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the junior editorial board members' vision – part 2

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REVIEW **Open Access**

Influence of next-generation artificial intelligence on headache research, diagnosis and treatment: the junior editorial board members' vision – part 2

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Abstract
Part 2 explores the transformative potential of artificial intelligence (AI) in addressing the complexities of headache disorders through innovative approaches, including digital twin models, wearable healthcare technologies and biosensors, and AI-driven drug discovery. Digital twins, as dynamic digital representations of patients, offer opportunities for personalized headache management by integrating diverse datasets such as neuroimaging, multiomics, and wearable sensor data to advance headache research, optimize treatment, and enable virtual trials. In addition, AI-driven wearable devices equipped with next-generation biosensors combined with multi-agent chatbots could enable real-time physiological and biochemical monitoring, diagnosing, facilitating early headache attack forecasting and prevention, disease tracking, and personalized interventions. Furthermore, AI-driven advances in drug discovery leverage machine learning and generative AI to accelerate the identification of novel therapeutic targets and optimize treatment strategies for migraine and other headache disorders. Despite these advances, challenges such as data standardization, model explainability, and ethical considerations remain pivotal. Collaborative efforts between clinicians, biomedical and biotechnological engineers, AI scientists, legal representatives and bioethics experts are essential to overcoming these barriers and unlocking AI's full potential in transforming headache research and healthcare. This is a call to action in proposing novel frameworks for integrating AI-based technologies into headache care.

Keywords Digital twin, Biosensors, Wearable devices, Drug discovery, Migraine, Machine learning, Chatbot

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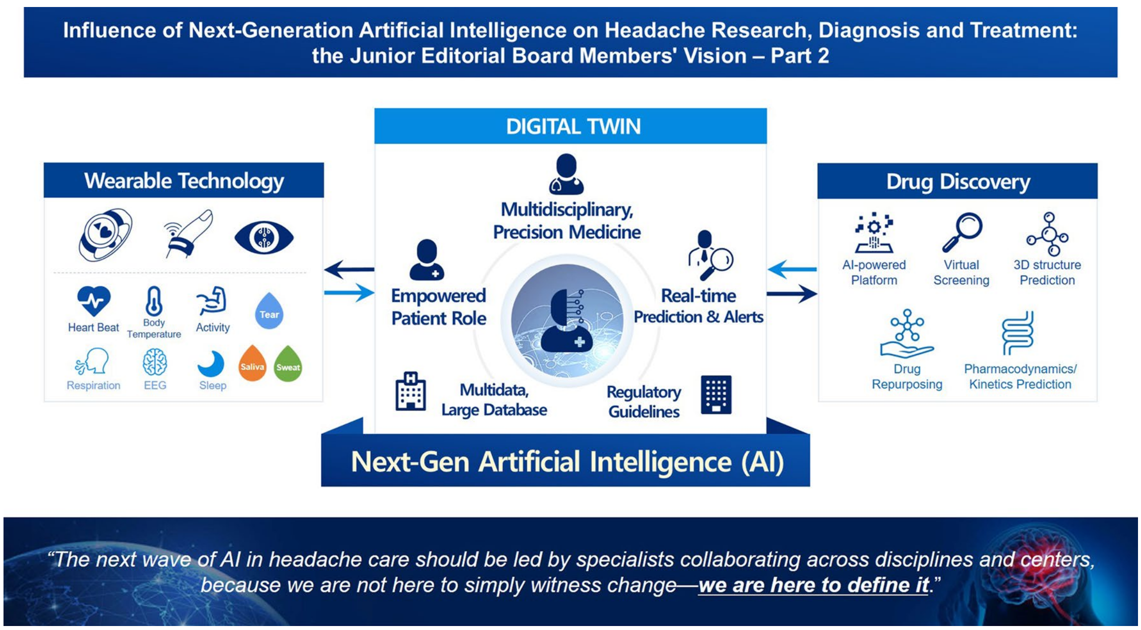
Graphical Abstract



Introduction

The year 2024 is very exciting for the artificial intelligence (AI) community. Geoffrey Hinton and John Hopfield were awarded the Nobel Prize in Physics for their foundational work on machine learning (ML) and artificial neural networks, which laid the groundwork for modern AI technologies. Additionally, the Nobel Prize in Chemistry honored David Baker, Demis Hassabis, and John Jumper for their pioneering work in using AI for protein structure prediction, with profound implications for drug discovery and understanding complex biological mechanisms [1]. This milestone signifies the convergence of AI with traditional scientific fields, suggesting exciting prospects for medical and healthcare innovation.

In the field of headache medicine, AI has the potential to advance understanding, improve diagnostic accuracy, and facilitate personalized treatment approaches, potentially redefining the standard of care for headache disorders [2–4]. An example is the study that received the American Headache Society 2024 Harold G. Wolff Award using ML to predict treatment response to migraine preventive medications, as a step forward to advance personalized, precision migraine treatment using AI [2]. By integrating diverse data sources—ranging from neuroimaging and genetic data to patient-reported outcomes and real-time data from wearable devices—AI can address the heterogeneity in headache presentations and enable more targeted interventions (See Fig. 1).

Building on Part 1 [4], this review aims to explore the current and future applications of AI in the headache field, presenting a forward-looking vision for personalized headache care. By outlining developments in the digital twin research field, as well as AI-driven wearable healthcare technology solutions and new treatment discoveries boosted by AI, we highlight the transformative role of AI in revolutionizing headache research, diagnosis, and treatment. This review calls for action to set a framework for the involvement of AI scientists and neuroengineers in headache research for the development of standardized frameworks, collaborative ecosystems, and equitable strategies for AI in headache diagnosis and treatment.

Digital twin

The digital twin concept

A digital twin is a digital representation of a real-world object. The concept originally stems from production technology [5, 6]. There, the digital twin is a digital model of a physical process (e.g. a machine) that is connected to the real-world object by a "digital thread". Via the digital thread, the digital twin continuously receives information from physical sensors capturing the state of the machine. This information is used to continuously update the model (i.e. adapt model parameters) to achieve the best current representation of the real-world machine [7]. However, information flow in the digital thread is bidirectional. For example, the digital twin can detect deviations between the desired output and the real output and initiate actions (e.g. parameter modifications of the real machine) to improve the real output. It can also predict

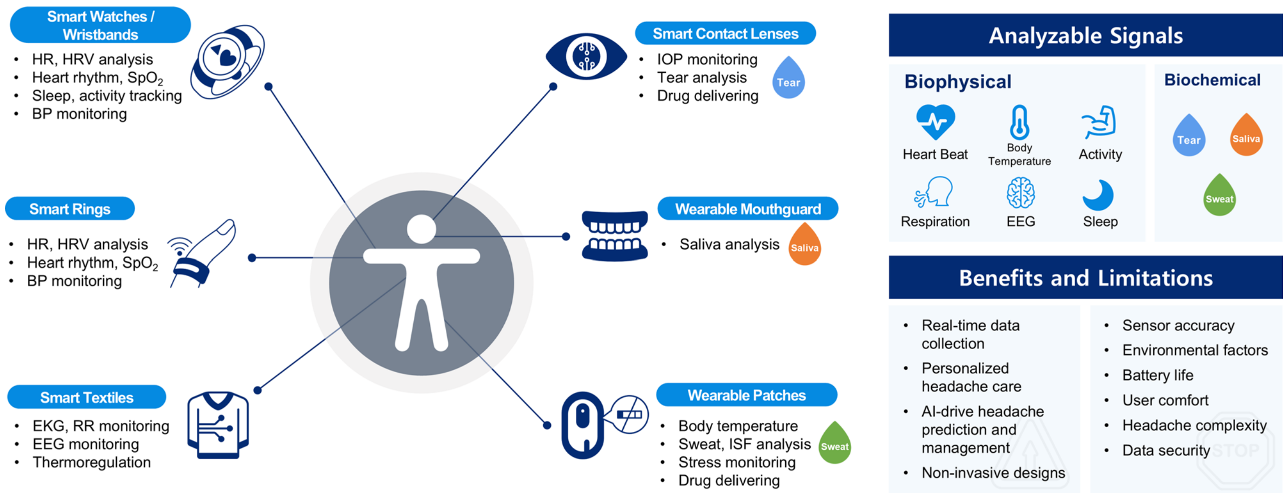


Fig. 1 Overview of current and proposed wearable devices for headache management

future outcomes and thus identify the need for preventive action, therefore saving time and money [8]. A digital twin can also be used to perform digital experiments. For example, the effects of parameter changes could first be evaluated using the digital twin, and only the most promising parameters tested in the real world—thereby saving both time and money. In addition, the digital twin provides detailed digital information on the current state of the real-world object without the need to be on-site [9]. The digital twin therefore is a dynamically changing digital representation of a real object, with a model based on several factors, including previous knowledge (i.e. of physical laws), historical data (i.e. from similar constellations), the current state of the real world object from physical sensors, and longitudinal data from previous states of the object and its reactions to external influences [10].

There is a multitude of emerging applications of digital twins in medicine, and these will allow groundbreaking steps towards personalized medicine [11]. Potentially, the digital twin could be a complete representation of the human body, including omics and imaging data, continuously updated through data from sensors monitoring body functions and environmental influences [9]. Practically, there is a need to first model smaller entities, and promising results of digital twin applications have been reported in different fields [12], including neuroscience [6]. For example, the onset of cerebral atrophy in multiple sclerosis has been analyzed by comparing it with "healthy" digital twins [13], and a virtual trial has been conducted to identify actions to improve pain control achieved by fentanyl patches in cancer patients [14]. In addition, digital twins in neuroscience enable the modeling of brain function and pathology, since they offer an in-silico approach to studying the brain, and illustrating the complex relationships between brain network dynamics and related functions [15]. Possible applications in migraine and other headache disorders have been previously discussed in detail [16].

Building a digital twin for headaches

The quality of a digital twin depends on the data available to the model. Factors having been identified as predictors of headache outcomes have to be included such as age, sex, body mass index, headache diagnosis, headache characteristics and other headache diary information (e.g. frequency, intensity, duration, medication, effect, headache location, associated symptoms and migraine attack triggers), psychological cofactors and psychiatric comorbidities (e.g. depression, anxiety, bipolar disorder), response to present and previous preventive medications, comorbidities and comedication [2, 17, 18]. In addition, omics and imaging data would make important contributions [19, 20]. Regarding sensor data, data-capturing known elements of headache or migraine pathophysiology might have the strongest potential [21–23]. This might include real-time assessment of cranial vasodilation, levels of calcitonin gene-related peptide (CGRP) or other potential biomarkers for migraine, neck muscle tension, electroencephalography (EEG) or evoked potentials. While these assessments are becoming more accessible, data from common methods (such as heart rate (HR), physical activity, sleep quality, and perceived stress level) are much easier to obtain, although they likely have a more indirect relationship to headache [24–26]. Automatically captured information collected through wearable technologies or personal devices is more user-friendly and offers a higher likelihood of comprehensive data collection compared to self-reported, or diary-based methods, which are often prone to low completion rates. In addition to data on body function, data from the environment should be incorporated (e.g. weather, noise, travel), as these factors have been used to forecast migraine attacks [27].

Possible applications of digital twins in headaches

Diagnosing headache disorders

One of the most time consuming aspects of headache medicine is the diagnosis of patients. When evaluating patients, prior medical history must be reviewed, since some comorbidities may play a significant role in patients' current headache, or may contraindicate certain acute or preventive drugs (e.g. asthma or gastric disorders) [28]. Prior medical history is relevant in the detection of certain secondary headache disorders, such as intracranial neoplasms or infections. Digital twins could eventually check whether patients exhibit any headache-specific red flags, and in that case, suggest which are the most adequate exams [29]. Once secondary headache disorders have been ruled out, the diagnosis of a primary headache disorder should be considered. The digital twin could identify the phenotypic aspects that support the specific diagnosis, such as migraine, tension-type headache or cluster headache [30]. However, a number of potential biases arise in clinical practice, such as insufficiently detailed data due to lack of time or inadequate data collection and inaccurate information due to recall bias. These challenges could be tackled with wearable multimodal AI-based biosensors capable of collecting and analysing continuous and objective data in individuals who are undergoing evaluation for specific headaches in real-world settings.

Prediction of individual therapy outcome

One of the most useful applications would be individual prediction of therapy outcome for specific treatment types, e.g. CGRP-targeting therapies or classical oral preventives. This would immensely improve headache care, reducing the time to find an effective medication [31]. As several predictors have already been identified in conventional studies [17] and with ML methods [2], there is a large potential for prediction by a digital twin with access to large amounts of data. After treatment initiation, the digital twin might be able to detect success or failure earlier, allowing modification of treatment decisions. However, a possible downside of employing treatment prediction tools might be insurance companies or reimbursing agencies limiting payments only to patients who are likely to respond, thus reducing treatment options for difficult-to-treat patients. In addition, digital twin decisions must be explainable, so that physicians, patients, and policymakers can understand how recommendations are made. Another important advantage is the early detection of adverse effects. They impair patients' quality of life, even when the therapies are effective, and there is no need for suffering from bothering symptoms when other treatment alternatives exist.

Forecasting migraine attacks

Another application would be to forecast impending attacks, allowing for early and effective acute treatment. Although migraine patients are able to predict their attacks from premonitory symptoms [32], continuously logging premonitory symptoms in electronic diaries would be time-consuming. However, some premonitory symptoms such as neck muscle tension might be accessible to wearable sensors, and additionally, AI sensors could collect EEG data during sleep and exposure to stress, two important trigger factors for headache attacks [25, 26, 33]. On the other hand, prediction of medium- and long-term headache course would also be useful. Knowing if a current exacerbation is temporary or the beginning of migraine chronification would allow to individually tailor treatment and initiate timely interventions.

Virtual trials

Digital twin technology can also be used to conduct virtual trials. Apart from using the digital twins of real patients for the simulation of treatment effects or forecast migraine attacks, larger virtual populations can be created by varying parameters obtained from real patients while observing parameter correlations. Virtual trials can then be performed on these larger virtual populations [13]. This approach could be especially useful in drug development.

Patient counselling

Based on continuously available patient data, e.g. on potential triggers such as sleep, stress or too little physical activity, or on exacerbating factors such as medication overuse, the digital twin could counsel the patient on health behaviors or interact with the treating physician via chatbots [34]. The digital twin might also advise a visit with the physician based on unfavorable headache developments, such as increased headache frequency or intensity, or a change in headache features. Furthermore, this could lead to the proactive involvement of the patient, upgrading the treatment experience and ultimately a more satisfactory relationship between patient and physician. The use of chatbots has also limitations. Some headache patients may present with unusual clinical features that require personal attention by a physician. Additionally, headache triggers may vary based on factors such as ethnic background, lifestyle, or geographical location. These factors should be accounted for when chatbots are fine-tuned for personalized counselling of headache patients.

Remote monitoring and telemedicine

Because digital twins could implement approaches such as the Internet of Things, including devices with sensors, processing ability, software, and other technologies that connect and exchange data with other devices and the cloud, telemedicine is much facilitated [35]. Studies have demonstrated high patient satisfaction using telemedicine for headache care [36]. One example would be that the digital twin could remote visits with physicians when headache deterioration or medication overuse occurs in a specific patient, making early interventions possible. Even more, physicians might be able to trial and adjust treatment plans in a risk-free environment, observing long-term impacts on migraine progression and management in a personalized digital twin platform, and changing prescriptions without the need for patients to visit the clinic [35]. However, the legal regulations and responsibilities need to be clearly outlined to create a safe environment for both physicians and patients.

For the best use of the technology, the large amount of information available within a digital twin must be displayed in an intelligent way so it can support decisions of the physician and the data-based discussion of treatment choices with the patient [37]. This needs user-friendly and customizable visualization of data and their correlations.

Medical education

The model derived from a fully trained digital twin could be used for interactive medical education, where students could learn from the effects of their treatment choices on a digital twin or even a cohort of digital twins [38]. Therefore, the use of digital twins in headache education would bridge the gap between theoretical knowledge and practical application. For example, some headache disorders or comorbidities, such as trigeminal autonomic cephalalgias, or moyamoya vasculopathy, are less commonly encountered during medical training given the low prevalence. A digital twin can model such cases, providing valuable exposure and practice in diagnosing and managing rare headache syndromes [39]. Also, neurology trainees could receive immediate feedback on their treatment choices, enabling them to learn from mistakes without patient harm, and reinforcing best practices in headache management. Moreover, offering a safe, interactive, and personalized learning environment, empowers physicians to make informed, evidence-based decisions, ultimately improving patient outcomes. The integration of such technology aligns with a growing focus on personalized medicine and precision training in neurology and other specialities related to headache diagnosis and treatment.

Next-generation digital twin in the headache field

While no digital twin for headache has been developed yet, elements are becoming available, as discussed in several recent reviews on the use of AI in headaches [3, 4, 40]. For example, wearable EEG data have been used for the prediction of the migraine phase [41] and AI has been used to diagnose migraine with aura based on imaging data [18], to classify headaches according to ICHD-3 diagnoses based on clinical data [42] and to predict response to preventive treatments [2, 16]. An important limitation to the creation of digital twins is the lack of definite biomarkers for primary headache disorders, so potential digital twins are based upon several hypotheses. Nevertheless, AI algorithms applied to large datasets could uncover latent patterns in headache disorders, compensating for the absence of single specific biomarkers, and thereby improving the identification of headache phenotypes.

In the process of development of digital twins in the field of headaches, we recognize the challenges to digital twins in medicine, such as limited accessibility of health data and high demands on information processing and storage. Furthermore, digital twins require a robust infrastructure for integrating diverse datasets (e.g., neuroimaging, electrophysiology, and clinical data). The heterogeneity in data quality, collection protocols, and formats across healthcare centers poses significant obstacles. In addition, digital twin models require sophisticated computational infrastructure, including real-time data processing and high-dimensional modeling. These requirements may be inaccessible in resource-limited healthcare systems, exacerbating global disparities in headache care. Ethical concerns also have to be considered, including the potential for discrimination based on health profiles [4, 35]. Data protection is of paramount importance when processing large amounts of personal and health data. Compliance with regulations like the General Data Protection Regulation (GDPR) is critical but complex to implement. Awareness is needed that digital twins are only statistical models that operate on probabilities and can, at least at the time being, never be a complete representation of an individual. Therefore, suggestions made by a digital twin need regular evaluation by a physician. AI models are often developed using datasets from academic centers, which may not adequately represent the general patient population and could introduce potential biases into the algorithms. Therefore, without large-scale, validated studies, the adoption of digital twins by clinicians and regulatory bodies will be slow. Thus, steps to enhance the usability of the digital twin paradigm in headache healthcare should be based on the prioritization of biomarker discovery (investing in multidisciplinary research to identify and validate biomarkers for headache disorders, focusing on neuroimaging, genetics, and proteomics markers), creating collaborative networks among headache researchers and AI scientists to develop shared data repositories and modeling standards, empowering pilot studies to test the utility of digital twins in specific headache subtypes (e.g., migraine with aura), and developing robust ethical and regulatory frameworks to address privacy, data ownership, and equitable access.

Wearable healthcare technology driven by artificial intelligence solutions

Wearable healthcare technology

Wearable healthcare technologies play a crucial role in building a successful digital twin model. They are innovative tools designed to continuously and non-invasively monitor physiological and biochemical parameters. These small electronic devices, worn on the body or integrated into clothing and accessories, have transformed how health data is collected and analyzed [43]. With advancements in electronics, computing, and materials science, wearable devices are now more compact, sensitive, and cost-effective [44]. They incorporate technologies such as photoplethysmography (PPG), gyroscopes, and accelerometers for physiological monitoring, enabling the application of precision medicine beyond traditional clinical settings [43, 45]. In the future, high miniaturization will allow the integration of multiple biosensors on the chip embedded in the human body, targeting a specific biomarker of interest or allowing a rich multiparametric analysis. Moreover, data will be wirelessly available to the patient or physician in real-time through a secured data infrastructure.

In the field of headache care, wearable devices have already opened new possibilities for diagnosis, treatment, and monitoring [40]. By leveraging AI, wearable devices can process vast amounts of data to identify patterns, predict symptoms, and guide personalized interventions.

Wearable devices and proposed applications for headache disorders

In addition to biophysical signals like HR, recent advances in electrochemical biosensors enable the measurement of biochemical signals directly from bodily fluids like sweat or interstitial fluid [46–48]. These sensors provide real-time insights into metabolic and hormonal activity, offering a deeper understanding of the physiological changes associated with headache disorders. The integration of biochemical and biophysical data would further enhance the potential of wearable devices. Here, we aim to examine the characteristics of various wearable devices, examples of their use in other medical fields, and their potential applications in headache disorders.

Smartwatches and wristbands

Smartwatches and wristbands are widely used for real-time monitoring of HR, HR variability (HRV), sleep patterns, and physical activity [44]. Equipped with sensors like accelerometers and optical HR monitors, they excel in seizure detection, atrial fibrillation monitoring, and sleep tracking [49–51]. Their portability, user-friendliness, cost-effectiveness, and wireless connectivity to smartphones make them practical tools for continuous health monitoring. However, some limitations exist. Data accuracy can vary significantly depending on how tightly the device is worn, leading to a trade-off between user comfort and ideal accuracy [52]. Additionally, there is often a noticeable difference in accuracy between daytime and nighttime measurements. Due to these factors, as seen in previous studies, research often focuses on using nighttime data to predict headaches for the following day [53]. One important advantage is the wide distribution of these devices in the population and the possibility of creating specific software that can be integrated into them.

Smart rings

Smart rings utilize PPG technology to measure HR and HRV, offering similar functionalities in a smaller, more convenient form [54]. The integration of PPG or bioimpedance with ML enables continuous, cuffless blood pressure monitoring, making them a valuable tool for health tracking [55]. While smart rings share many advantages and disadvantages with smartwatches, they tend to have a relatively higher price point. Additionally, their performance can be affected if the ring does not fit properly on the finger of the user, potentially leading to challenges in accurate data collection [54].

Smart contact lenses

Smart contact lenses are wearable ophthalmic devices that go beyond vision correction, incorporating advanced electronic components such as sensors, microprocessors, and wireless communication modules [46]. Recently, research has explored the use of piezoresistive sensors or microfluidic systems to enable continuous 24-hour monitoring of intraocular pressure (IOP) [56]. Additionally, these lenses can measure glucose levels in tears, allowing for continuous blood glucose monitoring in diabetic patients [56]. Some smart contact lenses are equipped with integrated heaters to improve blood circulation around the eyes and stimulate tear production, potentially alleviating symptoms of dry eye [56]. Their compact size and convenience make them ideal for daily wear and data collection. However, the durability of sensitive electronic components and the potential for discomfort or irritation with long-term use remain challenges.

In the context of headaches, IOP monitoring with smart contact lenses could help study the relationship between migraine and glaucoma, or identify headache triggers [57]. Furthermore, these lenses could track changes in IOP following optic nerve sheet fenestration for idiopathic intracranial hypertension [58]. The ability of the amperometric biosensor to analyze target analytes could potentially be applied to headache research for monitoring related biomarkers.

Wearable patches

Wearable patches are innovative devices designed to adhere to the skin and perform functions such as monitoring body temperature, sweat analysis, muscle activity, or delivering medications [46, 48]. Using microfluidic devices, these patches can analyze sweat secretion in real-time, while electrochemical sensors provide insights into biomarkers like sweat pH or levodopa levels [59]. Additionally, patches equipped with microneedle arrays enable pain-free insertion into the skin, allowing real-time monitoring of biomarkers such as lactate, glucose, or alcohol from interstitial fluid beneath the skin [60].

Imbalances in sweat electrolytes (e.g. sodium, potassium) or changes in pH may indicate metabolic shifts or autonomic dysfunction, which is associated with migraine and other headache disorders [61]. Furthermore, tracking cortisol levels via wearable patches could help identifying stress-induced headache episodes [62].

Mouthguard

Wearable mouthguard is an intraoral device that holds potential as a method for diagnosis and monitoring headaches, thanks to its ability to non-invasively collect saliva in real time [48]. Although research in this area is in its early stages, preliminary studies have demonstrated measuring and monitoring glucose, nitrate or uric acid levels in saliva [63, 64]. In the context of migraine, evidence suggests that saliva contains elevated levels of specific biomarkers during attacks, such as glutamate, inflammatory markers, and CGRP [65, 66]. This highlights the potential of wearable mouthguards for headache research, offering a non-invasive way to monitor these biomarkers in real-time. However, several challenges remain. Oral bacteria and food intake can interfere with sensor accuracy, and user compliance may be low due to discomfort [48].

Smart textiles

Smart textiles are fabrics with special functionalities such as electrical conductivity, moisture management, and sensing capabilities [48]. These have been utilized as smart shirts for ECG monitoring, respiratory rate monitoring, and headbands for EEG monitoring [67]. Additionally, smart textiles can adapt to ambient temperature by generating or dissipating heat, offering personalized thermal regulation. However, high manufacturing costs and washing durability remain key limitations.

Studies of wearable technologies in headache

Wearable technologies have been studied in clinical settings for their potential in headache management, primarily focusing on migraine prediction (Table 1).

Stubberud et al. employed ML on smartphone diaries and wearable data with a random forest model and showed promise for migraine attack forecasting [26]. Moreover, another study developed wearable-based models for early migraine detection, achieving over 84% balanced accuracy with sleep data and quadratic discriminant analysis [25]. Kapustynska et al. utilized wearable sensors and ML to monitor pre-migraine biomarker patterns, identifying electrodermal activity, skin temperature, and accelerometer data as key predictors with an XGBoost model achieving 81% accuracy [68]. Furthermore, De Brouwer et al. demonstrated that adapted ICHD-3 criteria and wearable-based data improve headache attack classification [69]. Pagán et al. assessed hemodynamic monitoring using wireless body sensor networks, demonstrating patient-specific models with a 47-minute prediction window and low false-positive rates using the numerical subspace state space system identification method [70]. Martins et al. analyzed EEG changes during migraine cycles, finding reduced delta and increased beta power at 24 h before migraine and reduced P300 amplitude during attention tasks [71]. Connelly et al. evaluated the feasibility of wearable biosensors and smartphones for migraine monitoring in adolescents, achieving high self-reported data compliance (89%) and wearable usage (18.7 h/day) with moderate acceptability (63–100%) [72]. These studies highlight the potential of wearable and ML technologies in enhancing migraine prediction, monitoring, and treatment. Future developments could incorporate additional environmental triggers, such as barometric pressure and outdoor temperature that are potential migraine triggers [73]. Large-scale, long-term passive tracking of vital parameters could provide robust training data for AI models. Furthermore, integrating multiple data sources from both diurnal and nocturnal recordings could enhance predictive accuracy, guide acute treatment strategies, and advance our understanding of migraine.

Limitations of wearable devices

Wearable devices present innovative possibilities in the diagnosis and management of headaches, but they also share some common and significant limitations. From a technical perspective, issues such as battery life and data accuracy, which can be influenced by sensor type, wearing style, and environmental factors, remain challenges [45]. Devices that prioritize accuracy often require

Table 1 Summary of studies utilizing wearable technologies in headache research

Study author(s)	Objective	Wearable device(s)	Measured parameters	Study population/duration	AI used	Methods	Key results
Stubberud et al. [26]	Predicting headache in subsequent day	Small surface EMG sensor, thermister, PPG	HR, TEMP, SEMG-voltage	295 days from 18 migraine patients	Yes	Logistic regression, SVM, random forest, gradient boosting, adaptive boosting, XGBoost	Random forest model achieved 0.56 for accuracy
Siirtola et al. [25]	Predicting pre-ictal night of migraine	Smartwatch (Empatica E4®)	HR, EDA, TEMP, Acc, BVP, HRV	200 days from 7 migraine patients	Yes	Quadratic discriminant analysis (QDA) and linear discriminant analysis (LDA)	QDA model achieved 0.84 for accuracy
Kapustynska et al. [68]	Predicting pre-ictal night of migraine	Smartwatch (Empatica EmbracePlus®)	HR, EDA, TEMP, MET, ACT, Acc, etc.	322 days from 10 migraine patients	Yes	XGBoost, HistGradient-Boosting, Random forest, SVM, KNN	XGBoost model achieved 0.806 for accuracy
De Brouwer et al. [69]	Classifying headache attacks	Smartwatch (Empatica E4®)	HR, EDA, TEMP, Acc, IBI	98 attacks from 14 migraine patients, and 35 attacks from 4 cluster headache patients	Yes	Catboost in activity recognition	Using adapted ICHD-3 criteria, 28/98 attacks were classified as MO, and 17/35 as CH.
Pagán et al. [70]	Predicting migraine attacks	Wireless ECG (PLUX-Wireless Biosignals) and finger-held device (Nonin Onyx II)	HR, EDA, TEMP, SpO2	23 attacks from two migraine patients	No	State-space-based algorithm (N4SID)	Average forecast windows of 47 min and a low rate of false positives
Martins et al. [71]	Identifying physiological changes preceding a migraine attack	Wireless EEG device (Brain-Station Neuroverse®)	EEG, ERP	24 migraine patients, 14-day each	No	Spectral analysis	Decrease in delta power and increase in beta power at 24 h before attack
Connely et al. [72]	Evaluating the feasibility of wearable biosensors in pediatric migraine patients	Smartwatch (Empatica Embrace®) and smartphone	EDA, Acc	30 migraine patients, 28-days each	No	Statistic analysis	Wearable biosensors were obtained for a mean of 18.7 h per day worn.

HR – heart rate, TEMP – temperature, EDA – electrodermal activity, Acc – accelerometer, BVP – blood volume pulse, HRV – heart rate variability, MET – metabolic equivalent of task, ACT – activity tracking, SpO2 – blood oxygen saturation, EEG – electroencephalography, ECG – electrocardiography, IBI – inter-beat interval of the heart rate, ERP – event-related potentials, SEMG – surface electromyography, ICHD-3 – International classification of headache disorders (3rd edition), QDA – Quadratic discriminant analysis, LDA – Linear discriminant analysis, SVM – Support vector machine complex calibration or maintenance, which can deter regular use. For example, EEG headbands for migraine monitoring may need precise placement and frequent adjustments to ensure reliable data capture. Furthermore, their widespread adoption is hindered by several limitations related to usability, user compliance, and data security. The trade-off between these factors limits the scalability of wearable devices in clinical practice, where both reliable data and ease of use are essential. In addition, psychological barriers, such as mistrust in the technology or perceived privacy risks, also affect compliance. Clear communication about the benefits and limitations of wearable devices is essential to build trust among users. Also, wearable devices often collect sensitive physiological and behavioral data, making them attractive targets for cyberattacks. Thus, ensuring adherence to privacy regulations requires robust encryption and data management protocols [44]. Given the large amount of information collected, data storage space in the cloud and computational resources should be considered. From the perspective of the user, concerns about comfort and adherence can affect their widespread adoption [72]. Headaches are highly complex conditions, with individual variations in symptoms, triggers, and treatment responses and fluctuating lifetime course of disease, making it difficult to develop generalized models that work for everyone [40]. Addressing all these challenges is critical to maximizing their potential in both clinical and research settings.

In summary, wearable devices hold great promise in the diagnosis, management, and treatment of headaches, offering innovative tools to monitor physiological and biochemical parameters in real-time. While challenges like data accuracy, cost, and privacy concerns remain, advancements in AI and wearable technology are expected to overcome these barriers. With further research and development, wearable devices could transform headache care into a more personalized, predictive, and preventive discipline.

Drug discovery and development boosted by artificial intelligence

Drug discovery and therapy optimization are among the most significant applications of digital twin models. The landscape of drug discovery and development is being transformed by the integration of AI through the use of ML and deep learning. AI has demonstrated its potential in addressing the complexities and challenges inherent in drug discovery processes by enabling advanced data analysis and predictive modeling, becoming a transformative technology in pharmaceutical development. For instance, AI techniques have facilitated virtual screening, drug design and drug-target interaction modeling, establishing novel paradigms for predicting both pharmacodynamic and pharmacokinetic properties, thereby accelerating the drug discovery process and improving cost-effectiveness [74]. The integration of AI in describing pharmacokinetic and pharmacodynamic properties can optimize drug delivery systems, improving the accuracy of pharmacological predictions, and evaluating potential drug interactions which would be particularly important in patients with multiple comorbidities [74].

The development of dedicated platforms like MolProphet or PandaOmics are revolutionizing the field of drug development by prioritizing drug targets with the highest probability of success. This is achieved by using ML algorithms that analyze diverse datasets, including genomic, proteomic, and clinical data, exemplifying the practical implementation of AI in early-stage drug discovery. For instance, MolProphet is a comprehensive tool that integrates various AI methodologies that allow for virtual screening, molecular generation, and structure optimization [75]. An example of the potential of AI in drug development is INS018_055, which was developed by Insilico Medicine, for the treatment of idiopathic pulmonary fibrosis [76]. This compound was AI-generated by using the PandaOmics target discovery platform, which evaluated lung and kidney fibrosis datasets, identifying potential target proteins, and highlighting the ones with the highest probability of success. Later, Chemistry42, a deep learning generative chemistry tool, was used to design a small molecule targeting the protein of interest [77]. This process was completed in less than two years, and Phase II trials are currently ongoing, highlighting the efficiency of this approach [78]. It is worth noting that the application of AI in drug discovery is not limited to small-molecule drugs but it also extends to biologics and complex therapeutic modalities [79].

In addition to novel compound generation, AI has been pivotal in optimizing existing drug candidates. AI tools can assist in predicting the three-dimensional structures of target proteins, which is essential for effective drug design, as well as drug repurposing. This predictive capability allows researchers to tailor drug candidates to specific biological targets, enhancing the likelihood of therapeutic success. The role of AI in drug repurposing has gained traction, particularly in response to public health challenges such as the coronavirus disease 2019 (COVID-19) pandemic [80]. AI-driven approaches have been employed to identify existing drugs that may be effective against type 2 severe acute respiratory syndrome coronavirus (SARS-CoV-2), thereby expediting the development of treatment options. A recent case study involving ChatGPT discussed the development of a drug for cocaine addiction, showcasing how AI can dissect protein-protein interaction networks to forecast drug repurposing opportunities [81].

Despite the great potential of AI in drug discovery and development, it is important to also consider its limitations. AI relies on large, often disease-specific, datasets, and its performance depends on training data; thus, disorders with small datasets are less likely to benefit from AI approaches. Further, the inclusion of clinical data adds a layer of complexity to the analysis, since it is not always consistent; therefore, data (re)processing and harmonization is crucial, which can be highly labor intensive. Most importantly, AI tools predict the efficacy of potential therapeutic targets based on pattern recognition and predictive analytics, but they do not provide the rationale behind the chosen targets, which is essential for the understanding of the pathophysiology of the disease [82]. Moreover, the ethical implications and regulatory considerations surrounding AI in drug discovery are critical. The FDA (U.S. Food and Drug Administration) has begun to establish guidelines for the safe and effective use of AI/ML technologies in drug development, reflecting the need for a balanced approach that fosters innovation while ensuring patient safety [83]. Of note, user compliance is a crucial factor in the success of AI-driven drug discovery, particularly in clinical trials and post-market monitoring. Therefore, ensuring user compliance involves fostering trust in AI systems. This requires explainable AI approaches that allow users to understand and validate predictions, particularly in drug safety monitoring. Lastly, we should consider the specific limitations of the use of AI for drug discovery in the field of headaches, where there is a lack of pharmacological targets and data scarcity issues. To date, CGRP is the only reliable therapeutic target in migraine, while several other targets are under investigation [84]. The discovery of new pathophysiological mechanisms will likely increase the number of available therapeutic targets and thus expand the potential of AI for drug discovery. Action is needed for international collaboration to make large databases collecting and integrating multidata about headache patients that should tackle the utilization of current small datasets.

Despite the above mentioned limitations, as AI continues to evolve, its role in clinical research will grow, offering a future where clinical trials are faster, more efficient, and more inclusive, including underrepresented groups and more diverse populations. For example, in decentralized clinical trials, AI helps faster patient identification by analyzing large electronic health records platforms and facilitates remote participation by monitoring the health of the patients through wearable devices and other remote tools. This reduces the need for in-person visits, broadening access to patients in diverse locations and making trials more convenient.

While AI-driven drug discovery is already making contributions across multiple medical fields, its potential to revolutionize the development of treatments for headache disorders remains largely untapped. Migraine, though a better-studied condition with an expanding treatment landscape, still presents significant challenges. A notable proportion of patients with migraine do not respond optimally to current therapies or experience debilitating side effects [85]. Tension-type headache, cluster headache, and trigeminal autonomic cephalalgias continue to lack targeted therapeutic options, representing an area of high unmet need [86, 87]. AI can accelerate the discovery of novel therapeutic targets for these conditions by leveraging large datasets from genomics, proteomics, and clinical data to identify potential drug targets that may have been previously overlooked. For example, the ability of AI to model drug-target interactions and predict responses based on patient-specific characteristics could enable the identification of novel compounds or the repurposing of existing drugs for use in tension-type headache or cluster headache, where conventional therapies often fall short. AI-based screening could help identify molecules that interact with specific nociceptive pathways, offering hope for more effective treatments. Furthermore, an AI-powered chatbot designed for headache patients involved in clinical trials could inform patients and involve them throughout clinical trials, leading to higher retention rates.

In summary, AI can be instrumental in uncovering new molecular targets that could lead to more personalized treatments, especially for patients who are non-responders to existing therapies. The ability of AI to generate predictive models based on complex biological data offers the potential for discovering more effective therapies for headache disorders, expanding beyond the current pharmacological toolbox. It holds particular promise in addressing the unmet needs of tension-type headache, cluster headache, and specific subgroups of migraine patients, facilitating the development of treatments that are both more targeted and effective.

Future perspectives and conclusion

The integration of AI into headache research and clinical practice represents a transformative approach to understanding, diagnosing, and treating headache disorders. AI-driven advancements in digital twin models and omics integration underscore the ability of AI to tackle complex data and uncover insights beyond traditional analysis in the headache field. However, realizing the full potential of AI in headache care requires overcoming several challenges, including the need for standardized data collection, ethical considerations, legal implications, and robust validation of AI models. Collaborative, multi-institutional efforts are essential to establishing standards for data handling and model development. Furthermore, closer collaboration between researchers, clinicians, bioethics experts, legal representatives, and neuroengineers is paramount for the realization of these objectives in the near future. This paper serves as a call to action for all international and national headache societies, including board members of relevant scientific journals, to unite in proposing novel frameworks for integrating AI-based technologies into headache care. Benchmarks can be established, and biases minimized for future AI solutions in headache research, diagnosis, and treatment through the collaborative efforts of all relevant stakeholders. Furthermore, the standardization of study protocols that incorporate AI is essential to advance headache classification and facilitate the discovery of new biomarkers [88]. A lack of cohesive strategy has already shown new pockets of inequality between worldwide healthcare systems that have begun implementing AI-based technologies and those that lack the resources to adopt them. To address this challenge, we propose creating a sustainable ecosystem that empowers task forces composed of international and multidisciplinary experts from AI-advanced healthcare centers, collaborating with emerging experts in AI-underserved countries. This collaboration could yield bidirectional benefits, such as establishing large databases, creating multiple hubs for external AI model validation, and optimizing systemic data collection approaches. These efforts will ensure that headache patients worldwide, especially those in underserved regions, receive equitable and adequate treatment.

In summary, while AI offers groundbreaking opportunities to revolutionize headache care, success will depend on a balanced approach that combines technical innovation with careful consideration of ethical and clinical implications. As research progresses, AI could pave the way for more personalized, efficient, and effective management of headache disorders, ultimately improving the quality of life for countless patients who suffer from various forms of headache disorders. The next wave of AI implementation in the headache field should be guided by headache specialists involved in multidisciplinary and multicentric hub collaborations because we are not here to simply witness change—we are here to define it.

Abbreviations

Acc	Accelerometer
ACT	Activity tracking
AI	Artificial intelligence
AUC	Area under the curve
BVP	Blood volume pulse
CGRP	Calcitonin gene-related peptide
ECG	Electrocardiography
EDA	Electrodermal activity
EEG	Electroencephalography
ERP	Event-related potentials
HR	Heart rate
HRV	Heart rate variability
IBI	Inter-beat interval of the heart rate
ICHD	3-International classification of headache disorders (3rd edition)
IOP	Intraocular pressure
LDA	Linear discriminant analysis
SEMG	Surface electromyography
MET	Metabolic equivalent of task
ML	Machine learning
PPG	Photoplethysmography
QDA	Quadratic discriminant analysis
SpO2	Blood oxygen saturation
SVM	Support vector machine
TEMP	Temperature

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Declarations

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Not applicable.

Competing interests
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References

1. Callaway E (2024) Chemistry Nobel goes to developers of AlphaFold AI that predicts protein structures. Nature 634:525–526. https://doi.org/10.1038/d41586-024-03214-7

2. Chiang C-C, Schwedt TJ, Dumkrieger G et al (2024) Advancing toward precision migraine treatment: Predicting responses to preventive medications with machine learning models based on patient and migraine features. Headache 64:1094–1108. https://doi.org/10.1111/head.14806
3. Ihara K, Dumkrieger G, Zhang P et al (2024) Application of Artificial Intelligence in the Headache Field. Curr Pain Headache Rep 28:1049–1057. https://doi.org/10.1007/s11916-024-01297-5
4. Petrušić I, Ha W-S, Labastida-Ramirez A et al (2024) Influence of next-generation artificial intelligence on headache research, diagnosis and treatment: the junior editorial board members' vision - part 1. J Headache Pain 25:151. https://doi.org/10.1186/s10194-024-01847-7
5. Javaid M, Haleem A, Suman R (2023) Digital Twin applications toward industry 4.0: a review. Cogn Rob 3:71–92. https://doi.org/10.1016/j.cogr.2023.04.003
6. Sandrone S (2024) Digital Twins in Neuroscience. J Neurosci 44:e0932242024. https://doi.org/10.1523/JNEUROSCI.0932-24.2024
7. Segovia M, Garcia-Alfaro J (2022) Design, modeling and implementation of Digital Twins. Sens (Basel) 22:5396. https://doi.org/10.3390/s22145396
8. Attaran M, Attaran S, Celik BG (2023) The impact of digital twins on the evolution of intelligent manufacturing and industry 4.0. Adv Comput Intell 3:11. https://doi.org/10.1007/s43674-023-00058-y
9. Laubenbacher R, Mehrad B, Shmulevich I, Trayanova N (2024) Digital twins in medicine. Nat Comput Sci 4:184–191. https://doi.org/10.1038/s43588-024-00607-6
10. Emmert-Streib F (2023) Defining a Digital Twin: A Data Science-based Unification. Mach Learn Knowl Extr 5:1036–1054. https://doi.org/10.3390/make5030054
11. Boulos MNK, Zhang P (2021) Digital Twins: from Personalised Medicine to Precision Public Health. J Pers Med 11:745. https://doi.org/10.3390/jpm11080745
12. Shen M, Chen S-B, Ding X-D (2024) The effectiveness of digital twins in promoting precision health across the entire population: a systematic review. NPJ Digit Med 7:145. https://doi.org/10.1038/s41746-024-01146-0
13. Cen S, Gebregziabher M, Moazami S et al (2023) Toward precision medicine using a digital twin approach: modeling the onset of disease-specific brain atrophy in individuals with multiple sclerosis. Sci Rep 13:16279. https://doi.org/10.1038/s41598-023-43618-5
14. Bahrami F, Rossi RM, De Nys K, Defraeye T (2023) An individualized digital twin of a patient for transdermal fentanyl therapy for chronic pain management. Drug Deliv Transl Res 13:2272–2285. https://doi.org/10.1007/s13346-023-01305-y
15. Fekonja LS, Schenk R, Schröder E, Tomasello R, Tomšić S, Picht T (2024) The digital twin in neuroscience: from theory to tailored therapy. Front Neurosci 18:1454856. https://doi.org/10.3389/fnins.2024.1454856
16. Gazerani P (2023) Intelligent Digital Twins for Personalized Migraine Care. J Pers Med 13:1255. https://doi.org/10.3390/jpm13081255
17. Gonzalez-Martinez A, Pagán J, Sanz-García A et al (2022) Machine-learning-based approach for predicting response to anti-calcitonin gene-related peptide (CGRP) receptor or ligand antibody treatment in patients with migraine: a multicenter Spanish study. Eur J Neurol 29:3102–3111. https://doi.org/10.1111/ene.15458
18. Raffaelli B, Fitzek M, Overeem LH et al (2023) Clinical evaluation of super-responders vs. non-responders to CGRP(-receptor) monoclonal antibodies: a real-world experience. J Headache Pain 24:16. https://doi.org/10.1186/s10194-023-01552-x
19. Mitrović K, Petrušić I, Radojičić A et al (2023) Migraine with aura detection and subtype classification using machine learning algorithms and morphometric magnetic resonance imaging data. Front Neurol 14:1106612. https://doi.org/10.3389/fneur.2023.1106612
20. Kogelman LJA, Esserlind A-L, Christensen AF et al (2019) Migraine polygenic risk score associates with efficacy of migraine-specific drugs. Neurol Genet 5:e364. https://doi.org/10.1212/NXG.0000000000000364
21. Dodick DW (2018) A phase-by-phase review of Migraine Pathophysiology. Headache 58:4–16. https://doi.org/10.1111/head.13300
22. Ashina M, Hansen JM, Do TP et al (2019) Migraine and the trigeminovascular system-40 years and counting. Lancet Neurol 18:795–804. https://doi.org/10.1016/S1474-4422(19)30185-1
23. Puledda F, Viganò A, Sebastianelli G et al (2023) Electrophysiological findings in migraine may reflect abnormal synaptic plasticity mechanisms: a narrative review. Cephalalgia 43:3331024231195780. https://doi.org/10.1177/03331024231195780
24. Houle TT, Turner DP, Golding AN et al (2017) Forecasting individual headache attacks using perceived stress: development of a multivariable prediction model for persons with episodic migraine. Headache 57:1041–1050. https://doi.org/10.1111/head.13137
25. Siirtola P, Koskimäki H, Mönttinen H, Röning J (2018) Sens (Basel) 18:1374. https://doi.org/10.3390/s18051374. Using Sleep Time Data from Wearable Sensors for Early Detection of Migraine Attacks
26. Stubberud A, Ingvaldsen SH, Brenner E et al (2023) Forecasting migraine with machine learning based on mobile phone diary and wearable data. Cephalalgia 43:3331024231169244. https://doi.org/10.1177/03331024231169244
27. Katsuki M, Tatsumoto M, Kimoto K et al (2023) Investigating the effects of weather on headache occurrence using a smartphone application and artificial intelligence: a retrospective observational cross-sectional study. Headache 63:585–600. https://doi.org/10.1111/head.14482
28. Viera AJ, Antono B (2022) Acute headache in adults: a Diagnostic Approach. Am Fam Physician 106:260–268
29. García-Azorín D, Abelaira-Freire J, González-García N et al (2022) Sensitivity of the SNNOOP10 list in the high-risk secondary headache detection. Cephalalgia 42:1521–1531. https://doi.org/10.1177/03331024221120249
30. Holle-Lee D (2024) Digitalisierung in Der Diagnostik Und Therapie Von Kopfschmerzen [Digitization in the diagnosis and treatment of headache]. MMW Fortschr Med 166:67–69. https://doi.org/10.1007/s15006-024-4435-9
31. Stubberud A, Gray R, Tronvik E et al (2022) Machine prescription for chronic migraine. Brain Commun 4:fcac059. https://doi.org/10.1093/braincomms/fcac059
32. Dodick DW, Goadsby PJ, Schwedt TJ et al (2023) Ubrogepant for the treatment of migraine attacks during the prodrome: a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial in the USA. Lancet 402:2307–2316. https://doi.org/10.1016/S0140-6736(23)01683-5
33. Pellegrino ABW, Davis-Martin RE, Houle TT et al (2018) Perceived triggers of primary headache disorders: a meta-analysis. Cephalalgia 38:1188–1198. https://doi.org/10.1177/0333102417727535
34. Manzo G, Calvaresi D, Jimenez-del-Toro O et al (2021) Cohort and trajectory analysis in Multi-agent Support systems for Cancer survivors. J Med Syst 45:109. https://doi.org/10.1007/s10916-021-01770-3
35. Vallée A (2024) Envisioning the future of Personalized Medicine: role and realities of Digital Twins. J Med Internet Res 26:e50204. https://doi.org/10.2196/50204
36. Chiang CC, Halker Singh R, Lalvani N et al (2021) Patient experience of telemedicine for headache care during the COVID-19 pandemic: an American Migraine Foundation survey study. Headache 61:734–739. https://doi.org/10.1111/head.14110
37. Armeni P, Polat I, De Rossi LM et al (2022) Digital Twins in Healthcare: is it the beginning of a new era of evidence-based medicine? A critical review. J Pers Med 12:1255. https://doi.org/10.3390/jpm12081255
38. Rovati L, Gary PJ, Cubro E et al (2023) Development and usability testing of a patient digital twin for critical care education: a mixed methods study. Front Med (Lausanne) 10:1336897. https://doi.org/10.3389/fmed.2023.1336897
39. Zhang J, Zhu J, Tu W et al (2024) The effectiveness of a Digital Twin Learning System in Assisting Engineering Education courses: a case of Landscape Architecture. Appl Sci 14:6484. https://doi.org/10.3390/app14156484
40. Stubberud A, Langseth H, Nachev P et al (2024) Artificial intelligence and headache. Cephalalgia 44:3331024241268290. https://doi.org/10.1177/03331024241268290
41. Cao Z, Lin C-T, Lai K-L et al (2020) Extraction of SSVEPs-Based inherent fuzzy Entropy using a wearable headband EEG in Migraine patients. IEEE Trans Fuzzy Syst 28:14–27. https://doi.org/10.1109/TFUZZ.2019.2905823
42. Katsuki M, Matsumori Y, Kawamura S et al (2023) Developing an artificial intelligence-based diagnostic model of headaches from a dataset of clinic patients' records. Headache 63:1097–1108. https://doi.org/10.1111/head.14611
43. Babu M, Lautman Z, Lin X et al (2024) Wearable devices: implications for Precision Medicine and the future of Health Care. Annu Rev Med 75:401–415. https://doi.org/10.1146/annurev-med-052422-020437
44. Hughes A, Shandhi MMH, Master H et al (2023) Wearable devices in Cardiovascular Medicine. Circ Res 132:652–670. https://doi.org/10.1161/circresaha.122.322389
45. Lu L, Zhang J, Xie Y et al (2020) Wearable Health Devices in Health Care: Narrative systematic review. JMIR Mhealth Uhealth 8:e18907. https://doi.org/10.2196/18907
46. Apoorva S, Nguyen NT, Sreejith KR (2024) Recent developments and future perspectives of microfluidics and smart technologies in wearable devices. Lab Chip 24:1833–1866. https://doi.org/10.1039/d4lc00089g

47. Sempionatto JR, Lasalde-Ramírez JA, Mahato K et al (2022) Wearable chemical sensors for biomarker discovery in the omics era. Nat Rev Chem 6:899–915. https://doi.org/10.1038/s41570-022-00439-w
48. Tan M, Xu Y, Gao Z et al (2022) Recent advances in Intelligent Wearable Medical devices integrating Biosensing and Drug Delivery. Adv Mater 34:e2108491. https://doi.org/10.1002/adma.202108491
49. Voelker R (2018) Smart Watch detects seizures. JAMA 319:1086. https://doi.org/10.1001/jama.2018.1809
50. Guo Y, Wang H, Zhang H et al (2019) Mobile Photoplethysmographic Technology to Detect Atrial Fibrillation. J Am Coll Cardiol 74:2365–2375. https://doi.org/10.1016/j.jacc.2019.08.019
51. Mehrabadi MA, Azimi I, Sarhaddi F et al (2020) Sleep Tracking of a commercially available Smart Ring and Smartwatch Against Medical-Grade Actigraphy in Everyday settings: Instrument Validation Study. JMIR Mhealth Uhealth 8:e20465. https://doi.org/10.2196/20465
52. Carpenter A, Frontera A (2016) Smart-watches: a potential challenger to the implantable loop recorder? Europace 18:791–793. https://doi.org/10.1093/europace/euv427
53. Stanyer EC, Jack Brookes J, Pang JR et al (2023) Investigating the relationship between sleep and migraine in a global sample: a bayesian cross-sectional approach. J Headache Pain 24:123. https://doi.org/10.1186/s10194-023-01638-6
54. Cao R, Azimi I, Sarhaddi F et al (2022) Accuracy Assessment of Oura Ring Nocturnal Heart Rate and Heart Rate Variability in Comparison with Electrocardiography in Time and frequency domains: Comprehensive Analysis. J Med Internet Res 24:e27487. https://doi.org/10.2196/27487
55. Sel K, Osman D, Huerta N et al (2023) Continuous cuffless blood pressure monitoring with a wearable ring bioimpedance device. NPJ Digit Med 6:59. https://doi.org/10.1038/s41746-023-00796-w
56. Seo H, Chung WG, Kwon YW et al (2023) Smart contact lenses as Wearable Ophthalmic Devices for Disease Monitoring and Health Management. Chem Rev 123:11488–11558. https://doi.org/10.1021/acs.chemrev.3c00290
57. Nguyen BN, Lek JJ, Vingrys AJ, McKendrick AM (2016) Clinical impact of migraine for the management of glaucoma patients. Prog Retin Eye Res 51:107–124. https://doi.org/10.1016/j.preteyeres.2015.07.006
58. Mullen M, Scofield-Kaplan SM, Ford WC, Mancini R (2022) The Effect of Optic nerve sheath fenestration on intraocular pressure in patients with idiopathic intracranial hypertension. J Neuroophthalmol 42:97–100. https://doi.org/10.1097/wno.0000000000001235
59. Nyein HYY, Bariya M, Tran B et al (2021) A wearable patch for continuous analysis of thermoregulatory sweat at rest. Nat Commun 12:1823. https://doi.org/10.1038/s41467-021-22109-z
60. Tehrani F, Teymourian H, Wuerstle B et al (2022) An integrated wearable microneedle array for the continuous monitoring of multiple biomarkers in interstitial fluid. Nat Biomed Eng 6:1214–1224. https://doi.org/10.1038/s41551-022-00887-1
61. Pavelić AR, Zebenholzer K, Wöber C (2024) Reconceptualizing autonomic function testing in migraine: a systematic review and meta-analysis. J Headache Pain 25:54. https://doi.org/10.1186/s10194-024-01758-7
62. Stubberud A, Buse DC, Kristoffersen ES et al (2021) Is there a causal relationship between stress and migraine? Current evidence and implications for management. J Headache Pain 22:155. https://doi.org/10.1186/s10194-021-01369-6
63. Arakawa T, Tomoto K, Nitta H et al (2020) A wearable cellulose acetate-coated Mouthguard Biosensor for in vivo salivary glucose measurement. Anal Chem 92:12201–12207. https://doi.org/10.1021/acs.analchem.0c01201
64. Kim J, Imani S, de Araujo WR et al (2015) Wearable salivary uric acid mouthguard biosensor with integrated wireless electronics. Biosens Bioelectron 74:1061–1068. https://doi.org/10.1016/j.bios.2015.07.039
65. Nam JH, Lee HS, Kim J et al (2018) Salivary glutamate is elevated in individuals with chronic migraine. Cephalalgia 38:1485–1492. https://doi.org/10.1177/0333102417742366
66. Alpuente A, Gallardo VJ, Asskour L et al (2024) Dynamic fluctuations of salivary CGRP levels during migraine attacks: association with clinical variables and phenotypic characterization. J Headache Pain 25:58. https://doi.org/10.1186/s10194-024-01772-9
67. Shi J, Liu S, Zhang L et al (2020) Smart Textile-Integrated Microelectronic systems for Wearable Applications. Adv Mater 32:e1901958. https://doi.org/10.1002/adma.201901958
68. Kapustynska V, Abromavičius V, Serackis A et al (2024) Machine learning and Wearable Technology: monitoring changes in Biomedical Signal patterns during Pre-migraine nights. Healthc (Basel) 12:1701. https://doi.org/10.3390/healthcare12171701
69. De Brouwer M, Vandenbussche N, Steenwinckel B et al (2022) mBrain: towards the continuous follow-up and headache classification of primary headache disorder patients. BMC Med Inf Decis Mak 22:87. https://doi.org/10.1186/s12911-022-01813-w
70. Pagán J, De Orbe MI, Gago A et al (2015) Robust and accurate modeling approaches for Migraine per-patient prediction from Ambulatory Data. Sens (Basel) 15:15419–15442. https://doi.org/10.3390/s150715419
71. Martins IP, Westerfield M, Lopes M et al (2020) Brain state monitoring for the future prediction of migraine attacks. Cephalalgia 40:255–265. https://doi.org/10.1177/0333102419877660
72. Connelly MA, Boorigie ME (2021) Feasibility of using SMARTER methodology for monitoring precipitating conditions of pediatric migraine episodes. Headache 61:500–510. https://doi.org/10.1111/head.14028
73. Fischer-Schulte LH, Peng KP (2023) Migraine prodromes and migraine triggers. Handb Clin Neurol 198:135–148. https://doi.org/10.1016/B978-0-12-823356-6.00014-7
74. Singh S, Kumar R, Payra S, Singh SK (2023) Artificial Intelligence and Machine Learning in Pharmacological Research: bridging the gap between data and Drug Discovery. Cureus 15:e44359. https://doi.org/10.7759/cureus.44359
75. Yang K, Xie Z, Li Z et al (2024) MolProphet: a One-Stop, General purpose, and AI-Based platform for the early stages of Drug Discovery. J Chem Inf Model 64:2941–2947. https://doi.org/10.1021/acs.jcim.3c01979
76. Ren F, Aliper A, Chen J et al (2024) A small-molecule TNIK inhibitor targets fibrosis in preclinical and clinical models. Nat Biotechnol (Online Ahead Print). https://doi.org/10.1038/s41587-024-02143-0
77. Ivanenkov YA, Polykovskiy D, Bezrukov D et al (2023) Chemistry42: an AI-Driven platform for Molecular Design and optimization. J Chem Inf Model 63:695–701. https://doi.org/10.1021/acs.jcim.2c01191
78. Xu W (2024) Current status of computational approaches for small Molecule Drug Discovery. J Med Chem 67:18633–18636. https://doi.org/10.1021/acs.jmedchem.4c02462
79. Tang X, Dai H, Knight E et al (2024) A survey of generative AI for de novo drug design: new frontiers in molecule and protein generation. Brief Bioinform 25:bbae338. https://doi.org/10.1093/bib/bbae338
80. Prasad K, Kumar V (2021) Artificial intelligence-driven drug repurposing and structural biology for SARS-CoV-2. Curr Res Pharmacol Drug Discov 2:100042. https://doi.org/10.1016/j.crphar.2021.100042
81. Wang R, Feng H, Wei G-W (2023) ChatGPT in Drug Discovery: a Case Study on Anticocaine Addiction Drug Development with Chatbots. J Chem Inf Model 63:7189–7209. https://doi.org/10.1021/acs.jcim.3c01429
82. Sidders B (2024) Elevating life science R&D success with AI: a framework. Drug Discovery Today 29:104211. https://doi.org/10.1016/j.drudis.2024.104211
83. Niazi SK (2023) The coming of age of AI/ML in Drug Discovery, Development, Clinical Testing, and Manufacturing: the FDA perspectives. Drug Des Devel Ther 17:2691–2725. https://doi.org/10.2147/DDDT.S424991
84. Al-Hassany L, Boucherie DM, Creeney H et al (2023) Future targets for migraine treatment beyond CGRP. J Headache Pain 24:76. https://doi.org/10.1186/s10194-023-01567-4
85. Ashina M (2020) Migraine. N Engl J Med 383:1866–1876. https://doi.org/10.1056/NEJMra1915327
86. Petersen AS, Lund N, Goadsby PJ et al (2024) Recent advances in diagnosing, managing, and understanding the pathophysiology of cluster headache. Lancet Neurol 23:712–724. https://doi.org/10.1016/S1474-4422(24)00143-1
87. Ashina S, Mitsikostas DD, Lee MJ et al (2021) Tension-type headache. Nat Rev Dis Primers 7:24. https://doi.org/10.1038/s41572-021-00257-2
88. Petrušić I, Savić A, Mitrović K et al (2024) Machine learning classification meets migraine: recommendations for study evaluation. J Headache Pain 25:215. https://doi.org/10.1186/s10194-024-01924-x