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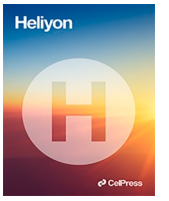

Review article

New management strategies for primary headache disorders: Insights from P4 medicine

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ABSTRACT

Primary headache disorder is the main cause of headache attacks, leading to significant disability and impaired quality of life. This disorder is increasingly recognized as a heterogeneous condition with a complex network of genetic, environmental, and lifestyle factors. However, the timely diagnosis and effective treatment of these headaches remain challenging. Precision medicine is a potential strategy based on P4 (predictive, preventive, personalized, and participatory) medicine that may bring new insights for headache care. Recent machine learning advances and widely available molecular biology and imaging data have increased the usefulness of this medical strategy. Precision medicine emphasizes classifying headaches according to their risk factors, clinical presentation, and therapy responsiveness to provide individualized headache management. Furthermore, early preventive strategies, mainly utilizing predictive tools, are critical in reducing headache attacks and improving the quality of life of individuals with headaches. The current review comprehensively discusses the potential application value of P4 medicine in headache management.

1. Introduction

Over 90 % of people experience headaches in their lifetime [1], with 47 % of the global adult population presenting with active headache disorders [2]. Primary headache disorders, which account for most headache attacks, consist of headache conditions such as tension-type headache (TTH), migraine, and cluster headache (CH) [3]. A high frequency of headache attacks can severely affect people's routine work, resulting in related disabilities and reduced quality of life. The most recent global burden of neurological diseases rankings, reported that migraine and TTH were the second and ninth largest contributors to global neurological disability-adjusted life-years, respectively [4]. Additionally, the high treatment costs associated with headaches place a substantial economic burden on patients and society [2]. Therefore, these headache-related issues should be addressed with great urgency.

Early and standardized diagnosis and treatments for headache are difficult to achieve due to their complex etiology and changeable symptoms. Many encouraging advances have been made in the headache field, such as biomarkers [5], calcitonin gene-related peptide (CGRP)-targeting drugs [6,7], and neuromodulation technologies [8]. However, the main concern of translating these developments into practice to improve the quality of headache management remains unresolved. Recently, precision medicine has emerged as a new

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treatment model that promotes personalized treatment via the comprehensive integration of phenotypic, psychosocial, genetic, and biomarker information [9]. Furthermore, P4 medicine, which incorporates predictive, personalized, preventive, and participatory approaches, is a representative paradigm of precision medicine. This concept has been widely researched in the past few years, including in respiratory medicine [10], cancer [11] and epilepsy [12]. P4 medicine employs systems biology data to obtain a more detailed definition of the disease phenotype to improve treatment success. Although no clinical application data are available for this new decision schema, this approach is still promising and has notable advantages.

Currently, no P4 medicine-related concept has been proposed in the headache field. The purpose of the review is to provide a new management strategy for primary headache disorders based on P4 medicine. We comprehensively reviewed the current knowledge and integrated the latest developments in headache care, including those from diagnosis and treatment to the systematic evaluation and management of patients with headaches. A narrative review rather than a systematic review was performed owing to the diverse and complex data. All steps followed the recommendations for a narrative review [13]. Related articles were searched using electronic databases, including PubMed, EMBASE and Web of Science, without filtering for the publication language. Search strategies used combinations of keywords, including terms such as “migraine”, “headache”, “risk factors”, “triggers”, “response”, “predicting”, and “efficacy”. We also conducted a manual search as a supplement to the screening.

This new strategy is still in its early stage, and has not yet been adopted in routine clinical practice. In the current narrative review, we mainly emphasize the potential clinical application value of P4 medicine to help physicians provide optimal management for headache patients. The following four approaches comprise the core of P4 medicine (Fig. 1). (1) A predictive approach to determining the risk of headache attacks using a range of warning signals. (2) A preventive approach for conducting therapeutic or lifestyle interventions to decrease the risk of headache progression. (3) A personalized approach for developing an individualized treatment strategy according to genetic factors, lifestyle factors, and comorbidities. (4) A participatory approach that strongly emphasizes the central role played by patients with headache, with a dependence on the long-term adherence and persistence of patients during headache management.

2. Exclusion of secondary headaches

According to clinical guidelines, secondary headaches must be excluded before diagnosing primary headaches [14]. Etiological treatment should be initiated as soon as a secondary headache is diagnosed. Here, we present a few strategies to quickly differentiate between primary and secondary headaches. In cases of new-onset headaches, red flags based on the SNNOOP10 list may help recognize secondary headaches [15]. The warning signs highlighted in the SNNOOP10 list include fever, neoplasm history, neurologic dysfunction (including decreased consciousness), sudden onset, papilledema, positional headache, pattern change or recent onset of new headache, progressive headaches, pregnancy, puerperium, older age (>50 years), headache precipitated by sneezing or exercise, painful eye with autonomic features, post-traumatic headache, immune function disorder, and medication overuse. Consequently, patients presenting with new-onset headaches and any of the above characteristics require further investigation and referral. Furthermore, a consensus exists on using green flags for distinguishing primary headaches, which consist of headaches since

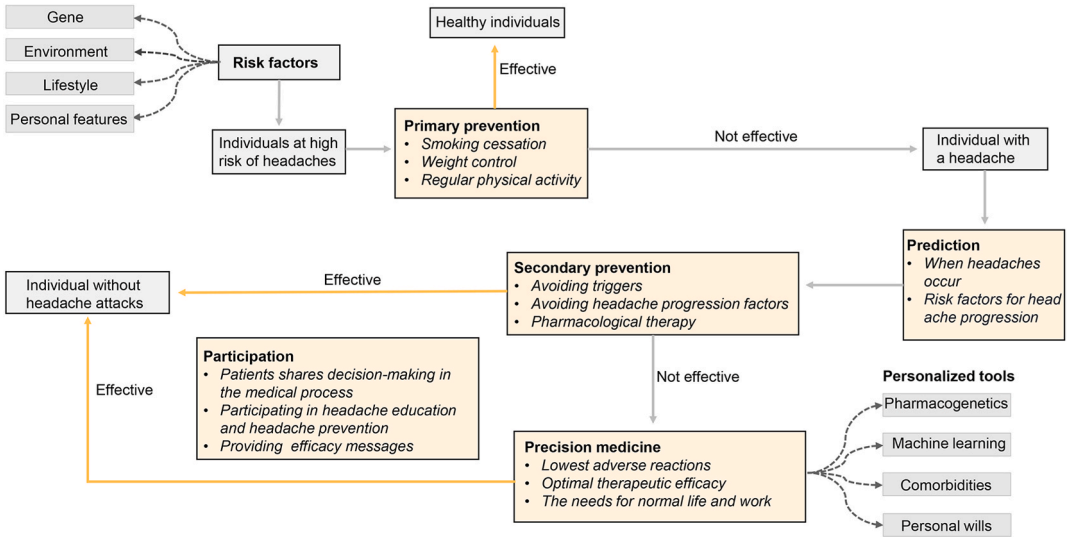

Fig. 1. The conceptual framework of P4 medicine strategies for primary headache management is based on predictive, preventive, personalized, and participatory approaches. The foundation of the predictive approach is to develop algorithmic models that integrate personal features, genetics, biomolecular, and neuroimaging data to predict headache risk and the timing of headache occurrence. The targeted preventive approach is implemented to lower headache risk (primary prevention) and headache attacks (secondary prevention). The personalized approach aims to identify the optimal treatment method using individualized techniques, incorporating pharmacogenetics and machine learning. Finally, the participatory approach is involved throughout the headache management process, emphasizing shared decision-making between the patients and their doctors.

childhood, headaches associated with the menstrual cycle, intermittent headaches, inherited headaches, and headache occurrences more than a week ago [16]. If red flags are detected, secondary causes should be suspected. Overall, rational use of these flags can improve diagnosis accuracy and reduce headache-related costs.

3. Advances in diagnosis biomarkers and models

Currently, no specific headache biomarkers are available for clinical use. However, they have shown great promise in guiding early headache diagnosis. For example, certain blood and neuroimaging biomarkers have demonstrated the potential to identify migraines. Elevated CGRP levels were observed in migraineurs during spontaneous migraine attacks [17–19]. Clinical studies have also shown increased pituitary adenylate cyclase-activating polypeptide (PACAP) levels in the blood of migraineurs during the ictal period [20,21]. Furthermore, a high PACAP-38 serum level may be used to distinguish chronic migraine (CM) from episodic migraine [22]. In addition to these biomarkers, structural neuroimaging investigations assessing cortical parameters in migraineurs have revealed that the grey matter volume (GMV) in the anterior cingulate cortex of migraineurs was lower than that of healthy controls [23,24]. Moreover, an increased GMV in the periaqueductal grey (PAG) of migraineurs was detected, suggesting PAG volume expansion can be a useful imaging biomarker for diagnosing and evaluating migraine patients [24,25]. There was also a study finding that the volume of iron deposits in the PAG was larger in migraineurs than in controls, particularly those with CM [26].

Recently, several machine learning models have been attempted to be developed for assisting with headache diagnosis [27,28]. A new guideline-based clinical decision support system (CDSS 2.0), developed by Han and his colleagues, is a good application for headache diagnosis based on doctor–patient interactions [27]. Clinical information is obtained through human-computer conversations conducted on a personal mobile device in an outpatient clinic. Subsequently, CDSS 2.0 automatically conveys probable headache classification and treatment guidance to clinicians for reference. This approach has greatly improved the efficiency of headache information acquisition and has demonstrated good reliability and satisfaction. Diagnostic sensitivity and specificity for primary headaches exceed 80 % and 95 %, respectively.

4. Predictive strategy

Our understanding of primary headaches has advanced due to growing research on the associated risk factors, triggers, and predictors. This progress has helped identify high-risk populations for headache development and facilitated the early initiation of related interventions. In addition, predicting headache prognosis may help understand overall headache development and adjust therapy plans accordingly. Thus, the prediction strategy is applicable throughout the headache management process and is crucial for personalized treatment.

4.1. Predicting individuals at high risk for headaches

Presently, no useful information exists to guide the accurate identification of people at high risk for primary headaches. While several risk factors for primary headaches have been highlighted, their effects vary from individual to individual. These risk factors comprise diverse aspects, including demographic, genetic, psychological, and metabolic characteristics [29]. Combining such different risk factors may enable the assessment of headache development in individuals. Table 1 presents a breakdown of these risk factors into non-modifiable and modifiable categories. Headache risk can be reduced by improving modifiable factors in patients.

4.1.1. Non-modifiable risk factors

Non-modifiable risk factors for primary headaches include age, gender, and genetic aspects, with women of childbearing age being a prominent focus in migraine risk. According to the 2019 Global Burden of Disease study, migraine prevalence was higher in females than in males and increased with age up to 44 years, followed by a gradual decrease [30]. Additionally, migraine prevalence is similar in boys and girls during childhood but increases in women after puberty and menarche [31]. Female gender is also a risk factor for TTH, demonstrating a higher prevalence in the middle-aged (31–40 years) group [32]. In contrast, CH frequency is higher in males,

Table 1
Summary of risk factors for the onset and chronic progression of primary headache disorders.

Headache Type	Non-modifiable risk factors		Modifiable risk factors		Refs
	At the beginning	Chronification	At the beginning	Chronification	
Migraine	Age, female sex, genetic	Age, female sex	Occupations (such as high physical exertion, night work), smoking status, lower levels of education, lower socioeconomic status, low physical activity, personality traits, obesity, PFO, hypercoagulability	Overuse of acute migraine medication, ineffective acute treatment, obesity, depression, stressful life events, high attack frequency per month, comorbidities	[29,32,49,50,52,59,80]
TTH	Age, female sex, genetic, maternal smoking history	–	Obesity, occupations (such as excessive computer use, night work), sleep disorders	Sleep disorders	[32,45,50,53,80]
CH	Male sex, genetic	–	–	–	[33,34]

CH, cluster headache; PFO, patent foramen ovale; TTH, tension-type headache.

with a mean age of onset of 30 years [33,34].

Another potential source of predictive information is genetics. Genome-wide association studies have identified about 40 multiple single-nucleotide polymorphisms (SNPs) associated with migraine [35]. In addition, genetics enables the identification of monogenic subtypes of migraine. For example, familial hemiplegic migraine (FHM) is caused by missense mutations in the CACNA1A (FHM1), ATP1A2 (FHM2), and SCN1A (FHM3) genes [36]. PRRT2 mutations have also been found in <5 % of patients with FHM, suggesting a link between PRRT2 mutations and FHM [37]. These genes may thus serve as genetic biomarkers for FHM and further help to determine clinical types. Other research reported that the location and type of gene polymorphism may determine the clinical subtype of migraine, i.e., migraine with aura (MA) or migraine without aura [36,38,39]. A strong family history of migraine is associated with MA occurrence as well as a lower age and higher frequency of MA onset [40]. Genetic factors are also important in identifying CH risk. Compared with the general population, first-degree and second-degree relatives were 5–18 times and 1–3 times more likely to develop CH, respectively [41]. However, identifying the CH genotype is difficult due to its high genetic heterogeneity. For example, some evidence indicated a link between CH attacks and four independent loci (rs11579212, rs6541998, rs10184573, and rs2499799) [42]. Another study found that participants with the MTHFR 677 T allele were more prone to chronic CH [43]. TTH has also been shown to be heritable; however, relevant clinical studies are rare [44]. Although genetic information is essential for the predictive diagnosis of certain patients, using genetic biomarkers in clinical practice is difficult due to limited progress. Thus, further research is required to clarify the precise relationship between genetic information and headaches.

The effect of prenatal events on the occurrence of primary headaches is poorly understood. Maternal smoking during pregnancy has been reported to significantly increase TTH risk in childhood [45]. This relationship can be attributed to low socioeconomic status, which indirectly prompts headaches. However, the specific reason underlying this association remains unclear. Another possibility is that smoking during pregnancy results in pathophysiological alterations related to headaches in the neonatal environment.

4.1.2. Modifiable risk factors

Modifiable risk factors for headaches include lifestyle, occupation, environment, and disease state characteristics. Obesity, smoking status, low levels of education, physical activity, and socioeconomic status are suggested to increase migraine risk [29,46–49]. In the case of TTH risk, obesity, excessive computer use (>12 h/day), and working for more than six-night shifts per month were identified as contributing risk factors [32,50]. The evidence linking alcohol use to headaches is conflicting, despite alcohol being recognized as a headache trigger. One investigation showed that males with TTH reported heavy consumption of alcoholic beverages, whereas females with TTH consumed low amounts of alcohol [49]. Finally, individual dispositions and cultural factors may also play a role in alcohol-induced headaches [51].

The prevalence of primary headaches is also associated with different occupations. In men, migraine is more common in occupations requiring intense physical exertion. In addition, migraine is more prevalent in jobs involving shift work or night work, with a comparatively higher prevalence among women [52]. Sleep disturbances are also a risk factor for headaches and are closely associated with new-onset TTH [53]. Waldie et al. [45] have further demonstrated that reduced sleep duration and problem behaviors may increase TTH risks in children. However, an early cross-sectional study by Winter et al. [54] found no association between lifestyle factors and primary headaches, suggesting that further clarification on these risk factors is required.

The relationship between migraine and personality traits has been reported, with certain personality traits being suggested to increase migraine prevalence, such as the tendency towards perfectionism, neuroticism, harm avoidance, persistence, low self-directedness, repressed aggression, and a depressive mood [55–57]. However, no unique personality traits have been identified to differentiate migraineurs from healthy controls. Patients with a high harm avoidance personality, which involves cautious, passive, fearful, insecure, negativist, or pessimistic traits, may have an increased risk for TTH [58]. In addition, the prevalence of patent foramen ovale (PFO) in patients with MA is significantly higher than in migraineurs without aura and nonmigraine individuals [59]. The basis for this comorbidity may be a genetic association. However, there is insufficient evidence to support a causal relationship. Increasing evidence also suggests that MA risk is associated with hypercoagulability [60].

4.2. Predicting headache occurrence

Recognizing triggers for headaches is important because clinicians can reduce headache attacks by instructing patients to cope with triggers. However, no consensus exists on a common list of headache triggers. Here, some common factors in the currently available lists are given. The following factors are recognized as common triggers for migraine, including increased stress, menses, sleep disturbances, negative affect, weather changes, tiredness, noises, sunlight, smells, physical inactivity, and difficulty concentrating [61–64]. Smoking and alcohol intake have also been shown to frequently trigger primary headache attacks, particularly migraine [51,64–66]. Patients with TTH usually report a high frequency of triggers such as negative affect, sleep disturbances, sunlight, weather changes, physical inactivity, and fatigue [63,64]. In the case of patients with CH, weather changes, mood changes, sleep disturbances, and smells are common triggers [67,68]. In addition, some foods and beverages have been reported to trigger headaches, such as chocolate, coffee, and so on [69,70]. However, there is currently insufficient evidence suggesting a causal relationship between these foods and headaches. Additional attention needs to be paid to gender differences in headache triggers. Fourier et al. [71] compared CH triggers between men and women and demonstrated that alcohol consumption was a more common headache trigger in men, while lack of sleep was more likely to trigger headaches among women.

Current evidence suggests an association between triggers and clinical headache phenotypes. Among individuals with CH, smokers are more likely to present with cranial autonomic symptoms and restlessness during attacks, whereas non-smokers have an increased likelihood of reporting fluctuating attack cycles throughout the year [72]. Compared with nondrinkers, drinkers have greater chances

of developing conjunctival injection than nasal congestion, vomiting, and photophobia during CH attacks [73]. Based on these triggers and phenotypes, researchers attempted to establish a multivariable model to predict headache attacks. However, the model did not perform satisfactorily, with only slightly better predictability than random chance [74]. In another study, Houle et al. [75] successfully developed a forecasting model for headache attacks using perceived stress, demonstrating good predictability. Furthermore, a model employing sleep duration and stress has been constructed to predict headache severity in patients with chronic headaches [76]. Considering that susceptibility levels based on the same trigger vary among patients, the efficacy of prediction models may differ across individuals. Therefore, future research should focus on establishing individualized models and improving their accuracy.

4.3. Predicting headache outcome and prognosis

Clinicians should be prospectively aware of the likelihood of headache relief and development before a patient first seeks healthcare and headache management is initiated. This knowledge will facilitate the development of the next steps and enhance patients' confidence in their doctors. The predictors of successful outcomes after acute treatment for migraine attacks have been thoroughly investigated [77]. Male gender, higher body mass index, higher migraine frequency, higher pain intensity, comorbidity, and no adherence to preventive drugs are a few predictors of inadequate pain relief at 2 h. Predictors of inadequate headache relief at 24 h include cutaneous allodynia, depression, and medication overuse. Furthermore, Hansen et al. [78] devised a novel algorithm based on the number of drug purchases to predict the treatment response of migraine. The study findings demonstrated that four records of purchasing prophylactic drugs and ten records of acquiring triptans predicted a positive treatment response. Future studies should investigate the application value of these predictors in a clinical setting.

People generally share concerns about the change or further progress in their current headache status. Therefore, predicting the evolution of headaches in various populations warrants investigation. Only approximately 10 % and 3 % of migraineurs acquire complete and partial clinical remission 1 year after migraine diagnosis, respectively [79]. Additionally, 3 % of migraineurs will develop CM [79], increasing the headache burden. The possible risk factors for CM include increased headache frequency, obesity, excessive use of migraine abortive drugs, stress, depression, female sex, and low educational status [80,81]. Moreover, patients with CM accompanied by anxiety, depression, sleep disorders, stress, or poor self-efficacy tend to have a poor prognosis [82].

5. Preventive strategy

Headache prevention is established through a typical three-tiered management strategy. First, primary prevention targets the etiology and risk factors, aiming to prevent headaches before they occur. Second, secondary prevention involves preventing or delaying disease progression during incubation. Finally, tertiary prevention includes preventing the potential complications and hazards caused by the disease.

5.1. Primary prevention

The etiology of primary headaches is not clearly elucidated; however, studies have indicated that headache risk can be reduced by modulating the related risk factors. Given the significance of tobacco consumption in cerebrovascular disorders and migraine development, smoking cessation should be strongly advised [48,65]. Although alcohol use may contribute to headaches, no satisfactory reasons exist to confirm that patients with headache should abstain from alcohol consumption. In contrast, some studies have even reported that migraineurs may benefit from moderate alcohol intake [48,64,65]. Other early interventions to prevent headaches include weight control and regular physical activity [64,65,83].

5.2. Secondary prevention

The detection, diagnosis, and treatment of primary headaches at an early stage are the key strategies for secondary prevention, which can influence the development of this condition. Therefore, spreading awareness and educating people about headaches is crucial, and emphasis should be given to urging patients to seek early medical care after headaches occurrence. Moreover, learning to cope with triggers is crucial for headache patients. Triggers that are potentially harmful to health should be avoided. For other triggers, planned exposure may promote desensitization and increase tolerance [84]. In the case of inevitable factors, thorough preparations can be made to respond to headache occurrences, including preparation of painkillers and adjustment of work plans. The timely initiation of preventive therapy is also vital because a high attack frequency increases the risk of progression to CM [81,85]. Weight loss and comorbidity management are some early interventions for other risk factors for headache progression, such as obesity, stressful life events, and concomitant diseases [81]. Finally, many studies have demonstrated that PFO closure can lower headache frequency and monthly migraine days, even resulting in complete migraine cessation [86,87]. However, research into whether PFO closure treatment can reduce migraine prevalence is still lacking. Thus, additional studies are necessary to investigate the efficacy of risk factor interventions, as well as identify patients suitable for these interventions.

5.3. Tertiary prevention

Current evidence suggests that primary headaches are associated with several adverse health events. Tertiary prevention can help patients reduce these long-term complications. For example, patients with MA have a higher risk for cardiovascular disease, ischemic

stroke, and cognitive impairment [88–90]. TTH increases dementia risk [91]. CH is related to a high incidence of suicidal intention [92]. Medication overuse headache (MOH) requires special attention because it typically arises in people who use medications frequently for headache attacks [93]. Combined MOH may further cause disabilities and reduced quality of life. A few machine learning algorithms have already been developed to assess the risk of MOH in migraineurs based on clinical and biochemical features, drug exposure, and lifestyle [94]. Individual susceptibility to these complications should be highlighted. The association between the individual characteristics of primary headaches and their susceptibility to vulnerability needs to be fully explored. Future research aimed at developing algorithm models may help improve the precision of preventive measures.

6. Personalized strategy

Pharmacologic therapy, consisting of abortive and preventive medications, is the mainstay of headache management [95]. Medications commonly used to stop headache attacks include non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, triptans, 5-HT1F receptor agonists (ditans), and CGRP receptor antagonists (gepants) [85,96–98]. Prophylactic management comprises antihypertensive agents, antidepressant agents, anticonvulsant agents, calcium-channel blockers, onabotulinumtoxinA, and CGRP inhibitors [96–98]. Furthermore, non-pharmacologic therapies have an increasingly important role in acute and preventive headache treatments, particularly for patients who have intolerance to medications, such as biobehavioural therapies, acupuncture, and neuromodulatory devices [8,99,100]. However, the clinical responses to these therapies differ due to the inter-individual variability in patients with headaches. Personalized medicine has recently been highlighted as a potential approach to achieving the best clinical response. This treatment strategy aims to develop optimal therapies based on individual clinical data and functional biochemical characterization.

6.1. Optimizing drug therapy using pharmacogenetics

Pharmacogenetics can be a helpful screening tool to determine individual patient responses to medications (Table 2). Migraineurs carrying the SNPs rs2651899 [101], rs6724624, or rs1024905 [102] frequently respond well to triptans, whereas patients with STin2 VNTR 12/12 [103], COMTrs4680 Met/Met [104], or DRD2 C939T C/C [105] polymorphisms exhibit a poor clinical response. The GNB3 rs5443 polymorphism confers an increased response rate to triptans in patients with CH [106]. Patients with TTH who have the LL genotype of the serotonin transporter gene-linked polymorphic region (HTTLPR) show a more effective response to amitriptyline [107]. Furthermore, genetic polymorphisms can influence drug toxicity because most antimigraine drugs are metabolized by liver enzymes (Table 3). For example, patients carrying cytochrome P450 (CYP)2C8*3, CYP2C9*2, or CYP2C9*3 variants have decreased CYP activity, which may increase the risk of NSAID-induced hepatotoxicity and gastrointestinal bleeding [107,108]. Thus, screening for associated gene mutation locations is a promising method to detect the drug-resistant population presenting with headaches. However, our present understanding of the significance of gene polymorphisms in therapeutic results is limited, indicating the requirement for further research to promote their clinical use.

6.2. Drug-drug interactions

Drug-drug interactions (DDIs) are one of the main reasons for pharmacologic treatment failure. Most DDIs occur through alterations within the CYP pathways, causing either ineffectiveness of the prescribed drug or potentiation of the side effects [109].

Table 2
Summary of pharmacogenetic tools for predicting drug therapy response in primary headache disorders.

Acute treatment	Polymorphisms related to sustained response	Polymorphisms related to non-sustained response	Refs
Triptans	rs2651899, rs6724624, rs1024905, GNB3 C825T	DRD2 C939 TC/C, COMT rs4680 Met/Met, STin2 VNTR 12/12, GNB3 gene C825CC	[101–105,107, 110]
Ditans	–	–	–
CGRP-RAs	–	–	–
Prophylactic treatment	***Polymorphisms related to sustained response***	***Polymorphisms related to non-sustained response***	***Refs***
CGRP/rec mAbs	–	–	–
Onabotulinum toxin A	TRPV1 rs222749, CALCA rs3781719	–	[107,110]
Antidepressant agents	NOS3 Glu298Asp T/T, HTTLPR L/L	CYP2D6 gene duplication, CYP2C19*17	[107,110]
Antiepileptics	MDR1 C3435T	CYP2D6 gene duplication, rs10504861 near MMP16	[107,110]
Calcium-channel blockers	PLCE1 rs10882386, ITGAL rs223043, EHBP1L1 rs6591182	–	[107]
ARBs	rs10504861 near MMP16, rs6790925 near TGFBR2, rs12134493 near TSPAN2	LRP1 rs11172113	[107]
Beta blockers	ADRB1 Ser49Gly, ADRB1 Arg389Gly, GRK5 Leu41Gln	ADRA2C Del322–325	[110]

ARBs, angiotensin II receptor blockers; CGRP, calcitonin gene-related peptide; CGRP-RAs, CGRP receptor antagonists; CGRP/rec mAbs, the monoclonal antibodies blocking CGRP or its receptor.

Table 3
Summary of drug-drug interactions and pharmacogenetic polymorphisms used to predict adverse effects in drug therapy for primary headache disorders.

Acute treatment	Polymorphisms related to high risk of adverse effects	Medications leading to DDIs	Refs
Paracetamol	UGT1A6*2, UGT2B15*2, CYP2E1 c1/c2	Sympathomimetic agents, SNRIs, TCAs, MAOIs	[107, 109, 110]
NSAIDs	CYP2C8*2, *3, *4, CYP2C9*2, *3, UGT2B7*2	Diuretics, anticoagulants, ACE-I/ARBs, SSRIs, CYP2C9 inhibitors (e.g., fluoxetine, paroxetine, the herbal supplement gingko biloba, cranberry juice, topiramate and valproic acid)	[107, 109, 110]
Triptans	–	MAOIs (e.g., phenelzine, tranylcypromine), ergot derivatives, SSRIs, CYP3A4 inhibitors (e.g., ketoconazole, macrolide antibiotics, nefazodone, anti-retrovirals, calcium channel blockers)	[109]
Ditans	–	Mirtazapine, meperidine, tramadol, pentazocine, St. John's wort, dextromethorphan, SSRIs, SSNRIs, TCAs, MAOIs, triptans, fentanyl, alithium, propranolol, central nervous system depressants	[109, 111]
CGRP-RA	–	CYP3A4 inhibitors, CYP3A4 inducers (e.g., phenytoin, barbiturates, rifampin, St. John's wort), grapefruit juice, CYP2C9 inhibitors	[109, 111]
Prophylactic treatment	***Polymorphisms related to high risk of adverse effects***	***Medications leading to DDIs***	***Refs***
CGRP/rec mAbs	–	No DDIs	[109, 111]
Onabotulinum toxin A	–	–	–
Antidepressant agents	CYP2D6*9, *10, *17, *29, *36, *41, *3–*8, *11–*16, *19–*21, *38, *40, *42, CYP2C19*2, *3, *4, *17, ABCB1 3435C > T, HTR1B rs11568817	Bupropion, adrenergic agents, opioids, barbiturates, orphenadrine, anticholinergics, diphenhydramine, lithium, carbamazepine, verapamil, alcohol, St. John's Wort	[107, 109, 110]
Antiepileptics	CYP2D6 *9, *10, *17, *29, *36, *41, *3–*8, *11–*16, *19–*21, *38, *40, *42, UGT1A3*5, UGT1A6 T19G, UGT1A6 A541G, UGT1A6 A552C, UGT2B7 –161C > T, CYP2C19*2, *3, *4, CYP2C9*2, *3	Central nervous system depressants (e.g., orphenadrine, hydrocodone, and buprenorphine), carbonic anhydrase inhibitors, metformin, oral contraceptives, aripiprazole, alcohol	[107, 109, 110]
Calcium-channel blockers	CACNA1C 527974G > A rs2239050 CACNA1D rs312481G > A rs3774426C > T CACNB2 rs2357928	Carbamazepine, eletriptan, oxycodone	[107, 109, 110]
ACEI/ARBs	–	NSAIDs	[109]
Beta blockers	CYP2D6	Adrenergic agents, ergot derivatives, rizatriptan,	[109]

ARBs, angiotensin II receptor blockers; ACE-I, angiotensin-converting enzyme inhibitors; CGRP, calcitonin gene-related peptide; CGRP-RAs, CGRP receptor antagonists; CGRP/rec mAbs, the monoclonal antibodies blocking CGRP or its receptor; DDIs, drug-drug interactions; MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; SNRIs, Serotonin and noradrenaline reuptake inhibitors; TCAs, tricyclic antidepressants.

Therefore, DDIs should be adequately considered, particularly in patients using multiple medications. For example, triptans should not be co-administered with drugs that inhibit CYP3A4 activity, such as ketoconazole, macrolide antibiotics, and calcium-channel blockers, because of the increased risk for adverse event occurrence [110]. In contrast, monoclonal antibodies that block CGRP or its receptor can avoid DDIs because their metabolic pathway does not involve liver enzymes [110,111]. However, other contraindications should be considered when employing monoclonal antibodies [99].

6.3. Personalized management based on clinical features

Individual characteristics can form an important basis for treatment decisions. In light of this concept, a growing emphasis is placed on establishing phenotypic classification in personalized medicine. Using these phenotypes, we can predict which patients will benefit most from a specific therapy. For example, in patients with CH, older age predicts a poor response to triptans, whereas patients with symptoms of nausea/vomiting and restlessness exhibit no response to oxygen therapy [112].

Machine learning models based on clinical features or imaging data have been developed for predicting drug responsiveness [113–121] (Table 4). Gonzalez-Martinez et al. [113] demonstrated a model for predicting patient response to anti-CGRP therapies at 6, 9, and 12 months based on variables such as headache days per month, migraine days per month, change in the number of headaches or migraine days per month from baseline to 3 and 6 months, and Headache Impact Test score. This model allows the assessment of the related benefits and risks before initiating anti-CGRP therapies in patients. A recent study investigating a strategy for developing personalized approaches found a link between migraine features and frovatriptan efficacy using deep phenotyping [114]. According to that study, frovatriptan was more likely to be effective in migraineurs with unilateral pain, phonophobia, cranial autonomic symptoms, and premonitory symptoms. Another study revealed that a left hippocampal volume of >4032.6 mm^3 may be used to identify sumatriptan responders among patients with migraine [115]. Furthermore, research has been conducted to develop a prediction tool to

Table 4
Applications of predicting models based on machine learning in guidance for personalized headache therapy.

Authors	Headache types	Reference variable in machine learning models	Clinical applications	Refs
Gonzalez Martinez et al	Migraine	Headache days per month, migraine days per month, change in the number of headache or migraine days per month from baseline to 3 months and 6 months, and Headache Impact Test (HIT-6) index	Predicted the response to anti-CGRP therapies at 6, 9 and 12 months	[113]
Viana et al	Migraine	Characteristics of migraine attacks: location (unilateral), quality (pulsating) and intensity of pain; presence of the following symptoms: Nausea and/or vomiting; photophobia, phonophobia, osmophobia, cranial allodynia; cranial autonomic symptoms; premonitory symptoms of yawning, tiredness, mood changes, neck stiffness, vertigo, nausea, photophobia, phonophobia, osmophobia, food craving, thirst, problems with concentration, speaking or reading in the previous 24 h; and time of frovatriptan intake from pain onset	Predicted the efficacy of oral frovatriptan 2.5 mg	[114]
Wu et al	Migraine	The regional brain volumes, including bilateral amygdala, anterior cingulated cortex, caudate, putamen, precuneus, orbitofrontal cortex, superior frontal gyri, middle frontal gyri, hippocampus, and parahippocampus	Predicted the response to sumatriptan therapies	[115]
Fisher et al	Migraine	Gender, migraine history, height, medical history of endocrine, medical history of neurologic disease, medical history of urologic and/or psychological conditions, and headache severity	Predicted patient preference for 25, 50, or 100 mg oral sumatriptan	[116]
Christian et al	Migraine	The pain drawing which illustrates the anatomical pain distribution of patients	Predicted the efficacy of trigger-site deactivation surgery for migraine patients	[117]
Lu et al	Migraine	Demographic data (e.g., age, sex and education level), migraine characteristics (e.g., age of onset, location, family history, nausea/vomiting, photophobia, disease duration, attack duration, frequency, headache intensity, and extent of impact and burden on quality of life), and some psychiatric comorbidities (e.g., anxiety, depression and sleep disorders)	Predicted the efficacy of non-steroidal anti-inflammatory drugs in migraine treatment	[118]
Fu et al	Migraine without aura	Fractional amplitude of low-frequency fluctuation of each voxel in areas including trigeminal cervical complex/rostral ventromedial medulla, thalamus, medial prefrontal cortex, and temporal gyrus	Predicted the efficacy of transcutaneous vagus nerve stimulation in reducing migraine attack frequency	[119]
Bravo et al	Migraine	HIT-6 index; clinical features including migraine characteristics (e.g., migraine days by month, history of migraine status, headache days by month, migraine type), medication use history, biochemical molecules (e.g., Vitamin B12, iron, creatinine), etc	Predicted patient's response to Onabotulinum toxin A treatment for migraine	[120]
Tso et al	Cluster headache	Clinical data such as demographics; duration, frequency, severity, laterality and location of attacks; associated symptoms; comorbid other headache; family history; history of pituitary abnormality or head trauma (recent or remote); and verapamil response. Imaging data such as grey matter density in the face-connected lobule VI of the cerebellum	Quantified the predictability of verapamil responsiveness	[121]

determine the appropriate oral sumatriptan dose for initial drug dose selection [116]. Similarly, Tso et al. [121] successfully established magnetic resonance imaging (MRI)-based sub-phenotypes of CH and attempted to quantify the predictability of patient response to verapamil. In that machine model, increased grey matter density in the face-connected lobule VI of the cerebellum predicted non responsiveness to verapamil; thus, this characteristic alteration may aid in determining whether a patient with CH is suitable for verapamil treatment. It should be pointed out that while neuroimaging may aid in screening effective medications, it also increases radiation exposure and the cost of treatment. An important concern for this is whether it could decrease the overall treatment time and be more cost-effective. Regrettably, no study could provide answers to the question. The next research step involves transitioning from model establishment to clinical application.

6.4. Management of patients with comorbidities

Comorbid conditions in patients with headaches increase the risk of chronic headaches and treatment failure [99,122]. These comorbidities have a highly complex association with headaches and are still not fully understood. Moreover, they necessitate the administration of more complex medication, resulting in difficulties in headache management. Psychiatric comorbidities (such as anxiety and depression) are the most common coexisting conditions. These comorbidities share a complex bidirectional relationship with headache development that leads to highly frequent and severe headache attacks [123–126]. Combined pharmacological–behavioral therapy is considered the best preventive method [127]. The drug delivery should avoid the use of β-blocker and flunarizine as much as possible [128]. For patients with obesity and migraine, topiramate is recommended to avoid weight gain [99]. Comorbid sleep disorders (including insomnia and restless leg syndrome) also contribute to more severe headaches and headache-related disabilities [129–131]. In migraineurs with insomnia, cognitive-behavioral therapy, rather than pharmacological treatments, is first recommended [132].

The reporting of other headache comorbidities includes stroke [133,134], hypertension [135], asthma [136], epilepsy [137],

gastrointestinal disorders [138], and fibromyalgia [139]. It is important to understand the effect of these diseases on headache status and to classify them into different subtypes (Fig. 2). Clear comorbidity subtypes can assist clinicians in making individualized treatment decisions for patients. Recently, Lipton et al. [140] established a subgroup model comprising eight classes of migraineurs based on an analysis of 62 comorbidities in 11,837 migraineurs. In this eight-class model, class 8 (fewest comorbidities) had the largest sample (34 %) and the lowest risk for developing CM. In contrast, classes with comorbid pain (classes 1, 3, and 7) were associated with a high CM risk, high Migraine Disability Assessment scores, increased allodynia, high medication overuse, aura, and increased headache severity. Additionally, patients in class 6 (cardiovascular comorbidities) were less likely to experience aura and severe migraine attacks. Future studies should develop similar models for other headache types as well.

7. Participatory strategy

The participatory approach emphasizes a patient-centered and shared decision-making strategy in the medical process. This method improves patients' understanding of their disease and gives them a more active role in their headache disorder. Furthermore, the interaction and participation of the patients, as a special type of supervision, encourage them to follow their clinicians' instructions.

7.1. Participation in headache education

Headache education is indispensable to headache management and heavily relies on active patient participation. This approach can improve the quality of life in migraineurs, reduce headache attacks, and lower migraine-related disability [141]. Research has also shown that guidance on rational drug use can help avoid excessive medication intake and prevent the development of MOH [93,142]. An electronic headache diary is particularly essential in this participatory approach. As an important self-monitoring tool, the headache diary allows patients to track their headache-related symptoms, thereby assisting in the accurate diagnosis, recognition of risk factors, and adjustment of the therapeutic regimen. A large number of smartphone apps have been developed to enable patients to document their headache data conveniently, such as "Migraine Buddy", "Migraine Insight", "Migraine Monitor" "iMigraine", "Headache Diary Free", and "My Cluster Headache" [143].

7.2. Telemedicine

Telemedicine is an effective method of providing medical assistance via remote consultation using telephone, email, video chat, or smartphone applications [144]. This remote consultation method is particularly suitable for the long-term management of patients with headaches and allows clinicians to track the evolution of headaches and provide timely treatment adjustments. Additionally, telemedicine can facilitate early access to specialized care and reduce caregiver and patient burden [145]. This approach also encourages more patients to participate in their health care process and improves therapy adherence [146]. The current research confirmed that the long-term treatment efficacy and safety of telemedicine consultation for non-acute headaches were comparable to traditional consultation [147]. Finally, recording clinical information electronically also provides abundant data for developing predictive tools in precision medicine.

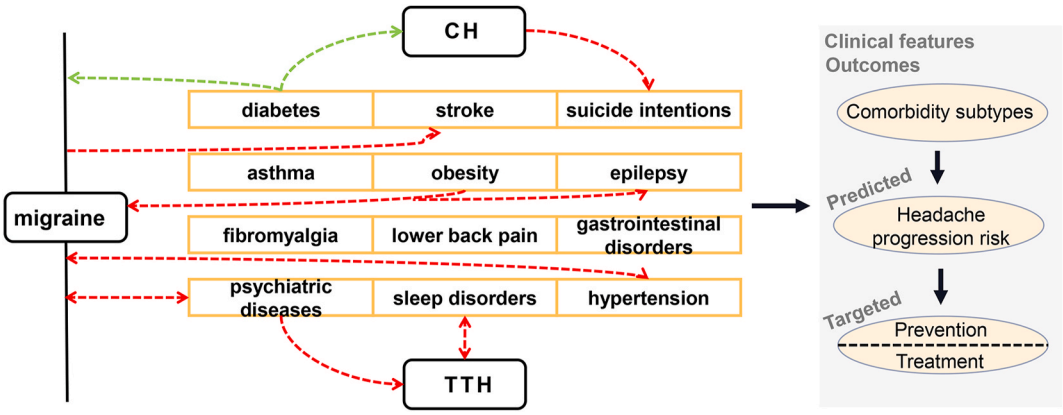

Fig. 2. Schematic diagram of the relationship axis of primary headache disorders and common comorbid diseases. The red arrow represents promoting effects (increased risk), and the green arrow denotes protective effects (decreased risk). Comorbidity networks can be used to group patients based on clinical features and headache outcomes, predicting headache progression risk for targeted prevention and treatment. CH, cluster headache; TTH, tension-type headache. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

7.3. Participatory preventive management for dietary intervention

The effects of dietary patterns on migraine remain inconclusive; nevertheless, diet modifications are recommended as a general migraine prevention strategy [148]. Dietary intervention is a classic participatory management process that stresses the importance of maintaining a balanced and regular diet and requires strong cooperation and long-term patient adherence [149]. The goals for such a diet control intervention include two components. The first part involves eliminating certain headache-inducing foods [148]. In this step, the key is identifying specific food triggers for a patient based on their records of headache occurrence. It is critical to emphasize the relevance of a causal relationship between headache onset and diet, rather than a simple chronological association [150]. This may result in ineffective elimination diets. The nutritional deficiencies associated with the elimination of certain foods must also be thoroughly evaluated [70]. The second portion is to find specific dietary patterns that aid in headache prevention, such as ketogenic, modified Atkins, supplement-based (e.g., vitamin D3, probiotics, magnesium, riboflavin, and coenzyme Q10), low-fat, high omega-3/low omega-6 fatty acid, and gluten-free diets [70,151,152]. However, emphasis should be placed that the efficacy of such dietary interventions is largely affected by the subjective initiative of patients.

8. Limitations and future research

When the included data and study topics are diverse, a narrative review rather than a meta-analysis or systematic review may be appropriate [153]. It should be noted, however, that such a narrative assessment is limited in scope and may be prone to selection bias. The absence of quantification of assessment outcomes, as well as significant data heterogeneity and varying evidence quality, all complicate the interpretation of the results. Other possible sources of bias include differences in cultural background and access to information.

This new strategy is still in the nascent stage, and certain issues should be addressed. First, although studies on recognizing individual features and treatment responsiveness have been conducted, no definite evidence exists on whether patients with headache could benefit from this approach or whether the associated risk-benefit ratio is satisfactory. Second, despite achieving several breakthroughs in identifying the diagnostic or prognostic biomarkers for headaches, no definitive conclusions can be drawn because these biomarkers are still in the early development stages. Therefore, their practical application should be investigated in future studies. Finally, the new medical strategy in our review focuses mainly on migraine. This limitation can be because clinical practice is limited for other headaches. Thus, we propose that future research should thoroughly investigate our model's superiority over other headache management models, providing the best evidence to support its widespread application.

9. Conclusion

The growing popularity of precision medicine has initiated a new era of headache management that is increasingly guided by individual characteristics. Here, we provide a promising headache management strategy based on the P4 medicine paradigm involving predictive, preventive, participatory and personalized concepts. This model integrates a comprehensive understanding of the current diagnostic and therapeutic strategies for headaches, to develop early and individualized interventions. We describe this comprehensive and personalized management philosophy from a clinician's perspective to facilitate its application in clinical practice.

Data availability statement

No data was used for the research described in the article.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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