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The Capacity of AI/ML Models to Predict Pharmacological Treatment Response in Migraine Patients: A Scoping Review protocol

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ADMINISTRATIVE INFORMATION

Support - None.

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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 17 June 2025 and was last updated on 17 June 2025.

INTRODUCTION

Review question / Objective This scoping review aims to systematically map the existing literature on the use of Artificial Intelligence (AI) and Machine Learning (ML) models for predicting pharmacological treatment response in migraine patients. The primary objectives are:
1. To identify and categorize the full spectrum of AI/ML architectures and algorithms that have been employed to predict pharmacological treatment response.
2. To map the various data modalities (e.g., clinical, genomic, imaging, real-world evidence from wearables) that have been utilized as inputs for these predictive models.
3. To synthesize the evidence for specific classes of acute and prophylactic drugs, identifying which therapies have been most frequently studied and where research gaps exist.
4. To describe how the performance and generalizability of these models have been evaluated, with a specific focus on the validation strategies employed.
5. To identify and discuss the key research gaps, methodological challenges, and limitations highlighted within the existing body of literature.

Background Migraine is a common and debilitating neurological disorder that is a major cause of disability, especially in women in their most productive years. The clinical management of migraine is greatly complicated by the large inter- and intra-individual variability in response to pharmacological treatments. This heterogeneity forces clinicians to adopt an inefficient, costly and often frustrating "trial and error" approach to find an effective therapy for each patient. This process can lead to prolonged suffering, poor adherence to treatment and an increased risk of headaches from medication overuse, all of which contribute to the significant socio-economic burden of the disease.

Rationale The fields of artificial intelligence (AI) and machine learning (ML) offer transformative potential to address these challenges by enabling a shift from a one-size-fits-all approach to a precision medicine approach. By analysing complex, high-dimensional data sets, AI/ML

models can potentially identify "responder phenotypes"," i.e. predict which patients are most likely to benefit from a particular therapy before it is initiated. Research in this area is highly dynamic and interdisciplinary, and results are spread across neurology, informatics and clinical informatics journals. A systematic mapping of the evidence is therefore essential to summarise the current state of the science, clarify the methods used, identify key achievements and highlight critical gaps that need to be addressed in order to move the field towards clinical implementation. A scoping review is the ideal method to comprehensively capture this emerging landscape and provide a foundation for future research.

METHODS

Strategy of data synthesis A comprehensive and systematic literature search will be conducted by two investigators (M.G. and S.T) in major electronic databases to ensure broad coverage of the relevant literature: PubMed, Web of Knowledge, Cochrane Library and OpenGrey. The search will cover the period from database inception onwards, with no date restrictions, to capture the entire history of research in this area. The search will be conducted using a structured query combining MeSH terms and free-text keywords. The following search string, designed for PubMed, will serve as the foundation and will be adapted to meet the specific syntax requirements of the other selected databases (Web of Science, Cochrane Library, and OpenGrey):
("migraine disorders"[MeSH] OR migraine[tiab]) AND ("artificial intelligence"[MeSH] OR "machine learning"[MeSH] OR "deep learning"[tiab] OR "neural networks, computer"[MeSH] OR "artificial intelligence"[tiab] OR "machine learning"[tiab] OR ai[tiab] OR ml[tiab] OR dl[tiab] OR "neural network*"[tiab] OR "intelligent system*"[tiab] OR "computational intelligence"[tiab] OR "predictive modeling"[tiab]) AND ("drug therapy"[MeSH] OR "treatment outcome"[MeSH] OR treatment*[tiab] OR therap*[tiab] OR medication*[tiab] OR drug*[tiab] OR pharmacotherap*[tiab] OR "pharmacological treatment"[tiab] OR "drug response"[tiab])
Any disagreements between investigators will be resolved through discussion and consensus.

Eligibility criteria The eligibility criteria were defined using the Population, Concept, and Context (PCC) framework to ensure a comprehensive and systematic selection process.
Participants or population: Studies must include patients of any age with a formal diagnosis of any migraine subtype (e.g., episodic migraine, chronic migraine, migraine with aura, migraine without aura) as defined by established criteria such as the International Classification of Headache Disorders (ICHD).
Intervention (concept): The core concept is the development, application or validation of an AI/ML model. This includes any supervised, unsupervised or deep learning algorithm that is explicitly used with the aim of predicting a patient's response to a particular pharmacological treatment, whether for acute or prophylactic use.
Comparator: Due to the nature of this scoping review, which aims to map existing evidence rather than compare interventions, a specific comparator group is not required for inclusion.
Exclusion criteria: We will exclude articles that are not original research, such as reviews, editorials, commentaries, case reports and conference abstracts. Studies conducted on animal models will also be excluded. In addition, we will exclude studies where the AI/ML model is primarily aimed at diagnosing disease, predicting seizures or evaluating non-pharmacological interventions (e.g. neuromodulation, behavioural therapies), unless a pharmacological predictor is also a primary component.

Source of evidence screening and selection The selection procedure will be carried out in two successive stages. First, two reviewers (M.G. and S.T.) will independently screen the titles and abstracts of all identified records against the predefined eligibility criteria. In a second step, the full texts of all articles identified as potentially relevant in the first phase will be retrieved and checked by the same two independent reviewers for final inclusion in the scoping review. Any discrepancies or disagreements in either phase of the screening process will be resolved in a formal discussion to reach consensus.

Data management A structured data collection form will be developed in Microsoft Excel to ensure systematic and consistent extraction of information from all included studies. Two reviewers will extract the data independently. Key variables to be extracted will include: study identifiers (first author, year of publication, country of origin); study design and sample size; detailed population characteristics (migraine subtype, age, sex); the specific pharmacological class and drug(s) evaluated; the precise definition of "treatment response" used by the authors (e.g., ≥50% reduction in monthly headache days, pain-free status at 2 hours, improvement on a Quality of Life scale); the specific AI/ML algorithm(s) employed; a comprehensive list of all input data modalities; the key features identified by the model as most

predictive of response; all reported performance metrics (e.g., Area Under the Curve (AUC), Accuracy, Sensitivity, Specificity, F1-score); and a clear classification of the validation strategy as either internal (e.g., split-sample, k-fold cross-validation, bootstrapping) or external (temporal or geographical).

Reporting results / Analysis of the evidence The analysis of the evidence will be conducted in two main steps. First, a descriptive numerical analysis will be performed to summarise the general characteristics of the included studies. This will involve calculating frequencies and distributions for variables such as year of publication, geographical location of research, study design and sample size. This summary will provide a broad overview of the scope and nature of the literature. Secondly, a thematic synthesis will be conducted to address the specific objectives of the review. The extracted data will be organised thematically according to the core concepts examined:
AI/ML methods: grouping the studies according to the type of algorithm used (e.g. tree-based models, deep learning, SVMs).
Data modalities: categorisation of studies based on the input data used (e.g. clinical, imaging, genomic, portable data).
Pharmacological classes: Grouping studies according to the specific acute or prophylactic drug classes for which they sought to predict a response.
This dual approach provides a comprehensive mapping of the research landscape and identifies important trends, common practises and significant gaps in the existing literature.

Presentation of the results The results of this scoping review will be presented through a combination of tables, figures, and narrative synthesis to ensure clarity and provide a comprehensive overview of the findings.
Narrative Synthesis: A detailed narrative will describe the key findings in relation to the review's objectives. This will include a discussion of the types of models and data used, the therapies studied, and the validation strategies employed, highlighting areas of consensus and inconsistency in the literature.
Tables: Summary tables will be used to present the characteristics of all included studies in a structured format. These tables will systematically detail key variables such as study design, population characteristics, AI/ML models, data modalities, and reported performance metrics, allowing for easy comparison across studies.
Figures: A PRISMA-ScR flow diagram will be created to visually represent the study selection process, from the initial number of records identified to the final number of included studies. Additional figures (e.g., bar charts, graphs) may be used to illustrate the distribution of publication years, geographical locations, or the frequency of different AI models and data types.
This multi-faceted presentation will ensure that the results are accessible, easy to interpret, and effectively communicate the current state of research on this topic.

Language restriction No language restrictions will be applied.

Country(ies) involved Italy.

Keywords Migraine; Artificial Intelligence; Machine Learning; Treatment Response; Prediction; Pharmacotherapy; Scoping Review.

Dissemination plans The findings of this scoping review will be disseminated through multiple channels to reach a broad audience of researchers, clinicians, and stakeholders. The primary output will be a manuscript submitted for publication in a high-impact, international peer-reviewed journal specializing in neurology, headache medicine, or digital health. Additionally, the key findings will be presented at relevant national and international scientific conferences to facilitate discussion and collaboration within the scientific community.

Contributions of each author

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