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Post-Marketing Safety of CGRP Inhibitors: A Systematic Review Protocol of Spontaneous Reporting Data

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 8 September 2025 and was last updated on 8 September 2025.

INTRODUCTION

Review question / Objective The aim of this study is to systematically review and summarize the results of pharmacovigilance studies that have analyzed adverse events for CGRP inhibitors, using data from the FDA Adverse Event Reporting System (FAERS), WHO's VigiBase, and the European EudraVigilance database.
The research question, defined using the PICOS framework, is as follows:
• P (Population): Patient data within spontaneous reporting databases (FAERS, VigiBase, EudraVigilance) who have received treatment with CGRP inhibitors.
• I (Intervention): Treatment with anti-CGRP monoclonal antibodies (erenumab, galcanezumab, fremanezumab, eptinezumab) or gepants (rimegepant, ubrogepant, atogepant, zavegepant).
• C (Comparator): Not applicable. This review will not directly compare interventions but will analyze safety signals based on disproportionality analyses within the databases.
• O (Outcome): Identification and synthesis of adverse event (AE) signals and adverse events of special interest (AESIs), as measured by disproportionality metrics (e.g., Reporting Odds Ratio - ROR, Proportional Reporting Ratio - PRR).
• S (Study designs): Pharmacovigilance studies.
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Rationale The introduction of calcitonin gene-related peptide (CGRP) inhibitors, which include both monoclonal antibodies and gepants, represents a revolutionary advance in migraine therapy. Initial evidence of their safety and efficacy comes from randomized controlled trials (RCTs) conducted prior to approval. However, the carefully controlled environment of an RCT study has its own limitations. These studies are designed to include highly selected groups of patients, often excluding people with concurrent medical conditions or those taking other medications. In addition, their limited scope and duration may not be sufficient to detect rare, delayed or long-term adverse effects.
This creates a critical knowledge gap, as the safety profile of a drug may differ significantly when used by broader, more diverse patient populations encountered in routine clinical practice. To close this gap, post-market pharmacovigilance is an essential part of a drug's lifecycle. Large databases for spontaneous reporting systems, such as FDA's FAERS and WHO's VigiBase, are important tools for this ongoing monitoring. They collect millions of adverse event reports worldwide and enable researchers to identify potential safety signals that were not visible in the controlled environment of the initial studies.
While individual pharmacovigilance studies are valuable for detecting signals, a single analysis is not sufficient to provide a definitive overview of the real-world safety profile of a drug class. Individual studies are inherently limited by their specific methodology, including the choice of database (which may have geographic bias), the time period analyzed, and the statistical methods used to detect signals. In addition, a study may focus narrowly on a specific drug or adverse event and overlook other potential safety concerns. A safety signal only gains strength and significance if it is consistently identified in multiple independent studies using different data sets and analytic approaches. This consistency is critical to distinguish a robust signal from a finding that may be an artifact of a particular methodology or reporting bias.
Given these limitations, a comprehensive synthesis of the new evidence from the field is essential. This systematic review aims to address this need by synthesizing and analyzing the evidence from the entire landscape of published pharmacovigilance studies. This approach provides a more thorough and up-to-date overview of the safety profiles of both the monoclonal antibody and gepant classes of CGRP inhibitors that goes beyond the limitations of a single research paper.

Condition being studied The disease under investigation is migraine. Migraine is a common and disabling neurological disorder that is considered one of the leading causes of disability worldwide, especially in young adults and women. The burden goes beyond the headache itself and significantly affects quality of life, productivity and mental health. The pathophysiology of migraine is complex, but the neuropeptide calcitonin gene-related peptide (CGRP) has been identified as a key player in mediating nociceptive signaling and vasodilation associated with migraine attacks. This discovery paved the way for targeted therapies aimed at inhibiting the CGRP signaling pathway: CGRP monoclonal antibodies and gepants, which are the subject of this review.

METHODS

Search strategy A systematic literature search will be conducted in the PubMed, Web of Knowledge, Cochrane Library and OpenGrey databases. The search will identify studies analyzing data from the main pharmacovigilance databases, including FAERS, VigiBase, and EudraVigilance. The comprehensive search string will be:
(FAERS OR VigiBase OR EudraVigilance OR Pharmacovigilance OR adverse event reporting OR spontaneous reporting) AND (CGRP inhibitor OR CGRP inhibitors OR CGRP antagonist OR CGRP antagonists OR anti-CGRP monoclonal antibody OR anti-CGRP monoclonal antibodies OR gepant OR gepants OR Erenumab OR Aimovig OR Galcanezumab OR Emgality OR Fremanezumab OR Ajovy OR Eptinezumab OR Vyepti OR Rimegepant OR Nurtec OR Vydura OR Ubrogepant OR Ubrelvy OR Atogepant OR Qulipta OR Zavegepant OR Zavzpret).

Participant or population The population to be analyzed results from the aggregation of individual case safety reports (ICSRs) contained in pharmacovigilance databases. This population represents real patients who have taken CGRP inhibitors for migraine and thus offers a broader perspective than the highly selected cohorts of clinical trials. It is characterized by considerable

heterogeneity in terms of demographics (age, gender), geographic location, comorbidities and use of concomitant medications. Data on these individuals is reported spontaneously from a variety of sources, including healthcare professionals, patients and consumers. Therefore, it is important to clarify that we will not directly access or analyze raw data from a predefined cohort of patients in this review. Instead, our analysis will be conducted at the study level. We will summarize the collective findings — including quantitative signals and qualitative conclusions — from the published pharmacovigilance studies that have looked at this diverse patient population.

Intervention The interventions to be evaluated are the CGRP inhibitor drugs, divided into two classes:
1. Monoclonal Antibodies (mAbs): erenumab, galcanezumab, fremanezumab, eptinezumab.
2. Gepants (small-molecule CGRP receptor antagonists): rimegepant, ubrogepant, atogepant, zavegepant.

Comparator No comparative intervention is defined. The purpose of the review is to synthesize absolute safety profiles based on pharmacovigilance signals, not to conduct a head-to-head comparison of interventions.

Study designs to be included Original research articles that have performed a pharmacovigilance analysis of data from the FAERS, VigiBase, or EudraVigilance databases for one or more CGRP inhibitors will be included.

Eligibility criteria The selection of studies for this review is based on a set of predefined inclusion and exclusion criteria to ensure relevance and methodological suitability.
- Inclusion criteria: Original research studies conducting pharmacovigilance analyzes of adverse event reports for CGRP inhibitors using spontaneous reporting system databases (e.g. FAERS, VigiBase, EudraVigilance).
- Exclusion criteria: Non-research articles such as editorials, letters, commentaries, conference abstracts, narrative reviews, systematic reviews, case reports not associated with database analysis, study protocols, and real-world efficacy studies that do not focus on analyzing pharmacovigilance databases.

Information sources This systematic review will use a two-stage approach to information sources. First, a comprehensive search for appropriate studies will be conducted using the PubMed, Web of Knowledge, Cochrane Library and OpenGrey databases as primary sources of biomedical and life science literature. Secondly, data from studies that evaluated one or more of the following major international databases for spontaneous reporting systems will be summarized:
- FAERS (FDA Adverse Event Reporting System): The U.S. Food and Drug Administration's database that collects adverse event reports from across the United States submitted by healthcare professionals, consumers, and manufacturers.
- VigiBase: The World Health Organization's global ICSR database, which collects data from over 170 countries and provides a comprehensive international perspective on drug safety.
- EudraVigilance: The European Medicines Agency's database for managing and analyzing information on suspected adverse reactions to medicines authorized in the European Economic Area.
These databases are the most comprehensive repositories for post-marketing drug safety monitoring and their use in primary studies ensures a comprehensive real-world evidence base.

Main outcome(s) The main outcome of this review is to identify and summarize post-marketing safety signals of CGRP inhibitors. A safety signal is defined as a reported association between a CGRP inhibitor and an adverse event that is strong enough to warrant further investigation. This outcome will be assessed using qualitative and quantitative measures from the included studies. The most important quantitative measures are the results of disproportionality analyzes. These are statistical methods used to assess whether an adverse event associated with a particular drug is reported more frequently compared to other drugs in the database. These measurements include:
- Reporting Odds Ratio (ROR): Compares the likelihood of a particular adverse event associated with the drug in question occurring to all other drugs in the database.
- Proportional Reporting Ratio (PRR): Measures the extent to which a particular SAR for a given drug is reported disproportionately often compared to all other drugs.
- Information Component (IC): A Bayesian measure used in the WHO International Drug Monitoring Program.
The synthesis will focus on the strength, consistency and clinical relevance of these signals across studies and databases.

Additional outcome(s) Additional outcomes will be:
- Identification of class-specific (mAbs vs. gepants) and drug-specific adverse event profiles.
- Analysis of adverse events of special interest (AESIs), such as alopecia, Raynaud's

phenomenon, cardiovascular and cerebrovascular events, and constipation.
- Synthesis of safety data in special populations (e.g., pregnant women), if available.

Data management We will manage the entire data management process, from study identification to data synthesis, with an emphasis on transparency and rigor. A two-stage screening process will be carried out independently by two reviewers: first, a review of titles and abstracts against eligibility criteria, followed by a full-text assessment of potentially relevant articles. We will use a standardized, pilot-tested data extraction form to capture key study characteristics. These include the author and year of publication, database used, population details, drugs analyzed, evidence of significant adverse events, and quantitative measures of disproportionality with confidence intervals. Any disagreements during screening or data extraction will be resolved through discussion to reach consensus.

Quality assessment / Risk of bias analysis The methodological quality of each included study is assessed independently by two reviewers using a predefined 12-point checklist specifically adapted for pharmacovigilance studies with spontaneous reporting system databases. This tool, based on the core principles of the STROBE and RECORD-PE guidelines, assesses five key areas: (1) clarity of objectives, (2) rigor of data management, (3) adequacy of statistical analysis, (4) handling of bias, and (5) caution in interpretation. Each element is assessed and studies are assigned one of four quality levels (High, Moderate, Low, or Critically Low) based on the overall assessment and fulfillment of four predetermined "major criteria" that are critical to the validity of the study, including handling of duplicates, use of appropriate statistical analysis, recognition of study limitations, and avoidance of causal claims. This assessment will help to contextualize the evidence and understand the robustness of each study's findings.

Strategy of data synthesis A thematic synthesis approach will be used to integrate and summarize the results of the included studies. The extracted data on the most important adverse events are first organized in evidence tables. These tables will be organized by drug class (mAbs and gepants) and further stratified by specific drugs and adverse events of special interest (AESIs). For each identified signal, quantitative measures of disproportionality (e.g., ROR, PRR, IC) with 95% confidence intervals, the number of cases, and the source study are provided in summary tables. A complementary narrative synthesis will then be developed to contextualize these data. This synthesis will describe patterns of adverse events, discuss differences in safety profiles between and within drug classes, and assess the overall strength and consistency of evidence for the most robust signals across studies.

Subgroup analysis The primary analysis will make a qualitative comparison of the adverse event profiles of monoclonal antibodies (mAbs) and gepants to distinguish between safety signals across classes and those specific to a single subclass. We will then perform subgroup analyzes on individual agents within each class to investigate the heterogeneity of their safety profiles. These analyzes aim to distinguish true class effects from drug-specific signals that may result from differences in mechanism of action (e.g., CGRP ligand vs. receptor targeting), pharmacokinetics, or potential off-target effects. All comparisons are based on the consistency and strength of the signals reported in the included studies.

Sensitivity analysis A quantitative sensitivity analysis is not planned, given the qualitative and thematic synthesis nature of this review of published studies. The validity of the identified signals will be strengthened by their consistency across multiple independent analyses.

Language restriction No language restrictions will be applied during the literature search to ensure comprehensive coverage.

Country(ies) involved Italy.

Keywords CGRP Inhibitors; CGRP Monoclonal Antibodies; Gepants; Migraine; Pharmacovigilance; FAERS; VigiBase, EudraVigilance; Adverse Events, Drug Safety.

Dissemination plans We will share the results of this systematic review with a wide audience of clinicians, researchers and patient associations. Our primary strategy is to publish a comprehensive manuscript in a peer-reviewed journal specializing in neurology, headache medicine or clinical pharmacology. In addition, we will present the results at national and international scientific conferences to promote discussion and engage with the research community.

Contributions of each author
Author 1 - Martina Giacon - Conceptualisation; Methodology; Data Collection; Data Analysis; Writing – Original Draft.

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