of migraine preventive therapy or end of the study period (31 March 2020). Only the first (incident) constipation event occurring during the follow-up period was included in the analysis.

Serious complications of inpatient constipation were assessed within 30 days following the inpatient constipation event. Serious complications were identified by the presence of at least one ICD-10 diagnosis code for fecal impaction, intestinal obstructions, anal fissures, fistulas, or related conditions identified in an ED or inpatient setting (Table S1 in electronic supplementary material).

Statistical Analysis

All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC). Patient characteristics were summarized for each of the cohorts before and after PS matching using frequencies and percentages for categorical variables and means and standard deviations for continuous variables. The PS matching process resulted in some unmatched erenumab cohort members. For transparency, characteristics of the unmatched erenumab cohort members were described. Standardized differences were examined to assess the balance of each risk factor between the matched erenumab and comparator cohorts. Covariates with an absolute standardized difference no greater than 0.1 were considered balanced [9, 10].

Risk (i.e., incidence proportion) and corresponding 95% confidence intervals (CIs) of inpatient constipation were estimated in the three cohorts by dividing the total number of patients with an event observed during follow-up by the number of cohort members at risk at the start of follow-up. Risk was calculated among the overall cohorts and the PS-matched cohorts. The risk of serious complications of

Table 1 Risk factors for constipation in erenumab and other CGRP monoclonal antibody initiators in the 12-month baseline period prior to the index date, pre- and post-propensity score matching

Baseline characteristic	Identified from 17 May 2018 to 31 March 2020										
	All initiators before matching				Propensity score-matched initiators					Unmatched erenumab initiators	
	Erenumab		Other CGRP mAb		Erenumab		Other CGRP mAb		SD	Erenumab	
	N = 17,902		*N* = 13,404		*N* = 13,200		*N* = 13,200			*N* = 4702	
	N	%	*N*	%	*N*	%	*N*	%		*N*	%
Demographics											
Age (years) (mean, standard deviation)	45.9	12.7	45.2	12.7	45.3	12.7	45.3	12.7	0.0006	47.5	12.7
Age group (years)											
18 to ≤ 34	3548	19.8	2824	21.1	2786	21.1	2748	20.8	0.0071	762	16.2
35 to ≤ 49	7287	40.7	5591	41.7	5480	41.5	5503	41.7	− 0.0035	1807	38.4
50 to ≤ 64	5848	32.7	4185	31.2	4124	31.2	4149	31.4	− 0.0041	1724	36.7
≥ 65	1219	6.8	804	6.0	810	6.1	800	6.1	0.0032	409	8.7
Sex											
Female	15,662	87.5	11,823	88.2	11,673	88.4	11,628	88.1	0.0106	3989	84.8
Male	2240	12.5	1581	11.8	1527	11.6	1572	11.9	− 0.0106	713	15.2
Geographic region											
Midwest	9590	53.6	6475	48.3	6529	49.5	6467	49.0	0.0094	3061	65.1
Northeast	2215	12.4	1167	8.7	1191	9.0	1167	8.8	0.0064	1024	21.8
South	4892	27.3	4877	36.4	4562	34.6	4682	35.5	− 0.0191	330	7.0
West	1205	6.7	885	6.6	918	7.0	884	6.7	0.0102	287	6.1
Migraine preventive agents											
Antihypertensives[a]	7040	39.3	5023	37.5	5011	38.0	4986	37.8	0.0039	2029	43.2
Antiepileptics[b]	1495	8.4	972	7.3	955	7.2	960	7.3	− 0.0015	540	11.5
Antidepressants[c]	9637	53.8	7073	52.8	6965	52.8	6985	52.9	− 0.0030	2672	56.8
Botulinum toxins[d]	4486	25.1	2419	18.1	2433	18.4	2417	18.3	0.0031	2053	43.7

Table 1 continued

Baseline characteristic	Identified from 17 May 2018 to 31 March 2020										
	All initiators before matching				Propensity score-matched initiators					Unmatched erenumab initiators	
	Erenumab		Other CGRP mAb		Erenumab		Other CGRP mAb		SD	Erenumab	
	N = 17,902		*N* = 13,404		*N* = 13,200		*N* = 13,200			*N* = 4702	
	N	%	*N*	%	*N*	%	*N*	%		*N*	%
Other migraine preventives[e]	3607	20.2	2305	17.2	2304	17.5	2296	17.4	0.0016	1303	27.7
Comorbidities related to migraine											
Anxiety	6832	38.2	5175	38.6	5043	38.2	5064	38.4	− 0.0033	1789	38.1
Depression	5587	31.2	4080	30.4	4027	30.5	4028	30.5	− 0.0002	1560	33.2
Chronic pain	9394	52.5	6797	50.7	6685	50.6	6701	50.8	− 0.0024	2709	57.6
Insomnia	3467	19.4	2507	18.7	2474	18.7	2477	18.8	− 0.0006	993	21.1
Thyroid disorder	3333	18.6	2490	18.6	2420	18.3	2436	18.5	− 0.0031	913	19.4
Drugs that may cause constipation											
Opioids/opiates	8000	44.7	5615	41.9	5586	42.3	5577	42.3	0.0014	2414	51.3
Anticholinergics	10,060	56.2	7241	54.0	7118	53.9	7168	54.3	− 0.0076	2942	62.6
Antipsychotics	326	1.8	204	1.5	204	1.6	203	1.5	0.0006	122	2.6
Antihistamines	6827	38.1	4780	35.7	4710	35.7	4748	36.0	− 0.0060	2117	45.0
Antispasmodics	1860	10.4	1382	10.3	1344	10.2	1344	10.2	0.0000	516	11.0
Antiparkinsonian drugs	187	1.0	122	0.9	117	0.9	118	0.9	− 0.0008	70	1.5
Tricyclic antidepressants	4544	25.4	3353	25.0	3277	24.8	3314	25.1	− 0.0065	1267	27.0
NSAIDs (prescription and OTC)	9710	54.2	7059	52.7	6901	52.3	6969	52.8	− 0.0103	2809	59.7
Cation-containing agents	1131	6.3	758	5.7	756	5.7	746	5.7	0.0033	375	8.0
Iron supplements	528	3.0	355	2.7	336	2.6	347	2.6	− 0.0052	192	4.1
Aluminum (antacids, sucralfate)	643	3.6	446	3.3	456	3.5	436	3.3	0.0084	187	4.0
5-HT_3 antagonists	6844	38.2	4889	36.5	4786	36.3	4814	36.5	− 0.0044	2058	43.8
Prescription drugs that treat constipation											

Table 1 continued

Baseline characteristic	Identified from 17 May 2018 to 31 March 2020										
	All initiators before matching				Propensity score-matched initiators					Unmatched erenumab initiators	
	Erenumab		Other CGRP mAb		Erenumab		Other CGRP mAb		SD	Erenumab	
	N = 17,902		*N* = 13,404		*N* = 13,200		*N* = 13,200			*N* = 4702	
	N	%	*N*	%	*N*	%	*N*	%		*N*	%
Prescription laxatives (lactulose, Dulcolax)	200	1.1	142	1.1	136	1.0	138	1.1	− 0.0015	64	1.4
Other prescription treatments (tegaserod, linaclotides, lubiprostone)	640	3.6	537	4.0	507	3.8	509	3.9	− 0.0008	133	2.8
OTC drugs that treat constipation	2037	11.4	1308	9.8	1292	9.8	1294	9.8	− 0.0005	745	15.8
Gastrointestinal disorders											
Irritable bowel syndrome	1326	7.4	980	7.3	947	7.2	951	7.2	− 0.0012	379	8.1
Crohn's disease	144	0.8	115	0.9	107	0.8	106	0.8	0.0008	37	0.8
Ulcerative colitis	112	0.6	85	0.6	85	0.6	79	0.6	0.0058	27	0.6
Diverticulitis/diverticulosis	653	3.7	419	3.1	425	3.2	416	3.2	0.0039	228	4.9
Hemorrhoids (excluding pregnancy-induced)	852	4.8	557	4.2	552	4.2	551	4.2	0.0004	300	6.4
Conditions that are associated with constipation											
Diabetes mellitus	1784	10.0	1203	9.0	1183	9.0	1192	9.0	− 0.0024	601	12.8
Autonomic neuropathy	136	0.8	69	0.5	71	0.5	69	0.5	0.0021	65	1.4
Multiple sclerosis	279	1.6	173	1.3	179	1.4	173	1.3	0.0040	100	2.1
Hirschsprung disease	1	< 0.1	1	< 0.1	1	< 0.1	1	< 0.1	0.0000	0	0.0
Spinal cord injury	8	< 0.1	2	< 0.1	1	< 0.1	2	< 0.1	− 0.0071	7	0.2
Parkinson's disease	36	0.2	37	0.3	31	0.2	34	0.3	− 0.0046	5	0.1
Hypothyroidism	2696	15.1	1978	14.8	1932	14.6	1947	14.8	− 0.0032	764	16.3
Hypokalemia	775	4.3	505	3.8	509	3.9	500	3.8	0.0036	266	5.7
Anorexia nervosa	186	1.0	118	0.9	114	0.9	117	0.9	− 0.0024	72	1.5

Table 1 continued

Baseline characteristic	Identified from 17 May 2018 to 31 March 2020										
	All initiators before matching				Propensity score-matched initiators					Unmatched erenumab initiators	
	Erenumab		Other CGRP mAb		Erenumab		Other CGRP mAb		SD	Erenumab	
	N = 17,902		*N* = 13,404		*N* = 13,200		*N* = 13,200			*N* = 4702	
	N	%	*N*	%	*N*	%	*N*	%		*N*	%
Pregnancy	276	1.5	213	1.6	193	1.5	210	1.6	− 0.0105	83	1.8
Panhypopituitarism	28	0.2	30	0.2	27	0.2	26	0.2	0.0017	1	< 0.1
Systemic sclerosis	23	0.1	11	0.1	12	0.1	11	0.1	0.0026	11	0.2
Myotonic dystrophy	4	< 0.1	1	< 0.1	0	0.0	1	< 0.1	NC	4	0.1
Constipation or complications of constipation during the 12-month baseline period											
Any constipation (OP/IP/ED)	1550	8.7	1210	9.0	1169	8.9	1150	8.7	0.0051	381	8.1
Idiopathic constipation (OP/IP/ED)	10	0.1	1	< 0.1	1	< 0.1	1	< 0.1	0.0000	9	0.2
Normal colonic transit	1318	7.4	1054	7.9	1024	7.8	1000	7.6	0.0068	294	6.3
Slow transit constipation	113	0.6	68	0.5	63	0.5	68	0.5	− 0.0054	50	1.1
Dyssynergic constipation	11	0.1	13	0.1	11	0.1	9	0.1	0.0055	0	0.0
Inpatient constipation (IP/ED)	340	1.9	228	1.7	234	1.8	223	1.7	0.0064	106	2.3
Complications of constipation (IP/ED)	95	0.5	75	0.6	72	0.6	71	0.5	0.0010	23	0.5
Bowel perforation	3	< 0.1	5	< 0.1	3	< 0.1	2	< 0.1	0.0055	0	0.0
History of constipation											
Family history of constipation[f]	17	0.1	16	0.1	13	0.1	14	0.1	− 0.0024	4	0.1
Personal history of constipation[f]	5769	32.2	3831	28.6	3783	28.7	3811	28.9	− 0.0047	1986	42.2
Procedures related to constipation treatment											
Mentions in clinical notes											
Gastrografin enema[f]	3	< 0.1	1	< 0.1	1	< 0.1	1	< 0.1	0.0000	2	< 0.1

Table 1 continued

Baseline characteristic	Identified from 17 May 2018 to 31 March 2020										
	All initiators before matching				Propensity score-matched initiators					Unmatched erenumab initiators	
	Erenumab		Other CGRP mAb		Erenumab		Other CGRP mAb		SD	Erenumab	
	N = 17,902		*N* = 13,404		*N* = 13,200		*N* = 13,200			*N* = 4702	
	N	%	*N*	%	*N*	%	*N*	%		*N*	%
Glycerin/Fleet enema[f]	58	0.3	37	0.3	39	0.3	37	0.3	0.0028	19	0.4

CGRP calcitonin gene-related peptide, *ED* emergency department, *IP* inpatient, *mAbs* monoclonal antibodies, *NC* not calculated, *NSAID* non-steroidal anti-inflammatory drugs, *OP* outpatient, *OTC* over-the-counter, *SD* standardized difference, *5-HT$_3$* serotonin receptor

[a]Includes beta blockers, calcium channel blockers, candesartan, clonidine, and lisinopril

[b]Includes levetiracetam and pregabalin

[c]Includes serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors

[d]Includes abobotulinumtoxinA, incobotulinumtoxinA, onabotulinumtoxinA, and rimabotulinumtoxinB

[e]Includes carisoprodol, cyproheptadine, guanfacine, memantine, methysergide, milnacipran, and tizanidine

[f]Identified using the semi-structured (NLP) data within the EHR database

Table 2 Risk factors for constipation in erenumab and standard of care antiepileptic drug initiators in the 12-month baseline period prior to the index date, pre- and post-propensity score matching

Baseline characteristic	Identified from 17 May 2018 to 31 March 2020										
	All initiators before matching				Propensity score-matched initiators					Unmatched erenumab Initiators	
	Erenumab		AEDs		Erenumab		AEDs		SD	Erenumab	
	N = 17,902		*N* = 49,497		*N* = 15,441		*N* = 15,441			*N* = 2461	
	N	%	*N*	%	*N*	%	*N*	%		*N*	%
Demographics											
Age (years) (mean, standard deviation)	45.9	12.7	45.2	14.6	45.6	12.9	45.9	13.3	− 0.0222	47.2	11.5
Age group (years)											
18 to ≤ 34	3548	19.8	12,793	25.9	3229	20.9	3042	19.7	0.0301	319	13.0
35 to ≤ 49	7287	40.7	17,945	36.3	6185	40.1	6168	40.0	0.0022	1102	44.8
50 to ≤ 64	5848	32.7	13,741	27.8	4939	32.0	5153	33.4	− 0.0296	909	36.9
≥ 65	1219	6.8	5018	10.1	1088	7.1	1078	7.0	0.0025	131	5.3
Sex											
Female	15,662	87.5	42,771	86.4	13,501	87.4	13,548	87.7	− 0.0092	2161	87.8
Male	2240	12.5	6726	13.6	1940	12.6	1893	12.3	0.0092	300	12.2
Geographic region											
Midwest	9590	53.6	28,366	57.3	8269	53.6	8337	54.0	− 0.0088	1321	53.7
Northeast	2215	12.4	5823	11.8	1794	11.6	1821	11.8	− 0.0054	421	17.1
South	4892	27.3	10,908	22.0	4365	28.3	4281	27.7	0.0121	527	21.4
West	1205	6.7	4400	8.9	1013	6.6	1002	6.5	0.0029	192	7.8
Migraine preventive agents											
Antihypertensives[a]	7040	39.3	15,414	31.1	5930	38.4	5954	38.6	− 0.0032	1110	45.1
Antiepileptics[b]	1495	8.4	2722	5.5	1192	7.7	1207	7.8	− 0.0036	303	12.3
Antidepressants[c]	9637	53.8	21,566	43.6	8147	52.8	8157	52.8	− 0.0013	1490	60.5
Botulinum toxins[d]	4486	25.1	2091	4.2	2112	13.7	2051	13.3	0.0116	2374	96.5

Table 2 continued

Baseline characteristic	Identified from 17 May 2018 to 31 March 2020										
	All initiators before matching				Propensity score-matched initiators					Unmatched erenumab Initiators	
	Erenumab		AEDs		Erenumab		AEDs		SD	Erenumab	
	N = 17,902		*N* = 49,497		*N* = 15,441		*N* = 15,441			*N* = 2461	
	N	%	*N*	%	*N*	%	*N*	%		*N*	%
Other migraine preventives[e]	3607	20.2	5415	10.9	2842	18.4	2780	18.0	0.0104	765	31.1
Comorbidities related to migraine											
Anxiety	6832	38.2	20,863	42.2	5956	38.6	5852	37.9	0.0139	876	35.6
Depression	5587	31.2	16,357	33.1	4798	31.1	4726	30.6	0.0101	789	32.1
Chronic pain	9394	52.5	27,820	56.2	8135	52.7	8113	52.5	0.0029	1259	51.2
Insomnia	3467	19.4	8332	16.8	2932	19.0	2853	18.5	0.0131	535	21.7
Thyroid disorder	3333	18.6	9335	18.9	2868	18.6	2776	18.0	0.0154	465	18.9
Drugs that may cause constipation											
Opioids/opiates	8000	44.7	23,372	47.2	6888	44.6	6737	43.6	0.0197	1112	45.2
Anticholinergics	10,060	56.2	25,165	50.8	8566	55.5	8437	54.6	0.0168	1494	60.7
Antipsychotics	326	1.8	662	1.3	246	1.6	236	1.5	0.0052	80	3.3
Antihistamines	6827	38.1	18,290	37.0	5774	37.4	5643	36.6	0.0176	1053	42.8
Antispasmodics	1860	10.4	5401	10.9	1619	10.5	1540	10.0	0.0169	241	9.8
Antiparkinsonian drugs	187	1.0	331	0.7	153	1.0	144	0.9	0.0060	34	1.4
Tricyclic antidepressants	4544	25.4	8114	16.4	3792	24.6	3853	25.0	− 0.0092	752	30.6
NSAIDs (prescription and OTC)	9710	54.2	27,694	56.0	8301	53.8	8242	53.4	0.0077	1409	57.3
Cation-containing agents	1131	6.3	3430	6.9	978	6.3	947	6.1	0.0083	153	6.2
Iron supplements	528	3.0	1909	3.9	463	3.0	452	2.9	0.0042	65	2.6
Aluminum (antacids, sucralfate)	643	3.6	1656	3.4	548	3.6	525	3.4	0.0081	95	3.9

Table 2 continued

Baseline characteristic	Identified from 17 May 2018 to 31 March 2020										
	All initiators before matching				Propensity score-matched initiators					Unmatched erenumab Initiators	
	Erenumab		AEDs		Erenumab		AEDs		SD	Erenumab	
	N = 17,902		*N* = 49,497		*N* = 15,441		*N* = 15,441			*N* = 2461	
	N	%	*N*	%	*N*	%	*N*	%		*N*	%
5-HT_3 antagonists	6844	38.2	19,758	39.9	5872	38.0	5695	36.9	0.0237	972	39.5
Prescription drugs that treat constipation											
Prescription laxatives (lactulose, Dulcolax)	200	1.1	748	1.5	184	1.2	184	1.2	0.0000	16	0.7
Other prescription treatments (tegaserod, linaclotides, lubiprostone)	640	3.6	1113	2.3	495	3.2	483	3.1	0.0044	145	5.9
OTC drugs that treat constipation	2037	11.4	8039	16.2	1801	11.7	1707	11.1	0.0192	236	9.6
Gastrointestinal disorders											
Irritable bowel syndrome	1326	7.4	3186	6.4	1112	7.2	1055	6.8	0.0145	214	8.7
Crohn's disease	144	0.8	449	0.9	129	0.8	117	0.8	0.0087	15	0.6
Ulcerative colitis	112	0.6	371	0.8	104	0.7	91	0.6	0.0106	8	0.3
Diverticulitis/diverticulosis	653	3.7	2201	4.5	568	3.7	544	3.5	0.0083	85	3.5
Hemorrhoids (excluding pregnancy-induced)	852	4.8	2461	5.0	732	4.7	729	4.7	0.0009	120	4.9
Conditions that are associated with constipation											
Diabetes mellitus	1784	10.0	5782	11.7	1574	10.2	1539	10.0	0.0075	210	8.5
Autonomic neuropathy	136	0.8	350	0.7	116	0.8	104	0.7	0.0092	20	0.8
Multiple sclerosis	279	1.6	674	1.4	238	1.5	236	1.5	0.0011	41	1.7
Hirschsprung disease	1	< 0.1	4	< 0.1	0	0.0	0	0.0	NC	1	< 0.1
Spinal cord injury	8	< 0.1	22	< 0.1	8	0.1	9	0.1	− 0.0028	0	0.0
Parkinson's disease	36	0.2	157	0.3	33	0.2	36	0.2	− 0.0041	3	0.1
Hypothyroidism	2696	15.1	7337	14.8	2317	15.0	2249	14.6	0.0124	379	15.4
Hypokalemia	775	4.3	2541	5.1	675	4.4	642	4.2	0.0106	100	4.1

Table 2 continued

Baseline characteristic	Identified from 17 May 2018 to 31 March 2020										
	All initiators before matching				Propensity score-matched initiators					Unmatched erenumab Initiators	
	Erenumab		AEDs		Erenumab		AEDs		SD	Erenumab	
	N = 17,902		*N* = 49,497		*N* = 15,441		*N* = 15,441			*N* = 2461	
	N	%	*N*	%	*N*	%	*N*	%		*N*	%
Anorexia nervosa	186	1.0	520	1.1	155	1.0	151	1.0	0.0026	31	1.3
Pregnancy	276	1.5	1746	3.5	266	1.7	241	1.6	0.0127	10	0.4
Panhypopituitarism	28	0.2	79	0.2	24	0.2	23	0.2	0.0017	4	0.2
Systemic sclerosis	23	0.1	67	0.1	20	0.1	22	0.1	− 0.0035	3	0.1
Myotonic dystrophy	4	< 0.1	7	< 0.1	4	< 0.1	5	< 0.1	− 0.0038	0	0.0
Constipation or complications of constipation during the 12-month baseline period											
Any constipation (OP/IP/ED)	1550	8.7	4547	9.2	1318	8.5	1246	8.1	0.0169	232	9.4
Idiopathic constipation (OP/IP/ED)	10	0.1	24	0.1	9	0.1	10	0.1	− 0.0026	1	< 0.1
Normal colonic transit	1318	7.4	4014	8.1	1,133	7.3	1058	6.9	0.0189	185	7.5
Slow transit constipation	113	0.6	300	0.6	91	0.6	88	0.6	0.0026	22	0.9
Dyssynergic constipation	11	0.1	57	0.1	9	0.1	9	0.1	0.0000	2	0.1
Inpatient constipation (IP/ED)	340	1.9	1373	2.8	297	1.9	308	2.0	− 0.0051	43	1.8
Complications of constipation (IP/ED)	95	0.5	388	0.8	89	0.6	86	0.6	0.0026	6	0.2
Bowel perforation	3	< 0.1	27	0.1	2	< 0.1	0	0.0	NC	1	< 0.1
History of constipation											
Family history of constipation[f]	17	0.1	56	0.1	13	0.1	11	0.1	0.0046	4	0.2
Personal history of constipation[f]	5769	32.2	15,555	31.4	4900	31.7	4801	31.1	0.0138	869	35.3

Table 2 continued

Baseline characteristic	Identified from 17 May 2018 to 31 March 2020										
	All initiators before matching				Propensity score-matched initiators					Unmatched erenumab Initiators	
	Erenumab		AEDs		Erenumab		AEDs		SD	Erenumab	
	N = 17,902		*N* = 49,497		*N* = 15,441		*N* = 15,441			*N* = 2461	
	N	%	*N*	%	*N*	%	*N*	%		*N*	%
Procedures related to constipation treatment											
Mentions in clinical notes											
Gastrografin enema[f]	3	< 0.1	4	< 0.1	1	< 0.1	3	< 0.1	− 0.0114	2	0.1
Glycerin/Fleet enema[f]	58	0.3	246	0.5	50	0.3	45	0.3	0.0058	8	0.3

AED antiepileptic drug, *ED* emergency department, *IP* inpatient, *NSAID* non-steroidal anti-inflammatory drugs, *OP* outpatient, *OTC* over-the-counter, *SD* standardized difference, *5-HT$_3$* serotonin receptor

[a]Includes beta blockers, calcium channel blockers, candesartan, clonidine, and lisinopril

[b]Includes levetiracetam and pregabalin

[c]Includes serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors

[d]Includes abobotulinumtoxinA, incobotulinumtoxinA, onabotulinumtoxinA, and rimabotulinumtoxinB

[e]Includes carisoprodol, cyproheptadine, guanfacine, memantine, methysergide, milnacipran, and tizanidine

[f]Identified using the semi-structured (NLP) data within the EHR database

inpatient constipation was estimated in the same manner.

The risk windows for outcome assessment included 30, 60, and 90 days following the index date, and all available follow-up, with the 90-day window specified a priori as the primary risk window. The accrual period for initiators was adjusted to ensure the patients included in the analysis for each risk window had the requisite amount of follow-up time. For each risk window, patients who initiated treatment during the following time periods were included:

- 30-day risk window: 17 May 2018 through 29 February 2020
- 60-day risk window: 17 May 2018 through 31 January 2020
- 90-day risk window: 17 May 2018 through 31 December 2019
- All available follow-up: 17 May 2018 through 31 March 2020

Odds ratios (ORs) and corresponding 95% CIs were estimated using logistic regression models to compare the risk of inpatient constipation in the matched erenumab cohort to the other CGRP mAb and, separately, to the AED cohorts. The OR approximates the estimate of interest, the risk ratio, because inpatient constipation is a rare outcome [11]. The outcome models were not adjusted for covariates as none were imbalanced following PS matching.

As a sensitivity analysis, the risk of inpatient constipation was calculated within the study cohorts after stratifying on the presence of epilepsy diagnosis and the use of constipation-causing medications during the baseline period. Additionally, among erenumab initiators only, the risk of inpatient constipation by prior use of AEDs was assessed. Finally, to ensure that amount of available follow-up time among initiators of erenumab and initiators of other CGRP mAbs was comparable, the risk of inpatient constipation was calculated among the subset of PS-matched initiators whose index date was on or after 1 January 2019.

RESULTS

Cohort Formation and Baseline Characteristics

Between 17 May 2018 and 31 March 2020, we identified 29,372 patients whose earliest prescription order was for erenumab, 21,962 patients whose earliest prescription was for other CGRP mAbs, and 243,183 patients whose earliest prescription was for AEDs (Fig. 1). Following application of all study criteria, 17,902 patients were included in the erenumab initiator cohort, 13,404 patients were included in the other CGRP mAb initiator cohort, and 49,497 patients were included in the AED initiator cohort. Among patients in the other CGRP mAb cohort, 63.4% had a prescription order for galcanezumab on the index date, 36.3% had a prescription for fremanezumab, 0.3% had prescriptions for both galcanezumab and fremanezumab, and 0% had a prescription for eptinezumab, which was approved on 21 February 2020 (data not shown).

Tables 1 and 2 present the baseline characteristics of the erenumab, other CGRP mAb, and AED initiator cohorts pre- and post-matching. Pre-matching, mean age was similar across cohorts, ranging from 45.2 years in the other CGRP mAb and AED cohorts to 45.9 years in the erenumab cohort. The majority of patients in each cohort were female: 87.5% of erenumab initiators, 88.2% of other CGRP mAb initiators, and 86.4% of AED initiators. Pre-matching, inpatient constipation during the 12-month baseline period was observed among 1.9% of patients in the erenumab cohort, 1.7% of patients in the other CGRP mAb cohort, and 2.8% of patients in the AED cohort.

For the erenumab–other CGRP mAb comparison, 13,200 initiators in each cohort were PS-matched (Table 1); 4702 erenumab initiators were unmatched. For the erenumab-AED comparison, 15,441 initiators in each cohort were matched (Table 2); 2461 erenumab initiators were unmatched. For both comparisons, there were no risk factors with an absolute standardized difference greater than 0.1 in the PS-matched cohorts, indicating the matched cohorts

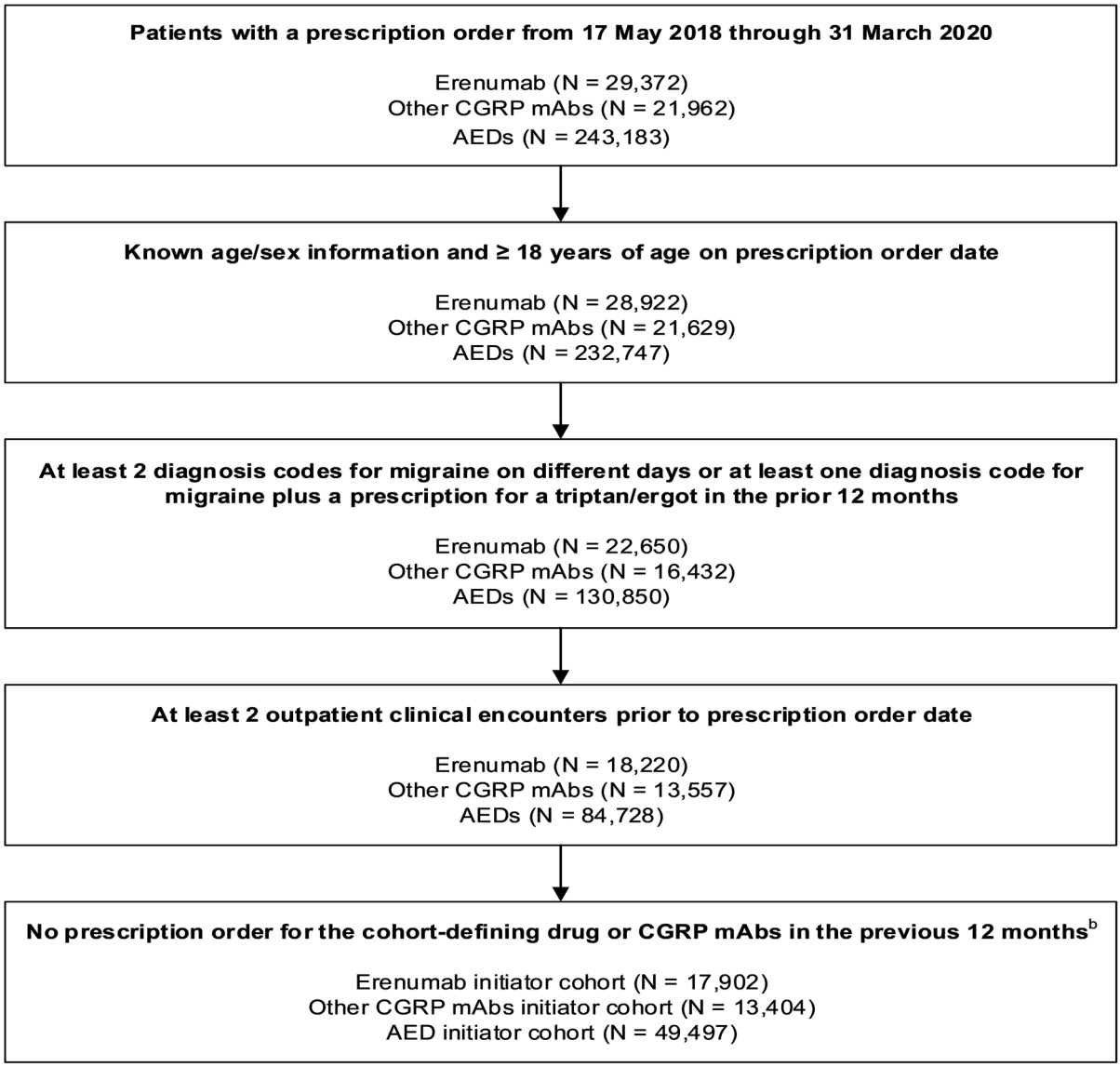

Fig. 1 Formation of erenumab, other CGRP monoclonal antibody, and standard of care antiepileptic drug initiator cohorts[a]. *AED* antiepileptic drug, *CGRP* calcitonin gene-related peptide, *mAbs* monoclonal antibodies. [a]To identify initiators, only the earliest prescription order during the study period was assessed for cohort eligibility. [b]Patients were also required to have known geographic region

were well balanced. The distribution of PSs before and after PS matching are shown in Figs. S1a and S1b for the erenumab and other CGRP mAb initiator cohorts and Figs. S2a and S2b for the erenumab and AED initiator cohorts (electronic supplementary material).

Risk of Inpatient Constipation and Serious Complications of Inpatient Constipation

Within the 90-day risk window following the index date, we observed 84 inpatient constipation events among 15,983 erenumab initiators, 50 events among 11,345 other CGRP mAb initiators, and 398 events among 43,810 AED initiators before PS matching (Table 3). The

Table 3 Risk of inpatient constipation within a 90-day risk window among erenumab, other CGRP monoclonal antibody, and standard of care antiepileptic drug initiators, pre- and post-propensity score matching

	Initiators[a]	Inpatient constipation[b]	Risk of inpatient constipation		Odds ratio (95% CI)[c]
	N	*N*	%	95% CI	
Pre-matching					
Erenumab	15,983	84	0.53	0.42–0.65	–
Other CGRP mAbs	11,345	50	0.44	0.33–0.58	–
AEDs	43,810	398	0.91	0.82–1.00	–
Post-matching					
Erenumab–other CGRP mAbs comparison					
Erenumab	11,670	54	0.46	0.35–0.60	1.06 (0.72–1.55)
Other CGRP mAbs	11,172	49	0.44	0.33–0.58	1.00 (Reference)
Unmatched erenumab initiators	4313	30	0.70	0.49–0.99	–
Erenumab–AEDs comparison					
Erenumab	13,669	72	0.53	0.42–0.66	0.69 (0.51–0.94)
AEDs	13,752	104	0.76	0.62–0.92	1.00 (Reference)
Unmatched erenumab initiators	2314	12	0.52	0.30–0.90	–

AED antiepileptic drug, *CGRP* calcitonin gene-related peptide, *CI* confidence interval, *mAbs* monoclonal antibodies

[a]This table includes initiators identified from 17 May 2018 to 31 December 2019

[b]Inpatient constipation events were identified within a 90-day risk window following the index date, starting from the day after the index date through the earliest of end of the 90-day risk window, switching of migraine preventive therapy, or end of the study period (31 March 2020)

[c]Odds ratio comparing propensity score-matched erenumab initiators to propensity-score matched comparators

corresponding risks were 0.53% (95% CI 0.42–0.65) for erenumab, 0.44% (95% CI 0.33–0.58) for other CGRP mAb, and 0.91% (95% CI 0.82–1.00) for AED initiators.

For the erenumab–other CGRP mAb comparison, results were similar after PS matching. The risk of inpatient constipation was 0.46% (95% CI 0.35–0.60) among matched erenumab initiators and 0.44% (95% CI 0.33–0.58) among matched other CGRP mAb initiators, with a corresponding OR of 1.06 (95% CI 0.72–1.55) (Table 3). For the erenumab–AED comparison, the risk of inpatient constipation was 0.53% (95% CI 0.42–0.66) among matched erenumab initiators and 0.76% (95% CI 0.62–0.92) among matched AED initiators, with a corresponding OR of 0.69 (95% CI 0.51–0.94).

Within 30 days after the inpatient constipation event, the risks of serious complications of inpatient constipation were 0.05% (95% CI 0.03–0.10), 0.04% (95% CI 0.02–0.10), and 0.10% (95% CI 0.07–0.13) among the erenumab, other CGRP mAb, and AED initiators, respectively (Table 4). After PS matching, the risk of serious complications remained low in each cohort.

Table S2 (electronic supplementary material) presents the risk of inpatient constipation among the erenumab, other CGRP mAb, and AED initiators within different risk windows following the index date. Within a 30-day risk and 60-day risk window, the risk was similar among matched erenumab and other CGRP mAb initiators. When assessed during the all

Table 4 Risk of serious complications of inpatient constipation within a 90-day risk window among erenumab, other CGRP monoclonal antibody, and standard of care antiepileptic drug initiators, pre- and post-propensity score matching

	Initiators[a]	Serious complications of inpatient constipation[b]	Risk of serious complications of inpatient constipation	
	N	*N*	%	95% CI
Pre-matching				
Erenumab	15,983	8	0.05	0.03–0.10
Other CGRP mAbs	11,345	5	0.04	0.02–0.10
AEDs	43,810	44	0.10	0.07–0.13
Post-matching				
Erenumab–other CGRP mAbs comparison				
Erenumab	11,670	2	0.02	0.00–0.06
Other CGRP mAbs	11,172	5	0.04	0.02–0.10
Unmatched erenumab initiators	4313	6	0.14	0.06–0.30
Erenumab–AEDs comparison				
Erenumab	13,669	7	0.05	0.02–0.11
AEDs	13,752	12	0.09	0.05–0.15
Unmatched erenumab initiators	2314	1	0.04	0.01–0.24

AED antiepileptic drug, *CGRP* calcitonin gene-related peptide, *CI* confidence interval, *mAbs* monoclonal antibodies

[a]This table includes initiators identified from 17 May 2018 to 31 December 2019

[b]Serious complications were identified within 30 days after the inpatient constipation events that were identified in the 90-day risk window following the index date. Serious complications were counted until the earliest of end of the 30-day period or end of the study period (31 March 2020). Risk was calculated using the number of initiators as the denominator

available follow-up risk window, the risk was 1.52% (95% CI 1.32–1.74) among matched erenumab initiators and 1.08% (95% CI 0.92–1.27) among matched other CGRP mAb initiators, with an OR 1.40 (95% CI 1.13–1.74). For the erenumab–AED comparison, the risk among matched erenumab initiators was lower than that among matched AED initiators within the 30-day, 60-day, and all available follow-up risk windows. Like the 90-day risk window, there were few serious complications of constipation observed within the erenumab, other CGRP mAb, and AED initiator cohorts for the other risk windows (Table S3, electronic supplementary material).

Table S4 (electronic supplementary material) provides the risk of inpatient constipation within 90 days following the index date among the erenumab, other CGRP mAb, and AED initiators stratified by presence of epilepsy. For all cohorts, the risk of inpatient constipation was higher among initiators with an epilepsy diagnosis during baseline compared to initiators without a diagnosis. However, the OR for the erenumab–other CGRP mAbs comparison was similar among those with an epilepsy diagnosis and those without a diagnosis. Similar results were observed for the erenumab–AEDs comparison; the ORs among patients with and without epilepsy were 0.76 (95% CI 0.35–1.62) and 0.67 (95% CI 0.48, 0.92), respectively.

The risk of inpatient constipation within 90 days following the index date stratified by baseline medication use is presented in Table S5 (erenumab and other CGRP mAb initiators) and Table S6 (erenumab and AED initiators) in the

electronic supplementary material. The risk of inpatient constipation was higher among erenumab, other CGRP mAb, and AED initiators with baseline use of opioids, anticholinergic medications, non-steroidal anti-inflammatory drugs (NSAIDs), cation-containing agents, and serotonin (5-HT_3) receptor antagonists compared to initiators without baseline use of these medications. Additionally, the risk of inpatient constipation was higher among erenumab initiators with AED use during baseline, compared to erenumab initiators without AED use during baseline.

Table S7 (electronic supplementary material) presents the risk of inpatient constipation and corresponding ORs within each risk window among the subset of erenumab and other CGRP mAb initiators whose index date was on or after 1 January 2019. Within a 90-day risk window, the OR for matched erenumab versus other CGRP mAb initiators was 0.90 (95% CI 0.57–1.40). For all available follow-up time, the OR was 1.14 (95% CI 0.87–1.49).

DISCUSSION

In the post-marketing setting, inpatient constipation with serious complications was reported following the use of erenumab. As such, this study assessed the risk of constipation and serious complications among patients with migraine who initiated preventive treatment with erenumab, other CGRP mAbs, or standard of care AEDs in the inpatient setting only; constipation associated with outpatient visits was not assessed. Since antiepileptics are commonly used as migraine preventive agents, they were chosen as the standard of care therapy for the second comparator cohort to avoid drug classes known to be associated with an increased risk of constipation (e.g., antihypertensives, antidepressants).

The risk of inpatient constipation in the 90 days following treatment initiation was similar for the erenumab and other CGRP mAbs cohorts, while a lower risk was observed among erenumab initiators compared to AED initiators. Moreover, inpatient constipation risk was higher among AED initiators than among initiators of erenumab or other CGRP mAbs, even after PS matching. A possible explanation for this finding may be that carbamazepine and valproic acid were among the antiepileptic medications included in the comparator cohort; constipation is a side effect of both treatments [12].

There were few serious complications of constipation observed in this study; the risk of serious complications of constipation was low overall and similar in the erenumab and other CGRP mAb cohorts, but slightly higher in the AED cohort.

The risk of inpatient constipation among all initiators of erenumab in this study was 0.53% within 90 days following treatment initiation. This estimate is similar to the incidence reported in a retrospective cohort study conducted within the MarketScan® Research Databases [13]. Among patients with migraine initiating various acute and preventive migraine treatments, the incidence of serious constipation (i.e., constipation claim in an ED or inpatient setting) was 0.63% [13]. However, the risk observed in this study was lower than that observed among patients in the erenumab clinical studies [3–5], where incidence of any constipation during the first 3 months was 1% with placebo, 1% with 70 mg erenumab, and 3% with 140 mg erenumab [6]. Other studies conducted using real-world data have also reported higher incidence of any constipation (13.5–23.9%) among patients treated with erenumab, although most cases were mild, suggesting that constipation may be a frequent but minor effect of erenumab treatment [14–16]. As our study assessed inpatient constipation only, it is expected that the risk would be lower than studies that identified any constipation, but may impact the generalizability of the results.

We observed a higher risk of inpatient constipation among erenumab, other CGRP mAb, and AED initiators with constipation risk factors during baseline, including an epilepsy diagnosis and use of medications known to be associated with constipation, such as opioids, anticholinergics, and 5-HT_3 receptor antagonists. This suggests that some cases of inpatient constipation may be partially attributable to these factors rather than to use of the CGRP mAbs alone.

In this study, we did not assess gepants which are small molecules that also target the CGRP pathway to treat migraine. Gepants were not approved by the FDA until late in the study period (December 2019 for ubrogepant and February 2020 for rimegepant) or after the study was completed (September 2021 for atogepant). Nonetheless, it is possible that some patients included in this study received a gepant prior to the index date or before the end of the study period.

An advantage of conducting this analysis within an EHR database versus a claims database is that patient assistance programs sponsored by pharmaceutical manufacturers are unlikely to have impacted the identification of treatment initiators in this study. While EHR data are valuable for the examination of clinical outcomes and treatment patterns, EHR databases have certain inherent limitations because the data are collected for the purpose of clinical patient management, not research. The presence of a diagnosis code may not represent the true occurrence of disease, as the diagnosis may be incorrectly coded or included as rule-out criteria rather than actual disease. Furthermore, a diagnosis code for inpatient constipation in this study may have included events for which constipation was the reason for the admission, present on admission, or developed during the hospital stay. Additionally, the prescription data represent the intent of the prescriber through the written prescription for a medication, and do not indicate that a medication was filled, consumed, or taken as prescribed.

It is possible that patients in the AED cohort took their index medication for an indication other than migraine. To ensure these cohort members were patients with migraine, a combination of two migraine diagnosis codes and/or prescriptions for migraine treatments were required in the 12-month baseline period. Analyses stratified by the presence of an epilepsy diagnosis code during the baseline period were also conducted; the OR of inpatient constipation for erenumab relative to AEDs was similar among initiators with a baseline epilepsy diagnosis and initiators without a baseline epilepsy diagnosis.

As is true for most clinical record-keeping systems, it is not possible to directly determine the completeness of data capture during baseline and follow-up periods within Optum's EHR database as some patients may receive only a portion of their care from a provider included in the database. Furthermore, we cannot confirm when a patient is lost to follow-up. This contrasts with claims databases, where baseline and follow-up are defined on the basis of dates of health plan enrollment, ensuring that capture of clinical encounters in the database during those periods is relatively complete. In this study, visit dates were available in the EHR database to determine when events of interest occurred. A proxy could have been used to define the end of follow-up, such as the date of last encounter, but this approach would enable sicker patients with more frequent medical visits to contribute more follow-up time than healthier patients with fewer medical visits. To avoid this form of selection bias, the risk (incidence proportion), which was calculated using the number of cohort members as the denominator, was estimated rather than the incidence rate, which is calculated using the person-time at risk as the denominator. Given that the primary objective was to identify inpatient constipation events within a relatively short period following drug exposure (i.e., 90 days), the incidence proportion could serve as a proxy of the cumulative incidence.

In this study, multiple risk windows for outcome assessment were evaluated, with the 90-day risk window specified a priori as the primary risk window of interest. When initiators of erenumab were compared to initiators of other CGRP mAbs, the risk of inpatient constipation was similar in the two cohorts for the 30-day, 60-day, and 90-day risk windows. However, for all available follow-up, risk of inpatient constipation was higher among erenumab initiators compared to the other CGRP mAb initiators. In contrast, when the erenumab cohort was compared to the AED cohort, the risk of inpatient constipation was consistently lower in the erenumab cohort across all risk windows. The consistency in the ORs obtained by assessing occurrence of outcomes in risk windows of varying lengths provides assurance

on the robustness of the estimates observed in this study.

The start of the study period was 17 May 2018, the date that erenumab was approved in the USA. However, fremanezumab and galcanezumab were not approved until September 2018. Consequently, the follow-up period was longer for erenumab compared to other CGRP mAb initiators, providing greater opportunity for the occurrence of outcomes among erenumab initiators. Indeed, when the main results were compared to those from the sensitivity analysis among the subset of matched initiators whose index date was on or after 1 January 2019, the ORs were attenuated in the sensitivity analysis. This finding suggests that a longer period of available follow-up among the erenumab compared to other CGRP mAb initiators may have contributed to the higher risk of inpatient constipation observed in this cohort, particularly during all available follow-up in the main analysis.

Although adjustment for confounding was implemented through PS modeling and matching, residual confounding is possible. As health plan coverage for erenumab may require prior authorization or a "step-through" therapy (i.e., failure of standard of care medications), the erenumab initiators may have been different from the AED initiators with respect to migraine severity. This difference could have resulted in biased measures of association if migraine severity is associated with constipation [17, 18]. Following PS matching, the study cohorts were found to be comparable with respect to the measured confounders. Nonetheless, migraine severity was not measured directly, although proxies for severity (i.e., use of migraine preventive agents, comorbidities related to migraine) were included in the PS model. Compared to initiators of AEDs, initiators of other CGRP mAbs were likely more comparable to initiators of erenumab with respect to migraine severity, as indicated by the prevalence of proxies for severity pre-matching. The findings observed in this study population, consisting predominantly of women who likely experienced moderate–severe migraine, may not be generalizable to the overall population of patients with migraine, despite the significance of migraine severity as a confounder.

CONCLUSION

The risk of inpatient constipation within 90 days following treatment initiation among patients who initiated erenumab was similar to the risk among patients who initiated other CGRP mAbs and lower than the risk among patients who initiated AEDs. Additionally, the risk of serious complications of inpatient constipation overall was low and comparable in the erenumab and other CGRP mAb cohorts, but slightly higher in the AED cohort. However, as few serious complications of inpatient constipation were observed and the 95% CI for the risks were wide, results for this outcome should be interpreted with caution. Nonetheless, these findings provide context to events observed in real-world post-marketing surveillance data.

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Compliance with Ethics Guidelines. The database is certified as de-identified by an independent statistical expert following Health Insurance Portability and Accountability Act statistical de-identification rules; the study protocol was exempt from institutional review board review.

Data Availability. The dataset analyzed during the current study is not publicly available, but is available from Optum through a data license agreement. More information can be found at the following website: https://www.optum.com/business/solutions/life-sciences/real-world-data/ehr-data.html.

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