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ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (C ROBINSON, SECTION EDITOR)

Artificial Intelligence and Virtual Reality in Headache Disorder Diagnosis, Classification, and Management

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Abstract

Purpose of Review This review provides an overview of the current and future role of artificial intelligence (AI) and virtual reality (VR) in addressing the complexities inherent to the diagnosis, classification, and management of headache disorders.

Recent Findings Through machine learning and natural language processing approaches, AI offers unprecedented opportunities to identify patterns within complex and voluminous datasets, including brain imaging data. This technology has demonstrated promise in optimizing diagnostic approaches to headache disorders and automating their classification, an attribute particularly beneficial for non-specialist providers. Furthermore, AI can enhance headache disorder management by enabling the forecasting of acute events of interest, such as migraine headaches or medication overuse, and by guiding treatment selection based on insights from predictive modeling. Additionally, AI may facilitate the streamlining of treatment efficacy monitoring and enable the automation of real-time treatment parameter adjustments. VR technology, on the other hand, offers controllable and immersive experiences, thus providing a unique avenue for the investigation of the sensory-perceptual symptomatology associated with certain headache disorders. Moreover, recent studies suggest that VR, combined with biofeedback, may serve as a viable adjunct to conventional treatment. Addressing challenges to the widespread adoption of AI and VR in headache medicine, including reimbursement policies and data privacy concerns, mandates collaborative efforts from stakeholders to enable the equitable, safe, and effective utilization of these technologies in advancing headache disorder care.

Summary This review highlights the potential of AI and VR to support precise diagnostics, automate classification, and enhance management strategies for headache disorders.

Keywords Machine learning · Natural language processing · Augmented reality · Migraine · Tension-type headache

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Introduction

On any given day, approximately 15.8% of the world's population experiences headaches, with migraine affecting over 1 billion people across diverse geographic regions and demographic groups [1, 2]. Characterized by discomfort or pain in the head or neck, headaches are one of the most common reasons for patients seeking care from their healthcare provider [3, 4]. The International Classification of Headache Disorders, 3rd Edition (ICHD-3), most recently revised in 2018, categorizes headaches into two main groups: primary headaches and secondary headaches [5]. Primary headaches, such as migraine, tension-type headaches (TTH), and trigeminal autonomic cephalalgias (TACs), lack an apparent underlying cause [5]. On the other hand, secondary headaches are due to specific medical conditions affecting pain-sensitive structures near the head or neck, with common causes including infections, vascular diseases, and trauma [3, 5]. Both primary and secondary headaches can significantly impact a patient's quality of life [3, 4].

According to the 2019 Global Burden of Disease Study, approximately 35% of the global population reported an active headache disorder of any type [1]. Headache disorders ranked third globally in causes of years-lived with disability (YLDs), contributing to 46.6 million YLDs, with 88% attributed to migraine [6]. When examining the relationship between migraine and demographics, it was determined that headache prevalence was higher in females, and in both genders, migraine was most prevalent in the 30–34 age group, affecting many individuals during their productive years [2, 7]. The consequences of headache disorders extend beyond individual health, impacting productivity, career potential, and social relationships. Estimates regarding the economic burden of migraine in the U.S. surpass $28 billion annually and report a significant increase in the costs associated with treating headache disorders over the past 10 years [8].

Advances in technology in recent decades have revolutionized healthcare, and the introduction of artificial intelligence (AI) and virtual reality (VR) into various medical disciplines is already underway [9]. As recent innovations, AI and VR represent new ways of interacting with the world around us and challenge conventional notions regarding the intersection of medicine and technology. This review aims to offer an overview of the role of AI and VR in headache disorders for enhancing assessment, diagnosis, and management.

Artificial Intelligence in Headache Disorders

AI is a multidisciplinary field of science and engineering dedicated to building systems capable of performing tasks that typically require human intelligence [10]. Modern AI encompasses a range of partially overlapping technological approaches, including machine learning (ML), natural language processing (NLP), computer vision, and robotics (See Table 1 for definitions).

AI has been explored as a tool for enhancing diagnostic approaches to headache disorders, automating their classification, guiding treatment selection, tracking treatment response, and fine-tuning treatment parameter adjustment, among other applications [11–13]. Pain conditions for which AI-based approaches have demonstrated efficacy in one or more of these domains include chronic low back pain, shoulder pain, neck pain, osteoarthritis, and sickle cell disease [14•, 15, 16]. Here, we explore applications that relate specifically to headache disorders.

Artificial Intelligence in Headache Disorder Diagnosis and Classification

Accurately diagnosing and classifying headache disorders, stratified broadly into primary and secondary forms, presents a considerable challenge due to reliance on patient-reported symptoms and significant symptomatic overlap between subtypes, often resulting in misdiagnoses or diagnostic elision [17, 18]. The release of the ICHD-3 by the International Headache Society, which delineates more than 200 headache disorders [19], has augmented the complexity of the diagnostic process, particularly for non-specialist providers.

In the face of these challenges, computerized approaches in general, and AI in particular, stand poised to revolutionize the diagnosis and classification of headache disorders. These systems offer robust pattern recognition and data integration capabilities that have been demonstrated to excel in deciphering the symptomatic complexities of headache disorders [20]. Indeed, a systematic review of 41 studies on computerized migraine diagnostic tools revealed a median diagnostic accuracy of 89%, with a wide range of trialed ML algorithmic approaches including case-based reasoning, deep learning (DL), classifier ensemble, and hybrid fuzzy expert systems [21].

Machine Learning in Headache Disorder Diagnosis

Recently, a number of ML models have demonstrated high diagnostic accuracy when attempting to identify new cases of specific headache disorders from easily accessible and unstructured data, such as electronic health records (EHR) or questionnaires [20]. This capability highlights the potential for ML models to be deployed as decision support systems that automate the identification of patients with headache disorders [20]. Analyzing questionnaire data from 6058 adult patients at a specialized headache clinic, an ML model using a gradient boosting classifier algorithm achieved a micro-average accuracy in identifying different primary headache disorders of 93.75% and particularly high

Table 1 Definitions of Concepts Associated with Artificial Intelligence and Virtual Reality

Virtual Reality (VR)	**Augmented Reality (AR)**	**Mixed Reality (MR)**	**Extended Reality (XR)**
Virtual reality enables users to experience and interact with a computer-generated, three-dimensional environment in real-time. Utilizing head-mounted displays and motion-tracking sensors, VR creates immersive simulations that aim to replicate experiences in the real world through visual, auditory, and haptic stimuli.	Augmented reality superimposes digital information and media, such as 3D models, sounds, and videos, onto the physical world, enriching the user's perception of their surroundings. This technology allows for real-time interaction with this enriched world, through devices like smartphones or specialized AR goggles.	Mixed reality allows real-world and virtual elements to coexist and interact in real time. It harnesses the combination of AR and VR to create environments where physical and digital objects can be manipulated simultaneously, often through advanced headsets or holographic displays.	Extended Reality is the umbrella category that brings VR, AR, and MR. These technologies extend the reality we experience by either merging the virtual and real worlds or creating a fully immersive experience, broadening the scope of human-computer interaction.
Artificial Intelligence (AI)	**Machine Learning (ML)**	**Deep Learning (DL)**	**Natural Language Processing (NLP)**
Artificial Intelligence is a multidisciplinary field concerned with the development of algorithms and computer systems capable of performing tasks that typically necessitate human-like cognitive processes. It involves the creation of computational entities that can reason, learn from data, recognize patterns, and solve complex problems, thereby emulating the cognitive functions associated with human intelligence	Machine Learning is a cornerstone of many modern AI systems. It encompasses a suite of algorithms and statistical models that empower computational systems to iteratively enhance their performance on a specified task. This improvement is achieved through the recursive processing of data or experience, circumventing the necessity for explicit programming.	Among the most prominent model classes within the ML domain is deep learning, which employs artificial neural networks mirroring the structure and function of the human brain. The use of multiple layers of computational nodes increases the capability of the system to discern complex patterns within large datasets. These models are particularly well-suited for tasks involving large amounts of unstructured data, such as images, sound, and text.	Natural Language Processing is an AI subfield, only partially overlapping with ML, that focuses on the interaction between computers and humans through natural language. The goal is to enable computers to interpret and generate human languages in a valuable way, supporting complex tasks such as sentiment analysis, language translation, and speech recognition.
Large Language Models (LLMs)	**Supervised Learning (SL)**	**Unsupervised Learning (UL)**	**Reinforcement Learning (RL)**
Large Language Models have been pivotal in NLP. Constructed using deep learning architectures, such as transformers, that analyze and generate text based on the patterns and structures learned from extensive corpuses of language data, their configuration enables high-level language understanding and generation with minimal to no task-specific training	Supervised Learning is a methodology for training ML models involving the use of labeled data from which the system infers a probabilistic mapping from input to output with the goal of generating predictive models. This method is well suited for classification and regression tasks. Prominent SL algorithms include SVM, Random Forest, Gaussian process regression, and Naïve Bayes.	Unsupervised Learning is a ML training methodology involving the use of unlabeled raw data from which the system attempts to find intrinsic patterns without the guidance of a known outcome variable or reward function. This method is well-suited for data exploration, clustering, and detection of patterns that deviate from expectations. Prominent UL algorithms include K-Means and Fuzzy Logic	Reinforcement Learning is an ML training methodology focusing on learning optimal behaviors or policies from trial-and-error to achieve the highest cumulative reward in a given context. This method is well-suited for complex tasks requiring optimization over time, such as autonomous driving, game playing, and medical treatment optimization. Prominent RL algorithms include Markov Decision Process and Q-Learning

diagnostic accuracy for migraine [22]. Similar results were found for pediatric patients experiencing migraine. An ML-based diagnostic model using the extremely randomized trees algorithm demonstrated high performance in extracting migraine diagnoses from a questionnaire dataset of 909 pediatric patients, with 94.5% accuracy, 88.7% sensitivity, and 96.5% specificity [23]. Both of these AI-models were developed using PyCaret by comparing different ML algorithms on a training dataset, selecting the best algorithm based on the highest average area under the receiver operating curve (AUC of ROC), and optimizing it through hyperparameter tuning [22, 23]. Although initial results are promising, further data collection and external validation are needed to support their applicability in broader clinical settings.

Machine Learning in Headache Disorder Classification

Leveraging the advancements in AI-enabled diagnosis of headache disorders, AI systems are increasingly demonstrating efficacy in the nuanced classification of such conditions. For example, employing a hybrid intelligent system that integrates mathematical, statistical, and a range of ML methodologies – including the analytical hierarchy process and weighted fuzzy c-means clustering algorithms – has yielded promising outcomes, achieving an average accuracy of 75% across 3 primary headache categories (migraine, TTH, and other primary headaches) [24]. Beyond accurately classifying disorders, AI models are also able to offer insights that clinicians can subsequently use to inform their future practices. For example, a recent ML model developed from questionnaire data from 173 patients for whom secondary headache disorders had been ruled out not only accurately discriminated between migraine and TTH but also identified key independent discriminative factors, such as nausea/vomiting and photophobia/phonophobia [25].

Given the complexity of headache diagnosis, non-headache specialists are positioned to benefit the most from diagnostic support systems powered by AI. A recent study revealed that an ML classifier, utilizing supervised training techniques, achieved higher accuracy than general practitioners in the classification of headache disorders by identifying symptom clusters within EHR data [26]. Furthermore, an AI-based headache diagnosis model, developed from an extensive questionnaire database at a specialized headache hospital, significantly enhanced the diagnostic accuracy of non-specialists from 46% to 83.20% in a cohort of 4,000 patients [27]. However, the reliance of this model on data from a single center and its diminished accuracy in diagnosing secondary headaches underscores the imperative for expanded data collection and model validation. A recent review of the literature on AI-based headache classification concluded that AI and DL could play a significant role in identifying urgent headache symptoms, potentially aiding in patient triage and reducing the demand on specialized headache care by facilitating early referral from primary care settings to neurologists for advanced evaluation [11].

Neuroimaging

Brain imaging can generate a wide array of intricate data, offering a fertile ground for the sophisticated analytical capabilities of AI to not only augment diagnosis and classification of headache disorders but also further elucidate their pathophysiology.

Recent studies in migraine research have employed various ML approaches to analyze activation patterns of brain regions captured by resting-state functional magnetic resonance imaging (rs-fMRI) data, achieving high diagnostic accuracy in distinguishing migraine patients from healthy controls and identifying migraine subtypes [28]. DL architectures such as convolutional neural networks (CNN) and bidirectional long short-term memory (BiLSTM) networks, as well as supervised learning techniques such as the support vector machine (SVM) algorithm have demonstrated classification accuracies exceeding 90% [16, 29, 30]. Beyond their diagnostic and classification accuracy, ML-based analytical approaches analyzing rs-fMRI data have demonstrated potential for the identification of the neural mechanisms underlying headache disorders. Using this approach, a recent study identified 17 dynamic functional connectome patterns (DFCPs) that distinguished migraine patients from healthy controls [31].

The application of ML algorithms for the analysis of data from other brain imaging modalities, such as structural MRI and positron emission tomography (PET), also demonstrates significant potential in enhancing the diagnosis and understanding of headache disorders [32, 33]. A recent study employed a novel ML method, termed Compressive Big Data Analytics (CBDA), to analyze the central μ-opioid and dopamine D2/D3 receptor profiles in migraine patients using PET data [34]. Analyzing 198 PET scans, this system achieved over 90% accuracy in differentiating between patients with migraine and healthy controls, identifying key distinguishing neurotransmitter receptor profiles in brain regions involved in sensory, motor, and motivational processing. This type of ML-based approach is expected to continue to shed light on the neurobiological underpinnings of migraine and its related neuropsychiatric comorbidities by better characterizing the dysfunction of critical neurotransmitter systems.

Natural Language Processing

Headache medicine is ideally grounded in the detailed collection and analysis of patient histories, enabling physicians to evaluate the unique characteristics and patterns of headaches, such as frequency, intensity, and associated symptoms, through patients' narrative reports. This meticulous process is essential for diagnosing and classifying headache disorders and allows clinicians to develop treatment strategies tailored to the individual patient's specific condition and needs. Within this context, natural language processing (NLP) is emerging as a promising tool, poised to enhance the precision of headache disorder diagnosis and classification by automatically analyzing and extracting relevant clinical information from these patient narratives (See Table 1 for definitions).

In a retrospective cross-sectional study, 4 large language model (LLM)-based generative NLP frameworks, including ClinicalBERT and various configurations of Generative Pre-trained Transformer-2 (GPT-2), were utilized to extract headache frequency from EHR data across 3 tertiary headache referral centers. The GPT-2 generative model emerged as the superior framework, exhibiting remarkable accuracy in data extraction from unstructured EHR databases [35]. Additionally, a custom-developed NLP algorithm was demonstrated as effective in discerning headaches as part of symptom clusters of acute COVID-19, extracting data with high precision from unstructured EHR data to accelerate the detection of new symptomatic cases and improve the determination of symptom onset [36].

NLP models can be combined with ML-based analytics to further optimize the diagnosis of primary headache disorders, their classification, and the characterization of clinical outcomes. A combination of NLP and ML for pattern recognition to optimize abbreviation decoding was utilized to scavenge unstructured EHR data from patients with headache disorders [37]. Relative to manual chart abstraction, this model achieved recall rates of 96.8% for migraine and 92.9% for cluster headaches, substantially higher than traditional NLP methods that require structured data as input. Additionally, a combination of NLP and ML was used to assess migraine treatment outcomes from EHR data [38]. The NLP model identified the evolution of migraine symptoms in clinical notes, while an ML algorithm refined the process by discerning patterns to accurately interpret abbreviations. The combined model closely matched manual extraction scores in 82.2% of 2,006 encounters. This synergistic approach demonstrates the potential of AI in reliably assessing subjectively reported outcomes, such as migraine progression, using unlabeled clinical data.

Artificial Intelligence in Headache Disorder Management

Utilizing AI in headache management could significantly enhance the precision of treatment protocols by enabling the synthesis of complex patient data to predict therapeutic responses. Moreover, the capacity of AI for real-time analysis and interpretation of diverse data streams, including symptomatic feedback and physiological indicators, could streamline the monitoring of treatment efficacy and adjusting of treatment parameters, enabling dynamic, data-driven clinical decision-making.

Guiding Treatment Selection

A notable recent example of leveraging predictive modeling for treatment selection is a ML model using random forest algorithms that was trained on patient-provided pain drawings to predict outcomes of pediatric headache surgery [39]. This system outperformed clinical evaluators with 94% accuracy in surgical outcome prediction while identifying specific pain patterns as indicators of surgical success. Such an application holds the potential to guide less experienced practitioners as well as patients in surgical decision-making for headache management.

Notably, AI is demonstrating potential in the prediction of pharmacological treatment efficacy for migraine disorders. A study testing a range of ML algorithms, such as SVM, random forest, and fuzzy clustering, analyzed data from chronic migraine (CM) and high-frequency episodic migraine (HFEM) patients treated with onabotulinumtoxinA [40]. This analysis revealed that while no anamnestic characteristics could distinguish responders from nonresponders in the CM group, a combination of 4 features (age of migraine onset, Migraine Disability Assessment Score (MIDAS), anxiety subscore, and opioid use) successfully predicted treatment response in HFEM. Another study developed a ML classification algorithm using random forest to predict the response to anti-calcitonin gene-related peptide therapy among patients with migraine [41]. This algorithm was able to predict the therapeutic response at 6, 9, and 12 months, with model accuracies exceeding 70%. Additionally, the system revealed key prognostic variables such as headache days per month, migraine days per month, and the Headache Impact Test (HIT-6). These findings highlight the potential of AI applications in enhancing treatment decision-making in clinical practice.

Beyond outcome prediction to indirectly guide treatment selection, AI might also have a role in supporting clinical decision making through big data-driven prescription policy generation. A recent study analyzing 1446 CM patients with a causal multitask Gaussian process model identified significant variability in treatment response to pharmacologic agents [42]. A ML-generated prescription policy developed from these data was determined to reduce adequate treatment response time by 35% compared to traditional expert guidelines. These findings highlight a promising role for high-dimensional modeling and machine-driven prescriptions in the future management of conditions with high heterogeneity in treatment response and multiple possible causal mechanisms, such as CM.

Predicting Acute Events of Interest

AI approaches have the capacity to transcend pattern recognition for diagnosis and classification in order to produce predictive models capable of forecasting acute events of interest in headache disorder management. In the realm of migraine management, the ability to accurately forecast migraine episodes continues to represent a crucial objective [43]. The current analytical process involves clinicians attempting to identify migraine triggers from patient reports, with the goal of helping the patient avoid them and thereby avert subsequent episodes. A newer approach, often termed "preemptive treatment," involves proactively administering medication in anticipation of identified triggers or during times of heightened risk, such as menstrual cycles or high-altitude exposure, with the objective of preventing the headache rather than treating symptoms post-onset [44]. Within this context, AI is ushering in a new era of personalized migraine management, offering the capacity to identify previously unrecognized triggers through the detailed profiling of individual trigger patterns and patient-specific temporal associations with migraine attacks. Such a process advances the precision of preemptive management strategies.

A recent retrospective cross-sectional study of over 4,300 participants with migraine and non-migraine headache disorders employed a DL-based system to analyze big data from a mobile application-based headache diary. The authors successfully identified significant associations between meteorological variables (reduced barometric pressure, heightened humidity, increased precipitation) and the occurrence of headache episodes [45]. Furthermore, another study tested the migraine forecasting capabilities of various ML analytical approaches using data obtained from pairing headache diary inputs with physiological parameters – such as heart rate, peripheral skin temperature, and muscle tension – all of which were recorded through wearable devices during biofeedback sessions facilitated by a mobile application [46]. The best-performing model, a random forest classifier, demonstrated modest forecasting ability with an AUC of ROC of 0.62, highlighting the promise of using high-dimensional modeling and data from mobile and wearable technology in predicting migraines.

A second event of interest in headache disorders with substantial implications in management is medication overuse (MO), which can lead to debilitating headaches that can be difficult to treat [47]. A recent study introduced an advanced ML-based decision support system integrating SMV and random optimization (RO-MO), which analyzed demographic, clinical, and biochemical data from 777 patients with migraine to identify key predictors of MO [48]. The resultant RO-MO system achieved an AUC of ROC of 0.83 with a sensitivity and specificity of 0.69 and 0.87, respectively, when predicting MO. These findings demonstrate significant potential for ML in enhancing precision when identifying individuals at risk of MO by leveraging a comprehensive analysis of clinical features and demographic factors.

Tracking Treatment Response

Emerging research in omics and neuroimaging is increasingly producing extensive datasets of potential biomarkers for headache disorders [49]. The advancement of precision medicine, with its aim to tailor treatments to patient subgroups, track treatment response, and predict therapeutic outcomes, necessitates the application of ML for the processing of these complex data. In alignment with this paradigm, a recent study investigated the use of an artificial neural network (ANN) to predict the effectiveness of biofeedback in migraine treatment, focusing on the correlation between serum levels of nitric oxide decomposition products (NOx), superoxide dismutase, and MIDAS [50]. Involving 20 women with CM undergoing EMG-biofeedback treatment, the ANN demonstrated 75% accuracy in predicting post-treatment MIDAS scores while revealing a significant correlation between NOx levels and MIDAS. This finding demonstrates the potential of ML for analyzing complex biological phenomena in migraine therapy.

Guiding Treatment Parameters

Integrating AI with advanced therapeutic strategies offers the transformative potential to monitor and adapt treatment responses dynamically. Such AI-powered closed-loop systems could enable the real-time tracking of patient responses to treatment, facilitating the prompt modification of therapeutic protocols [51]. A recent application showcasing this potential in headache medicine is the Relivion® system, a multi-channel head-mounted device integrating the self-administration of external combined occipital and trigeminal neurostimulation with advanced AI-based data processing algorithms [52]. The system leverages cloud-based analytics to dynamically adapt treatment regimens for migraine based on data collected via a custom mobile application and securely stored in a cloud database. This AI-driven approach enables healthcare providers to personalize stimulation parameters in real-time, pioneering a data-centric model for the non-invasive, self-administered management of headache disorders.

Virtual Reality in Headaches

VR is a technology that immerses users in a computer-generated, 3-dimensional environment through visual, auditory, and haptic stimuli (See Table 1 for definitions).

VR-based applications are increasingly recognized for their potential in enhancing assessment and management of acute and chronic pain across a variety of conditions and clinical settings [53, 54]. This innovative approach demonstrates particular promise in enhancing the remote delivery of pain care [55]. The potential analgesic mechanisms of VR, alongside the effectiveness of VR applications in supplementing the treatment of both acute and chronic pain syndromes, have been reviewed extensively elsewhere [56, 57•, 58•, 59, 60]. Compared to research on VR applications for other chronic pain conditions, the potential of VR for specifically addressing headache disorders remains significantly understudied [61, 62]. Moreover, the prevailing body of literature predominantly focuses on headaches as a side effect of VR-based interventions for other indications. Despite these current limitations, the utilization of VR for headache assessment and management represents a burgeoning field of interest, as evidenced by the recent studies reviewed hereafter.

Virtual Reality in Headache Disorder Assessment and Research

The immersive, highly controlled environments provided by VR enable the replication of complex, real-world sensory experiences within a laboratory or clinical setting, providing a unique opportunity to systematically investigate the nuances of sensory-perceptual symptomatology associated with headache disorders. This technology affords researchers and clinicians the ability to meticulously measure vestibular and spatial orientation responses, which are often part of the semiosis of a subset of headache disorders [63, 64].

A focused examination into body balance among individuals with vestibular migraine utilizing VR posturography compared 26 patients in their interictal phase to 30 age- and gender-matched controls [65]. Results indicated no significant difference in the limit of stability area, although revealed significant disparities in sway velocity and center of pressure displacement across most VR-delivered sensory conditions. Similarly, the employment of a relatively low-cost VR system run on mobile devices to administer the subjective visual vertical (SVV) test to patients with migraine, TTH, and healthy subjects demonstrated no significant variances in verticality perception among the groups [66]. These findings highlight the potential of VR to not only serve as a powerful tool for advancing our understanding of headache disorders but also to improve the granularity of clinical assessments for a select subset of conditions, paving the way for more tailored and effective therapeutic interventions.

Virtual Reality in Headache Disorder Management

The growing interest in leveraging VR for the management of chronic headache disorders is evidenced by ongoing clinical trials and the recent publication of feasibility and acceptability studies. A recent feasibility study investigated a novel VR application for patients with either vestibular migraine, mild-traumatic brain injury (mTBI), or peripheral vestibular disorders undergoing vestibular rehabilitation [67]. The intervention recreated complex real-world settings, such as airports or subway stations. Although limited sample size constrained the potential conclusions, the investigation yielded significant functional improvements in individuals with peripheral vestibular hypofunction, albeit not in those diagnosed with vestibular migraine or mTBI. Furthermore, an ongoing RCT is investigating the potential of the enfacement illusion – a phenomenon in which individuals experience the perception of another person's face, or a modified version of their own face, as their own – via immersive VR as a non-pharmacological intervention to reduce pain perception in CM patients [68]. Additional ongoing clinical trials include separate investigations on the effects of VR as an adjunct to the conventional management of migraine headaches and TTH [69, 70]. These ongoing studies underscore the potential of VR as a novel therapeutic approach in the management of headache disorders, indicating an evolving frontier for research and clinical application in this field.

Extended Reality-Assisted Biofeedback in Headache Disorders

Among the most noteworthy explorations of the potential applications of extended reality (XR)-based applications for chronic headache management is their integration with biofeedback techniques. Notably, a pilot study in 2013 examined an intervention combining VR and biofeedback through galvanic skin response (GSR) monitoring as an abortive treatment for pediatric chronic headache [71]. The system utilized VR-delivered visual feedback of the patients' facial expressions reflecting emotional states, whereby shifts in GSR indicating relaxation transformed these expressions from pain to calm, thus facilitating a therapeutic transition based on the patient's physiological responses. Building upon this foundation, a recent study revisited XR-assisted biofeedback in headache disorders, comparing the acceptability and efficacy of three XR-based relaxation training methods (fully immersive VR with and without neurofeedback and augmented reality with neurofeedback) in pediatric migraine patients [72]. Findings from this investigation underscored a preference for fully immersive VR as a means for relaxation, with minimal reported side effects, highlighting the potential of XR interventions in the management of migraines in younger populations.

Additionally, a recent randomized controlled pilot study investigated the efficacy of a portable device that integrates heart rate variability (HRV)-based biofeedback with VR in improving headache-related outcomes for adult patients with CM [73]. The intervention employed the Oculus Go head-mounted display (HMD) to immerse participants in tranquil environments, such as beach or hilltop landscapes. During the biofeedback sessions, participants were instructed to modulate their respiratory patterns and HRV to achieve a state of coherence, which was visually indicated by a sine wave-like curve on the display. Distinct from most VR-biofeedback pairing systems, the VR environment in this intervention did not change in response to patient performance; rather, participants could explore it ad libitum to maximize engagement and relaxation. Compared to standard medical therapy alone, results indicated no significant reduction in mean monthly headache days at 12 weeks. However, statistically significant decreases were observed in acute analgesic use (65% versus 35% decrease) and depression scores (65% versus 35% decrease) in the experimental group. Although further research is needed, these findings suggest VR in combination with biofeedback therapy might have a role as an adjunct treatment for CM, particularly for those seeking to reduce medication use or favoring non-pharmacological interventions. The recent introduction of Remote Therapeutic Monitoring billing codes by the Centers for Medicare & Medicaid Services (CMS) has opened up potential avenues for leveraging VR-based applications such as VR-assisted biofeedback in the remote monitoring and management of headache disorders.

Challenges and Barriers to The Broader Adaptation of AI and VR Technology in Headache Disorders

With AI and VR technology having been rapidly introduced into healthcare systems over the past decade, barriers have arisen to their implementation in the assessment and management of headache disorders [74, 75]. Some of the more prevalent barriers include challenges with health insurance, existing technological infrastructure, ethical concerns, patient and provider concerns, and the lack of long-term efficacy data.

In the U.S., the CMS has begun to approve the use of AI and VR systems for reimbursement, although the lack of widespread insurance coverage poses a challenge to clinical use in chronic pain disorders such as headache [76, 77]. To date, CMS has not issued formal guidance regarding coverage of AI software and devices, and the existing per-use reimbursement policies has the potential to lead to the overuse of medical AI and therefore overspending [78]. The use of VR as a treatment modality is also not currently a widespread billable service, with few providers able to obtain insurance reimbursement and fewer able to bill VR sessions at an enhanced rate [79, 80]. Additionally, limited organizations have regulatory oversight over healthcare AI [81]. The implementation of VR in healthcare has also faced organizational challenges, with poor technological support infrastructure, ineffective training, and lack of integration resources commonly cited [82•]. In addition, technical barriers such as malfunctioning VR hardware and software coupled with concerns regarding patient safety while wearing VR headsets in treatment rooms are also frequently cited issues [82•].

The large-scale implementation of AI and VR into healthcare raises ethical considerations. Inequities are magnified in safety-net healthcare systems, in which, for example, an English-only VR therapy would be ineffective in linguistically diverse patient populations in addition to varied cultural acceptance of VR [80]. The limited funding resources for technological advancements in these systems may further serve as additional barriers for the equitable implementation of AI and VR in headache [80]. Moreover, as mentioned above, issues of AI and VR insurance coverage in headache treatment may result in a “cash-only” reimbursement paradigm, which clearly results in compromise of the bioethical principle of distributive justice. Additionally, the adoption of AI and VR also introduces challenges to data privacy and confidentiality given the sensitive nature of the information being handled. Patients may be unaware of what information is being extracted from their interactions, with VR technologies capturing a potentially identifiable “kinematic footprint” consisting of eye and body movements, behavioral response patterns, and geolocation [83, 84]. While data accessibility is paramount for accurate AI models and innovations such as VR systems, concerns regarding the legal and ethical requirements for data privacy have been raised [84, 85].

Although overall attitudes toward the use of AI and VR in healthcare have been positive, reservations have been expressed by both patients and providers [75]. Common concerns include doubts regarding AI accuracy, liability issues, and potential harm to the patient-provider relationship [86]. Research also indicates that patients have greater confidence in a physician’s decision-making ability than in AI technology [87]. Regarding VR use, reservations include the technological learning curve, cost, and potential adverse effects such as cybersickness, dizziness, and falls [75, 88]. Particularly concerning is the risk of motion sickness and simulation sickness when applying VR in the management of headache disorders [89].

The lack of long-term efficacy data for AI and VR applications in headache poses a challenge to their widespread implementation. While short-term efficacy of VR therapy for headaches has been demonstrated, long-term efficacy remains mixed and less examined [90•, 91, 92]. Due to the recurrent nature of some headache disorders, there is a need to evaluate VR treatment modalities over extended periods [3, 90•]. AI-based digital health interventions for chronic pain yield comparable results to non-AI interventions while increasing cost-effectiveness, although diagnostic accuracy varies between headache classification, and evidence for long-term efficacy is also limited [93–97]. Addressing these barriers is crucial prior to achieving widespread implementation of AI and VR in headache disorders.

Conclusion

The integration of AI and VR in the realm of headache disorders represents a significant stride toward modernizing medical diagnostics and treatment approaches. The sophisticated pattern recognition and predictive modeling capabilities of AI, alongside the immersive simulation environments offered by VR, offer novel pathways for the assessment, classification, and management of headache disorders. These technologies promise to alleviate the substantial burden of headache disorders on public health by refining the precision of clinical care, tailoring treatments to individual needs, and enhancing patient engagement. Despite promising developments and applications, the full potential of AI and VR in headache medicine remains limited by challenges related to funding, ethical considerations, and the need for further validation through clinical trials and long-term efficacy studies. Overcoming these barriers will require collaborative efforts among researchers, clinicians, policymakers, patients, and industry to ensure that these innovative tools can be harnessed equitably, safely, and effectively to improve headache disorder care.

Author Contributions IHC, EZ, MD: Planned, wrote, and revised the manuscript. MA, ML, SA, MES, RJY: Wrote, edited, and provided expertise. AF: Planned, wrote, provided expertise, revised the manuscript, and is the primary investigator.

Data Availability No datasets were generated or analysed during the current study

Compliance with Ethical Standards

Conflict of Interest IHC: Receives consulting fees from Layer Health. ML: Serves as an Associate Partner at MEDA Angels and Vice President of Operations at AMXRAAS. SA: Provided consulting and teaching services for Allergan/Abbvie, Eli Lilly and Company, Impel NeuroPharma, Linpharma, Lundbeck, Satsuma, Percept, Pfizer, Teva, and Theranica. MES: Serves as a research consultant to Modoscript and was a member of an Advisory Committee for Syneos Health.

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