

Supplementary Material

Monthly Headaches and Severity in Patients on Galcanezumab or Traditional Preventive Migraine Medication: A 24-Month Claims and Electronic Health Records Study

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Methodology

Conversion of migraine headache days from Acute Migraine Medications

Monthly migraine days

A claims-based proxy for migraine headaches was created based on a conversion calculation for acute migraine medication doses to number of headaches. The Pharmacy Quality Alliance (PQA) developed and endorsed the quality measure for Migraine Preventive Therapy (MPT) which compares headache frequency derived from acute migraine treatment medications against a set threshold (i.e., 12 headaches per ≤ 120 day evaluation period), to determine measure eligibility for preventive treatment. This methodology has been assessed for reliability in measure performance. Components of the measure were adapted to calculate the number of migraine headache days per 30 days at the patient-level during the following observation periods: 12-month baseline period, fixed 24-month follow-up period, and variable follow-up period as follows:

- The calculation only used prescription claims for acute migraine medications. The observation period was the 12-month baseline period, fixed 24-month follow-up period, or variable follow-up period.
 - Note: the PQA measure uses ≤ 120 -day evaluation periods for each acute migraine medication fill, with the highest being compared against the threshold for qualifying for preventive treatment. This calculation is modified to use longer evaluation periods (defined relative to a preventive treatment initiation index date) in order to understand the impact of medications on long-term treatment outcomes, among patients already taking preventive treatment.
- For each acute migraine medication claim during the observation period, the number of headaches was calculated, multiplying the quantity times a conversion factor (see **Table S1**).

- If there were multiple claims for acute migraine medications with the same date of service, all prescription claims were used to calculate the number of migraine headaches.
- Note: the PQA MPT measure excludes the prescription claim(s) with the latest date of service during the observation period. This is because the measure extends the observation period to up to four months, instead of three months (typical assessment period for chronic migraine) to capture acute medication refills, to indicate medication usage and the occurrence of migraine headaches. Because the observation period is longer in this study and given a comparator group is included, all acute medication fills were counted.
- Per patient, the number of headaches across prescription claims was totaled, then divided by the number of months (12 for baseline, 24 for fixed follow-up, or number of 30-day intervals for variable follow-up) during the observation period. For patients with no acute migraine medication claims during the observation period, their value was zero.
- Note: count of fills, total days supply, and total quantity per medication/route were summarized for context. Total days supply was not adjusted for concurrent use, but this served as a comparison as a different measure of use.

Table S1. Conversion of headaches from acute migraine medications

Medication/Medication Class	Route/ Dosage Form	Quantity Unit	Quantity	Headaches
Triptan	Oral	2	Tablets	1
Triptan	Subcutaneous	1	mL	1
Triptan	Nasal	2	Sprays	1
Triptan	Nasal powder	4	Nosepieces	1
Butorphanol	Nasal	2.5	mL	6
Ergotamine derivatives	Nasal	1	mL	1
Ergotamine derivatives	Injection	2	mL ampule	1
Ergotamine derivatives	Oral	2	Tablets	1
Ergotamine derivatives	Rectal	2	Suppositories	1
Cambia® (diclofenac)	Oral	2	Packets	1
Butalbital (including combination products)	Oral	2	Tablets/ Capsules	1
Midrin®-type medication (isometheptene combination)	Oral	2	Capsules	1
Ubrogepant	Oral	2	Tablets	1
Rimegepant (where quantity ≤ 8)	Oral	1	Tablets	1
Lasmiditan 50 mg	Oral	1	Tablets	1
Lasmiditan 100 mg	Oral	2	Tablets	1

PQA, Pharmacy Quality Alliance.

Reference: Table MTP-C: Migraine Headache Conversion Factors. Migraine Preventive Therapy measure. PQA Measure Specifications—Measure Manual. July 2022.

Note: conversions are limited to migraine-related acute treatments included in the PQA measure specification.

Natural Language Processing

The available structured data lacked information on migraine frequency, baseline and current headache frequency and mean number of migraine days, necessitating the utilization of Natural Language Processing (NLP) techniques to extract it from clinical notes.

To identify the clinical notes with migraine, we used the International Classification of Diseases, 9th and 10th Revisions (ICD-9 and ICD-10) codes along with mentions of Migraine and related concepts in the notes. A total of 11,960 notes corresponding to 4,838 patients were identified that fulfilled the criteria of presence of ICD codes with one or more than one term of interest. From these set of notes, 678 notes (444 in phase 1 and 234 in phase 2) were considered for manual annotation. Additionally, 140 notes were used to test the model for bias and the performance was found to be consistent for all the demographic categories. The notes were divided into *train* (70%), *test* (15%), and *validation* (15%) set. The training set was used for model development, the validation set for tuning hyperparameters and preventing overfitting, and the test set was used for evaluating final model performance.

Handling conflicting information:

To handle ambiguous or conflicting information in EHR notes, each note was manually annotated (reviewed) by two clinicians, ensuring that migraine and migraine frequency related terms were accurately labelled. Annotation or manual review of notes is a process of examining and labelling clinical notes. This involved correcting, modifying or confirming the labels assigned automatically by the algorithm based on pre-defined terms. Following annotation, curation of the annotated notes was done to ensure the quality and coherence of the annotated data.

Curation was conducted to review and validate annotations, resolve inconsistencies, and integration of the annotated data into a useful format. This step is critical in refining the data for better quality and reliability and preparing the data for further analysis. Annotation and

curation ensure that the data meets the required standards and specifications for machine learning applications.

In this analysis, only tags with 100% inter-observer agreement (Cohen's kappa statistic) were accepted. For tags having less than 100% inter-observer agreement, a secondary curator reviewed such tags and used best judgement to accept the right tag (the secondary curator could modify the tags created by the primary curator but was not able to create new tags).

Model fit and statistics:

Our NLP model was developed using a custom approach tailored to the healthcare domain. We utilized embeddings trained on a combination of PubMed, ICD10, UMLS, and MIMIC III corpora (HealthCare Embeddings).

Healthcare / clinical embedding was selected as it outperformed other models due to several factors as highlighted below:

Specialization:

These embeddings are specifically fine-tuned for healthcare applications, ensuring they capture the nuances and complexities of medical language better than the general-purpose models.

Retrieval-Augmented Generation (RAG):

John Snow Labs (JSL) employs a RAG framework, which combines information retrieval with text generation. This approach ensures that the generated responses are grounded in up-to-date, reliable sources, which is crucial for medical contexts.

Comprehensive Toolset:

The Healthcare/ clinical embeddings NLP Library includes over 2,400 pre-trained models and pipelines for tasks like clinical information extraction and named entity recognition (NER). This extensive library supports a wide range of healthcare-specific tasks.

Efficiency and Relevance:

Smaller, specialized models within the RAG framework can deliver performance comparable to larger, general-purpose models. This makes them both efficient and highly relevant for healthcare tasks.

Advanced Algorithms:

The models are built on advanced algorithms and are regularly updated to maintain high accuracy and reliability in processing medical data.

We evaluated our model using standard metrics to ensure robust performance, including sensitivity (recall), specificity (Precision), and F1 score. On the test data, the model achieved an overall precision of 0.84, recall of 0.90, and F1 score of 0.87. On the validation data, the model achieved an overall precision of 0.83, recall of 0.84, and F1 score of 0.83. These metrics demonstrate the model's ability to accurately identify and extract migraine-related information from EHR notes.

Table S2. Acute migraine medications used by the galcanezumab and standard of care cohorts.

Classification	Drug class	Examples of drugs included
Migraine specific	CGRP gepants	Rimegepant (where quantity ≤ 8); ubrogepant
	Serotonin 5-HT _{1F} receptor agonist	Lasmiditan
	Triptans	Almotriptan; eletriptan; frovatriptan; naratriptan; rizatriptan; sumatriptan and sumatriptan combinations; zolmitriptan
	Ergotamine/ergotamine derivative/other forms of dihydroergotamine	Dihydroergotamine; ergoloid mesylates; ergotamine
Non-specific	Nonsteroidal anti-inflammatory drugs	Aspirin; celecoxib oral solution; diclofenac; etodolac; fenoprofen calcium; flurbiprofen; ibuprofen; indomethacin; ketoprofen; meclofenamate sodium or meclofenamic acid; meloxicam; nabumetone; naproxen; oxaprozin; piroxicam; sulindac; sumatriptan + naproxen sodium; tolmetin sodium
	Acetaminophen and combinations	Acetaminophen + aspirin + caffeine
	Butalbital-containing combinations	Butalbital + acetaminophen + caffeine; butalbital + aspirin + caffeine; butalbital + codeine + aspirin + caffeine
	Antiemetics	Chlorpromazine; droperidol; haloperidol; metoclopramide; ondansetron hydrochloride, maleate, or edisylate; prochlorperazine; promethazine
	Isometheptene-containing compounds	Isometheptene mucate/dichloralphenazone/acetaminophen
	Opioids	Codeine; fentanyl; hydrocodone; hydromorphone; levorphanol tartrate; meperidine hydrochloride; morphine sulfate; nalbuphine hydrochloride; oxycodone + combinations; pentazocine + combinations; sufentanil citrate; tapentadol; tramadol + combinations

CGRP, calcitonin gene-related peptide.

Table S3. List of required migraine concepts extracted from notes using the natural language processing model.

Concepts	Description
Migraine concepts extracted from notes using natural language processing	
Frequency	• Explicit frequencies of migraine or headache days were captured • Included numeric frequency amounts and countable expressions like “daily” • Numeric ranges for frequency were included • Narrative expressions such as “decreased frequency” and modifiers such as “greater than” were not included
Frequency unit	• Denominator or unit of frequency statement were included • Extracted frequency unit mentioned when available • Only countable units of time such as 3 headache days per month were considered; relative dates or months like “September” were not included
Migraine concepts extracted manually	
Chronology	• Extracted chronology associated with a migraine/headache frequency • Included “baseline” and “previous”; excluded “current” and “present”