

Migraine Headaches: Opportunities for Management with Precision Nutrition

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Abstract

Chronic migraine headaches are estimated to affect between 1.4% and 2.2% of the population, and have a huge impact on wellbeing and quality of life. A diverse range of therapeutic nutritional options have been explored for migraine headaches, with varying degrees of benefit. Dietary interventions include generally healthy food plans, identification and avoidance of trigger foods, weight-loss diets, low-glycaemic-load diets, ketogenic diets, gluten-free diets, IgG-led elimination diets and a high-omega-3/low-omega-6 diet. Nutritional supplement interventions include riboflavin, niacin, homocysteine-lowering B vitamins, vitamin B12, vitamin E, vitamin D, magnesium, zinc, iron, omega-3 fatty acids, coenzyme Q10 (CoQ10), lipoic acid, soy phytoestrogens, ginger, turmeric, carnitine, 5-hydroxytryptophan (5-HTP), palmitoylethanolamide (PEA), and multi-ingredient formulas. The wide range of therapeutic options may make it challenging to approach nutritional management of migraine in a clinical setting, so a pragmatic model that helps personalise interventions from clinical signs and symptoms and reliable biomarkers would be useful, so-called 'precision nutrition'. The aim of this narrative review is to explore the clinical evidence for nutritional medicine for migraines, including diet and nutrient-based interventions, from the perspective of personalised or precision nutrition.

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Introduction

Migraine headaches are recurrent headaches characterised by painful attacks lasting 4–72 hours. Chronic migraines are estimated to affect between 1.4% and 2.2% of the population, and have a huge impact on wellbeing and quality of life.^{1,2} The frequencies of migraine attacks are typically high, with 31.3% experiencing three or more attacks per month, and attacks are often severe, with 53.7% reporting severe impairment or being bedbound during the attacks.³

The diagnosis of migraine is based on clinical criteria, in particular recurrent headache attacks of unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea, vomiting, photophobia and phonophobia.⁴ Although synonymous with headache attacks, migraine is more appropriately considered a symptomatically diverse neurological disorder, of which headache is just one symptom.⁵ During the premonitory stage up to 3 days before headache, tiredness, mood changes, yawning, thirst, cravings, urinary frequency, light and sound sensitivity, and cranial autonomic symptoms may occur, while symptoms in the postdrome phase up to 48 hours post-headache include tiredness and difficulty concentrating.⁶

The development of chronic migraine is understood to be a gradual process, with predisposing risk factors interacting with genetic susceptibility and frequent headache pain to lower the threshold of migraine attacks and consequently increase the risk of chronic migraine.^{7,8} The pathophysiology of migraine varies between individuals, but evidence does suggest features that distinguish migraineurs from non-migraineurs in the interictal phase (between headaches), including neuronal hyperexcitability,⁹ systemic oxidative and

nitrosative stress,¹⁰ systemic low-grade inflammation,¹¹ and altered blood glucose metabolism.¹² Neurobiological changes are evident in the premonitory stage and include alterations in nociceptive signalling, while the headache phase involves activation of the trigeminovascular system and, in migraine with aura, a cortical spreading depression-like event characterised by an electrophysiological wave of excitation followed by inhibition in cortical neurons.¹³ Better understanding of the complex pathophysiology and underlying pathophysiological mechanisms of migraine may improve treatment options.¹⁴

Over-the-counter and prescription medications for both acute relief and prevention are common treatments for migraine, but treatment response is often poor and there are important potential side-effects, thus pharmacological treatment options are limited and only result in reduction of symptoms in a portion of migraine sufferers.^{15,16}

Management of migraine would benefit from an approach that extends beyond pharmacotherapy alone, and identifies exacerbating factors and relevant comorbid conditions, examines past and current medications and other therapies, and a management plan with preventive, acute and lifestyle components as well as self-monitoring with a headache diary.¹⁷ Personalised lifestyle medicine, including sleep hygiene, stress management, aerobic exercise and dietary modification as well as nutraceuticals, should be considered in a migraine management plan.^{18,19,20} The aim of this narrative review is to explore the clinical evidence for nutritional medicine for migraine, including diet and nutrient-based interventions, from the perspective of personalised or precision nutrition.

Methods

The author searched PubMed for publications describing human clinical interventions involving diet, nutrient-based supplements, plant extracts with common food use, and migraine. There was no limit on date of publication. Articles assessing the effects of diet, nutritional and nutraceutical interventions in patients with migraine were included in the final review. Phytomedicines including feverfew (*Tanacetum parthenium*) and butterbur (*Petasites hybridus*) were excluded from the review, except where they were used as components of nutrient-based interventions, and are reviewed in detail elsewhere.²¹ Citations in these articles were also reviewed and located when related to additionally relevant clinical trials. Some articles not indexed on PubMed were identified and included if they were from a peer-reviewed journal. The review is based on this search and the author's collection of studies on the topic used in previous academic and continuing professional education lectures. Only studies published in English were included in the review.

Towards precision nutrition for migraine

A diverse range of therapeutic nutritional options have been explored for migraine headache, with varying degrees of benefit. Dietary interventions include generally healthy food plans, identification and avoidance of trigger foods, weight-loss diets, low-glycaemic-load diets, ketogenic diets, gluten-free diets, IgG-led elimination diets, and a high-omega-3/low-omega-6 diet. Nutritional supplement interventions include homocysteine-lowering B vitamins, niacin, vitamin B12, vitamin E, vitamin D, magnesium, zinc, iron, omega-3 fatty acids, riboflavin, coenzyme Q10 (CoQ10), lipoic acid, soy phytoestrogens, ginger, turmeric, carnitine, 5-hydroxytryptophan (5-HTP),

palmitoylethanolamide (PEA), and multi-ingredient formulas. The wide range of therapeutic options may make it challenging to approach nutritional management of migraine in a clinical setting, so a pragmatic model that helps personalise interventions from clinical signs and symptoms and reliable biomarkers would be useful, so-called 'precision nutrition'.²² Such a model may also be informative for future clinical research that attempts to explore precision nutrition approaches for migraine. The structure of this review is based on a preliminary and theoretical model that incorporates and organises nutritional interventions into specific clinical and biochemical indications; however, it should be emphasised that this model is hypothetical and requires further evaluation before being translated to practice (Figures 1 and 2).

Healthy food plans

It has been speculated that healthful dietary changes could positively influence several aspects of migraine pathophysiology, including serotonergic dysfunction, neuronal excitability, redox stress, brain mitochondrial function, neuroinflammation and platelet aggregation.²³ Observational studies have suggested a relationship between food pattern and migraine. Higher diet quality, calculated with the Healthy Eating Index, was found to be significantly inversely associated with chronic migraine and headache attack frequency in women.^{24,25} Similarly, a higher Dietary Inflammatory Index score, and thus higher dietary inflammatory potential, has been found to be associated with migraine and headache frequency.^{26,27} Also a higher Dietary Diversity Score, a proxy indicator of nutritional adequacy, was inversely associated with migraine disability, pain severity and headache frequency in another study.²⁸ In addition to food relationships, better hydration has also been associated with lower migraine severity.²⁹

Figure 1: Dietary interventions for migraine.

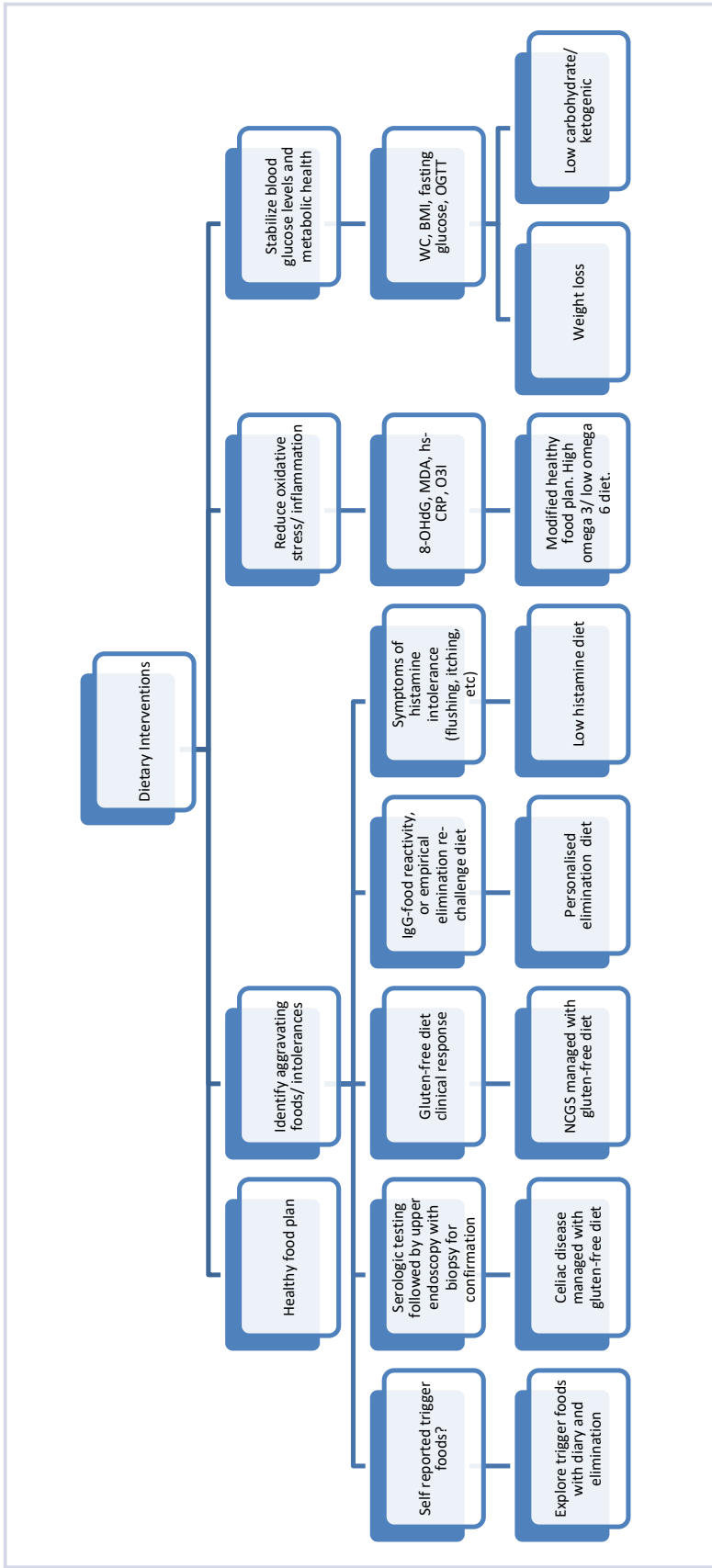


Figure 1: Dietary interventions for migraine. Dietary interventions can be broadly divided into three major categories that may also be indications for their clinical use: adopting a generally healthy diet; identifying aggravating foods or intolerances; and modifying underlying pathophysiology or dysfunction. Clinical indications, such as dietary history, and biomarkers or results of investigations, such as the positive confirmation of coeliac disease, may help identify which dietary interventions are best suited to an individual. 8-OHdG, 8-hydroxy-2'-deoxyguanosine; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; MDA, malondialdehyde; NCGS, non-coeliac gluten sensitivity; O3I, Omega-3 Index (red blood cell omega-3 fatty acids); OGTT, oral glucose tolerance test; WC, waist circumference.

Figure 2: Individualised nutrition for migraine.

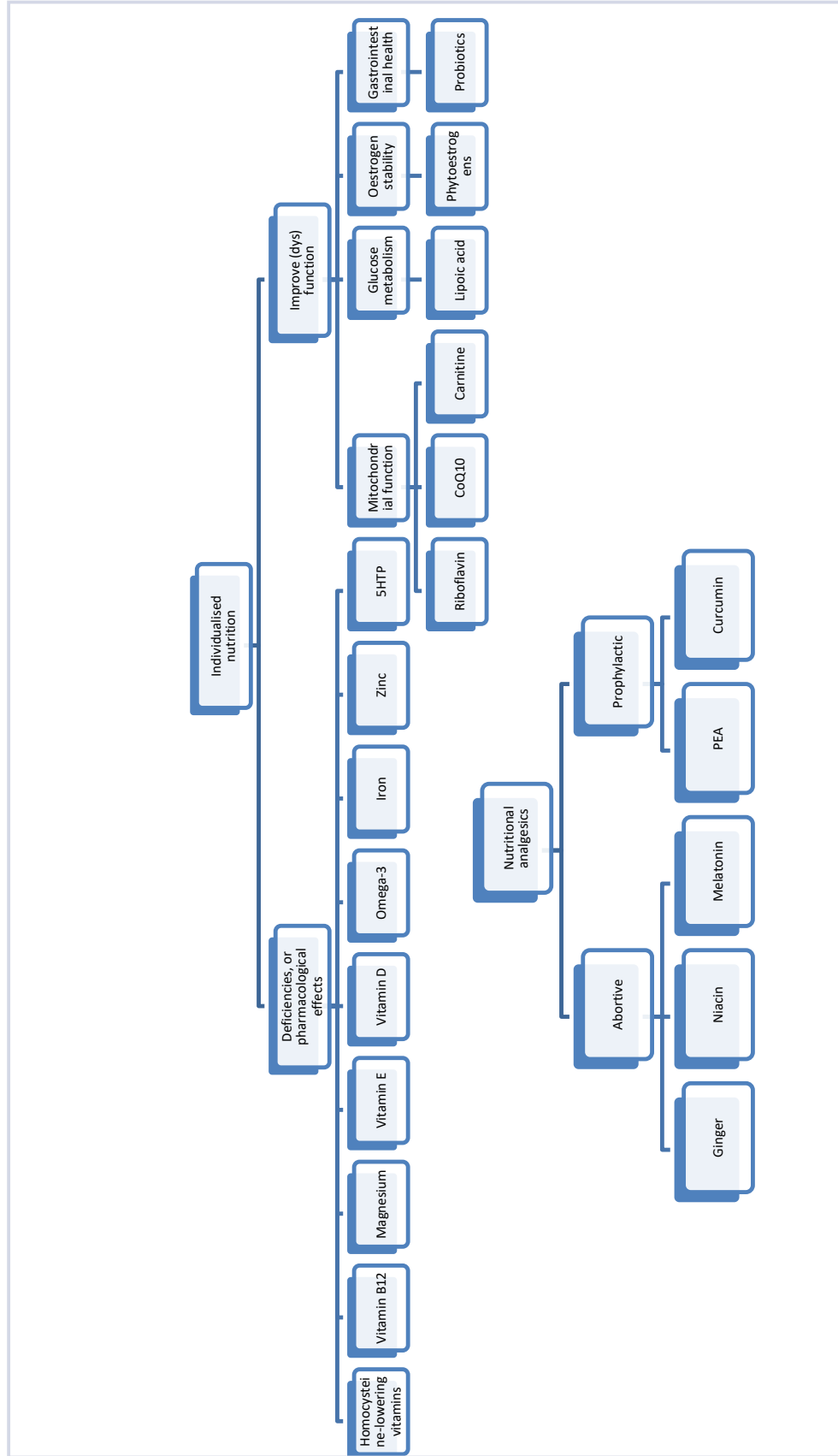


Figure 2: Individualised nutrition for migraine. A broad range of nutritional interventions is possible, so a pragmatic model that rationalises their indications and use may be helpful in clinical practice. Suboptimal intakes or deficiencies of vitamins, minerals and fatty acids can be assessed through dietary recall and/or laboratory testing, although both have limitations and may not accurately identify treatment responders, and nutrients may have pharmacological effects independent of deficiency or low dietary intake. Other nutrients have more specific indications like improving mitochondrial function, blood glucose metabolism or oestrogen stability; however, it should be emphasized that nutritional compounds have diverse mechanisms of action so this may be an oversimplification. 5-HTP, 5-hydroxytryptophan; CoQ10, coenzyme Q10; PEA, palmitoylethanolamide.

Some dietary intervention studies have assessed the impact of improving overall diet quality in migraineurs, and those that have been performed do suggest healthier eating could result in important clinical benefits for some people. A 90-day intervention ($n = 52$) based on healthy dietary guidelines for the Brazilian population, and personalised for body weight, improved dietary habits, dietary quality, and significantly reduced migraine severity and depressive symptoms, independent of changes in body weight.³⁰

A retrospective study of the impact of a 3-month dietary intervention ($n = 30$; based on the Healthy Eating Plate created by Harvard School of Public Health) on migraine found a significant improvement in headache frequency, disability scales and use of abortive drugs per month (6.07 ± 7.83 versus 9 ± 8.2 at baseline).³¹ Patients statistically ate less sweets, white bread, and red or processed meat, and more whole cereals and legumes, fish, snacks (mainly with yogurt), and also water intake increased to 1.5 L a day. A second larger 12-week study ($n = 97$; also based on the Healthy Eating Plate) found that those who changed their eating behaviours had a statistically significant reduction in monthly migraine days (from 10 to less than 6) and a non-significant decrease in monthly painkiller intake (from approximately 12 to 8), with reductions in total carbohydrate, and red and processed meat consumption appearing to have the most pronounced benefit.³²

Dietary changes characteristic of overall healthy eating patterns have individually demonstrated some benefit, including moderating fat intake and increasing plant foods. Moderating fat intake (< 20 g daily) for 12 weeks was found to reduce migraine frequency, intensity and duration, and medication intake.³³ Reducing fat intake to < 20% of total calories, but not less than 45 g daily and mostly from olive oil, for 3 months significantly reduced the frequency and severity of headache attacks.³⁴ A whole-food plant-based (vegan) diet was reported to result in complete remission of migraine after 3 months in one patient.³⁵

Overall, there is preliminary but compelling evidence to suggest that nutrition education and counselling with subsequent improvements in dietary quality can have an important impact on migraine frequency and severity, and can reduce medication requirement.

Migraine trigger foods

A variety of foods and food ingredients can immediately (within hours) or chronically (within days or weeks) trigger migraine attacks in susceptible individuals, with anywhere from 12% to 60% of migraine sufferers reporting food as a trigger.³⁶ Several have been identified, including alcohol (especially red wine and beer), chocolate, coffee, caffeine, dairy products (especially aged cheese and processed products such as ice-cream), processed meats, citrus fruits, tomatoes, onions, nitrates and nitrites, biogenic amines (such as histamine, tyramine and phenylethylamine), monosodium glutamate (MSG), aspartame, sucralose, and high or low sodium intake.^{37,38,39} Of these, caffeine withdrawal and MSG exposure have the strongest evidence as triggers because they are supported by positive provocation studies.⁴⁰ The mechanisms by which foods and their components may contribute to migraine are +diverse, and appear to depend on individual susceptibility, dosage and timing of exposure.⁴⁰

Studies examining the effects of avoiding trigger foods have produced mixed results. For example, in people with self-reported chocolate-triggered migraines, chocolate triggered migraine more frequently than placebo in one study,⁴¹ but not in others.^{42,43} Chocolate does contain caffeine, so caffeine withdrawal may have been a confounder. Similarly, when compared with placebo, aspartame administration was found to increase headache frequency in some,^{44,45} but not all studies.^{46,47} Clinically, however,

identification and avoidance of trigger foods is an important component of nutritional therapy for migraine, and can be based on observation if the food trigger is clear or a food diary if less obvious. Alternatively, suspected triggers could be included in an elimination and re-challenge diet. Identification and elimination of trigger foods has been shown to be a useful clinical strategy. In one study, a group of migraineurs ($n = 50$) who suspected food triggers was split into two groups, and embarked on dietary restriction for 2 or 4 months. At 2 months, for both groups, monthly attack frequency, attack duration and attack severity were significantly decreased, and this benefit was maintained at 4 months only in the group who continued to avoid trigger foods.⁴⁸ The same research group assessed this approach in elderly patients with migraine ($n = 31$) and found similar benefit, with significantly lower frequency of attack, attack duration, pain severity, and analgesic and triptan use at 2 months.⁴⁹ Also, an intervention ($n = 42$) based on a low-fat, plant-based diet that incorporated elimination of common trigger foods found a significant reduction in headache intensity and pain; however, issues related to study design such as the use of a vegan diet, short duration of elimination and a non-personalised approach to trigger food elimination limit the generalisability of this particular study.⁵⁰ Overall, this clinical evidence shows that identification of trigger foods with a food diary and subsequent avoidance may be a useful strategy for some people with migraine.

Gluten-free diet

Chronic and migraine headaches have been reported as a common presentation in coeliac disease, with a prevalence of up to 30%.^{51,52,53} Also, gastrointestinal symptoms are more frequent in coexisting migraine and coeliac disease when compared with coeliac disease alone.⁵⁴ Importantly, gluten sensitivity may

initially present with extra-intestinal symptoms in the absence of gastrointestinal symptoms or enteropathy, and has been associated with neurological disorders, including migraine.^{55,56}

Gluten-free diets have been successful in reducing headaches and migraine in some studies. In one report of 10 people with episodic headache and gluten sensitivity, defined by the presence of antigliadin antibodies as well as HLA-DQ2 or HLA-DQ8 genotype, nine responded to a gluten-free diet.⁵⁷ And in a group of people with coeliac disease ($n = 90$) who were treated with a gluten-free diet, three out of four people who initially had migraine attacks had an improvement in frequency, duration and intensity, while the remaining one became migraine free.⁵⁸ A survey of people ($n = 866$) with headache and coeliac disease revealed that 24% reported headache as the main symptom that led to diagnosis of coeliac disease and, after initiation of a gluten-free diet, the frequency and intensity of migraine headaches significantly improved; symptoms relapsed on gluten exposure.⁵⁹ In contrast, one investigation found that 28% of patients with coeliac disease ($n = 72$) had migraine despite a persistent gluten-free diet.⁶⁰

Non-coeliac gluten sensitivity (NCGS) has been suggested to play a role in migraine, but evidence is currently limited. A significantly higher incidence of migraine has been reported in people with NCGS compared with controls.⁶¹ A preliminary study identified a subset of migraine patients with NCGS ($n = 10$) who, after commencing a gluten-free diet for 3 months, experienced a significant reduction in migraine disability.⁶² Additionally, a gluten-free diet has been shown to reduce symptoms of headache in people with suspected NCGS.⁶³

Because migraine may be an extra-intestinal manifestation of coeliac disease, testing for coeliac disease if indicated may help identify an underlying contributory dietary factor in some people with migraine, which in some cases could improve headache symptoms after initiation of a strict gluten-free diet.⁶⁴ If suspected, NCGS is

determined with clinical response to a gluten-free diet for at least 6 weeks and subsequent blinded gluten challenge.⁶⁵

IgG-based elimination diet

Diet restriction based on IgG antibodies may be a useful strategy for reducing the frequency of migraine attacks, with evidence from clinical studies generally reporting beneficial effects.⁶⁶ The first evidence came from a proof-of-concept study in which migraine patients ($n = 39$) embarked on an IgG-based elimination diet with 30–40% reporting clinical benefit.⁶⁷ In another study, 43 out of 65 patients with migraine refractory to traditional treatment had a complete remission of their migraine after 1–6 months of an IgG-based elimination diet.⁶⁸ In the first randomised-controlled clinical trial, a 6-week IgG-based elimination diet ($n = 30$) found a significant reduction in the number of headache days and number of migraine attacks in the elimination diet period.⁶⁹ However, in contrast, one study ($n = 138$) reported a significant reduction in migraine-like headaches with an IgG-based elimination diet at 4 weeks, but only a small non-significant reduction at 12 weeks of dietary therapy.⁷⁰ This study lends only modest support for an IgG-based elimination diet, but may have been limited by differences in study design such as participants having self-reported migraine and thus possibly other forms of headache, lack of dietary support for participants compared with other trials, and inability to measure dietary adherence.

People with irritable bowel syndrome (IBS) are at higher risk for migraine,⁷¹ and gastrointestinal symptoms may respond to IgG-based elimination diets.⁷² In patients with a co-diagnosis of migraine and IBS ($n = 21$), a double-blind, randomised-controlled, crossover clinical trial reported significant reductions in symptoms of both disorders, including headache frequency, severity

and duration, and gastrointestinal pain and bloating after a 6-week IgG-based elimination diet.⁷³ In another study of a group of patients with migraine and IBS ($n = 60$), a 14-week IgG-based elimination diet with a probiotic was more effective than a control diet with a probiotic for reduction of migraine and gut symptoms.⁷⁴ Overall, it appears that an IgG-based elimination diet may be useful in cases of migraine related to suspected food sensitivities.

Empirical oligoantigenic diets, also known as elimination re-challenge diets, were examined for migraine as early as the 1980s, but since then have received little attention.⁷⁵ In a pioneering study involving migraine patients ($n = 9$) with suspected food triggers, *Monro et al.* mitigated symptomatic and immunological food reactivity with an antihistamine,⁷⁶ and then went on to report that an elimination re-challenge diet, followed by an antigen desensitisation regime, was able to reduce symptoms in people with migraine ($n = 11$).⁷⁷ Another research group reported that an elimination re-challenge diet resulted in recovery from migraine in 93% of a paediatric population ($n = 88$).⁷⁸ The same research group reported benefit of the same dietary approach in children with migraine and epilepsy or attention-deficit hyperactivity disorder.^{79,80} In another study of a group of adults with migraine ($n = 43$) who were treated with an elimination re-challenge diet, 13 had a 66% or greater reduction in headache frequency, and six became headache free.⁸¹ Elimination re-challenge diets appear to be a useful clinical approach, but would benefit from renewed interest and research.

Low-histamine diet

Elevations in histamine due to an imbalance between detoxification and dietary exposure can cause histamine receptor-mediated complications and allergic-type symptoms,

including headaches and migraine. Typically, histamine intolerance (HIT) presents with symptoms such as asthma-like symptoms, rhinitis, urticaria and gastrointestinal symptoms, including diarrhoea and abdominal pain, after ingestion of foods with a high histamine content.⁸² Histamine is found at a high concentration in aged foods (e.g. cheeses, alcoholic beverages, cured meats, fermented or spoiled foods), where it is produced by bacterial or yeast fermentation of the amino acid histidine to histamine. Other foods, such as citrus fruits, may have the capacity to enhance histamine release, even though they contain low levels of histamine themselves.⁸³

Detoxification of dietary histamine normally occurs in intestinal epithelial cells via the enzyme diamine oxidase (DAO). If DAO fails to inactivate histamine, it is absorbed through the gut epithelium and enters systemic circulation where it may contribute to typical symptoms of HIT in some people.⁸⁴ There have been associations between genetic variants that affect DAO activity and migraine headache, suggesting increased susceptibility to HIT in genetically predisposed individuals.⁸⁵ Furthermore, blood DAO levels were found to be more frequently deficient (defined as levels below 80 HDU/ml) in migraine patients compared with controls (87% versus 44%).⁸⁶

While there appear to be no studies of a low-histamine diet in migraine sufferers, one study found that pre-treatment with an oral anti-histamine prevented headaches after ingestion of a high-histamine food in people with HIT.⁸⁷ A potential role for a low-histamine diet is also suggested by a clinical trial of DAO enzyme supplementation in patients with migraine ($n = 100$), which reported a significantly reduced duration of migraine attacks after 1 month of treatment.⁸⁸ If clinical assessment suggests HIT, a low-histamine diet or therapeutic trial of DAO supplementation may be warranted.⁸⁹

Weight-loss diet

Obesity can increase the risk for migraine as well as exacerbate migraine frequency and severity, a relationship that may be in part due to amplification of the inflammatory response in migraine.⁹⁰ Nutritional and behavioural weight loss is useful for people with comorbid migraine and obesity as it can reduce migraine severity and impact.⁹¹ In one study ($n = 135$), a year-long weight-loss intervention that included diet, physical activity and cognitive behavioural training was found to significantly decrease body weight, headache frequency and intensity, use of acute medications, and disability within 6 months in obese adolescents with migraine. Furthermore, benefits persisted at least 12 months after treatment.⁹² While diet and lifestyle counselling and subsequent weight loss may be beneficial, it is also possible that diet and physical activity, independent of weight change, may mitigate migraine.

Low-glycaemic-index/-load diet

Poor blood glucose regulation, especially reactive hypoglycaemia and hyperinsulinaemia, has been associated with migraine attacks, with several early studies reporting beneficial effects of low-carbohydrate diets.^{93,94} In one such study, dietary therapy (a low-sugar diet and six meals daily) resulted in at least 75% reduction of frequency of attacks in all diabetic patients (100%), and most migraine sufferers (63%) who previously demonstrated reactive hypoglycaemia.⁹⁵ More recently, a clinical study of a very-low-carbohydrate ketogenic diet and a case report of a low-carbohydrate diet reported important clinical benefits in migraine sufferers, further supporting the rationale for a low-carbohydrate diet in migraine associated with dysglycaemia.^{96,97} Also, a low-glycaemic-index diet significantly decreased monthly attack frequency and

migraine severity in patients ($n = 147$) after 3 months.⁹⁸ Overall, patients with migraine, and especially those with concomitant dysglycaemia, could benefit from a low-glycaemic-index/-load diet.

High-omega-3/low-omega-6 diet

An increased ratio of dietary omega-6 to omega-3 fatty acids in industrialised diets has been proposed to contribute to inflammatory disorders, including migraine.⁹⁹ In support of this, a high plasma omega-6 to omega-3 ratio was more strongly positively correlated with elevations in inflammatory mediators than levels of each fatty acid alone.¹⁰⁰ In a clinical study ($n = 56$), a combination of increasing dietary omega-3 with concurrent reduction in omega-6 fatty acids produced statistically clinically relevant improvements in headache hours per day, severe headache days, headache-related quality of life, and reduction in use of migraine-specific medications.¹⁰¹ There was also a reduction in psychological distress and an improvement in health-related quality of life and function.¹⁰² A subsequent study was able to demonstrate that increasing dietary omega-3 with concurrent reduction in omega-6 fatty acids is more effective than increasing dietary omega-3 alone, suggesting that the dietary omega-6 to omega-3 fatty acid ratio is indeed important.¹⁰³ The suitability of a dietary intervention that improves omega-3 to omega-6 fatty acid ratios could be based on dietary assessment or laboratory values of fatty acid status.

Ketogenic diet

Ketogenic diets have a long history of investigation in neurological diseases and have a variety of mechanisms that may explain their clinical effects, including improvement of brain energy metabolism,

mitochondrial function, redox balance, reduction of neuroinflammation, pro-excitatory and inhibitory neurotransmitters, and modulation of the gut microbiome.^{104,105}

The use of ketogenic diets for migraine dates back to 1928 when an investigative clinical trial found 9 out of 23 patients (39%) with migraine responded well to a ketogenic diet.¹⁰⁶ Then in 1930 a study reported a reduction in headache frequency of at least 50% in 75% of patients, and total remission of headache in 50% of patients with migraine.¹⁰⁷

More recently the use of ketogenic diets for migraine has been once again investigated, in part due to the publication of a few case reports describing beneficial effects that led to larger scale investigations.^{108,109} In a prospective observational study ($n = 52$), a ketogenic diet intervention had a 90% treatment response rate and reduction in medication use over a 1-month period while, in contrast, a standard low-calorie diet had no effect.¹¹⁰ A proof-of-concept study ($n = 45$) found a significant reduction in attack frequency, number of days with headaches, and medication use intake over 1 month.¹¹¹ A randomised double-blind, crossover trial ($n = 35$) comparing the effects of a very-low-calorie ketogenic diet and a very-low-calorie non-ketogenic diet found the ketogenic diet had a 50% better response rate for days with migraine (74% versus 8%), and was superior for reducing the number of days with migraine (-3.73 days) and migraine attacks (-3.02).¹¹²

In a 12-week randomised-controlled crossover trial, a ketogenic diet lowered migraine duration, although the effect was not statistically significant.¹¹³ However, there was a high dropout rate with only 11 out of 26 people completing the study, and all participants reported fatigue as a side-effect. In another study ($n = 38$), patients with drug refractory chronic migraine and medication overuse headache who were treated with a ketogenic

diet for 3 months had a decrease in days with symptoms (from 30 days to 7.5 days), migraine duration (from 24 hours to 5.5 hours), migraine pain (55% response rate), and medication use (from 30 doses a month to 6 doses a month).¹¹⁴ In two trials, patients with refractory migraine (total $n = 48$) treated with a ketogenic diet had a significant reduction in the frequency of migraine attacks, intensity of headache and medication use when compared with a control diet with a similar reduction of carbohydrate.¹¹⁵

Exogenous beta-hydroxybutyrates (ketones) have been proposed as an alternative to ketogenic diet therapy, but a clinical trial assessing supplementation with beta-hydroxybutyrate (7.4 g daily for 12 weeks) found no benefit for migraine frequency or intensity.¹¹⁶ In contrast, medium-chain triglycerides (MCTs), which are sometimes used as a component of ketogenic diet therapy, were shown to have potential in one study. Treatment with MCTs (13 g total fat per serving from coconut oil) for 30 days with no other dietary changes ($n = 14$) reduced the number of migraine episodes (–39%) and migraine duration (–61%).¹¹⁷

There is promising evidence for ketogenic diets for migraine, but clinical trials to date suggest they need to be strictly ketogenic and not very-low-calorie or low-carbohydrate diets as these appear not to produce the same therapeutic effects. Furthermore, ketogenic diets for migraine may differ from ketogenic diets for other neurological disorders or those used for weight loss due to unique dietary triggers, and different ketogenic ratio (ratio between fats and carbohydrates + proteins) requirements. Di Lorenzo *et al.* have published clinical guidelines and recommendations.¹¹⁸

Riboflavin

Riboflavin has been shown to reduce migraine frequency. Several mechanisms may explain the therapeutic effect of riboflavin, including reduction of oxidative stress, improvement

in mitochondrial function, amelioration of neuroinflammation and modulation of glutamate excitotoxicity.¹¹⁹ A meta-analysis of 11 clinical trials in adolescents and adults concluded that riboflavin is well tolerated and that most clinical trials have shown modest reductions in migraine headache frequency after 2–3 months. However, benefits in children and adolescents were inconclusive.¹²⁰

The optimal dose of riboflavin for migraine prevention is uncertain. Clinical studies in adolescents have typically used doses ranging from 50 mg to 400 mg daily,^{121,122,123,124,125} while adult studies used doses ranging from 100 mg to 400 mg daily.^{126,127,128,129} Lower doses may be as effective as higher doses but are not as well studied. In adolescents, as little as 10 mg of riboflavin daily was found to be effective for migraine prevention in one study,¹³⁰ and in adults a dose of riboflavin 25 mg daily was as effective as a combination nutritional formula providing 400 mg of riboflavin with magnesium and feverfew.¹³¹ The maximal absorption of riboflavin after doses of up to 60 mg is 27 mg,¹³² so it is plausible that there is no advantage to higher doses but this needs to be tested in dose comparison studies.

It is unlikely that overt riboflavin deficiency explains the benefit of supplementation for migraine.¹³³ However, it is possible that people prone to migraine have a higher requirement for riboflavin, with one study suggesting that riboflavin may be more effective in patients with certain mitochondrial DNA genetic variations, specifically those who did not have mitochondrial haplogroup H.¹³⁴ This observation is consistent with the notion that individuals have wide variations in micronutrient requirements that are genetically determined.¹³⁵

Niacin

Niacin has been reported to prevent migraine and to be used acutely to avert migraine attacks, although research is limited. Several

reports of intravenous (IV) and oral niacin have described important clinical benefits for migraine and tension-type headaches, including for aborting acute attacks.¹³⁶

It has been proposed that niacin may be a useful acute treatment due to its vasodilatory effect, which may counter the cranial vasoconstriction associated with the development of migraine aura and pain.¹³⁷ In case reports, 500 mg of oral niacin taken at the onset of acute symptoms prevented migraine.¹³⁸ And in another case report, 375 mg of sustained-release niacin 1–2 times daily for 3 months prevented migraine.¹³⁹ A subsequent systematic review identified 11 clinical reports describing positive effects of IV or oral niacin for headache and migraine headache prevention and acute treatment.¹⁴⁰

Vitamin B12

Vitamin B12 status has been found to be significantly associated with migraine, and correction of deficiency could resolve headaches in some people. Vitamin B12 deficiency has been associated with elevated serum tumour necrosis factor- α (TNF- α) and treatment with vitamin B12 lowers TNF- α , suggesting inflammation may underlie the relationship.¹⁴¹ Vitamin B12 also possesses antioxidant properties, and subclinical deficiency has been associated with oxidant stress.¹⁴²

In a study of patients with migraine ($n = 140$), those with serum vitamin B12 in the highest quartile had an 80% decrease in the odds of having migraine, while those in the highest quartile of methylmalonic acid (a biomarker of B12 deficiency) had a more than five times increased risk of having migraine.¹⁴³ Relevant to migraine patients using analgesics, aspirin use may contribute to vitamin B12 deficiency by damaging the gastric mucosa and interfering with vitamin B12 absorption.¹⁴⁴

Several studies suggest that vitamin B12 supplementation could be useful for preventing migraine, but are limited by small sample sizes and administration of vitamin B12 with other vitamins in most studies.¹⁴⁵ In one study ($n = 20$), treatment with hydroxocobalamin (1000 mcg daily, intranasally) for 3 months was reported to reduce migraine attack frequency, duration of attacks, total number of migraine days and the number of medication doses for acute treatment used in treatment responders.¹⁴⁶ No relationship between cobalamin serum concentrations and efficacy was observed, suggesting a pharmacological effect independent of B12 deficiency. Identification of vitamin B12 deficiency in children and adolescents with tension-type headaches and subsequent correction with 3 months of supplementation was found to completely resolve headaches, anaemia and concomitant anxiety.¹⁴⁷

Homocysteine-lowering vitamins: folate, vitamin B6 and vitamin B12

Folate, vitamin B6 and vitamin B12 supplementation for migraine is supported by several clinical studies, and could be personalised based on measurement of homocysteine, while the presence of certain 5,10-methylenetetrahydrofolate reductase (MTHFR) polymorphisms may result in a better clinical response to supplementation in some people.¹⁴⁸

Elevated serum homocysteine is a frequent finding in migraine sufferers, especially migraine with aura.¹⁴⁹ Studies examining associations between MTHFR C677T and A1298C polymorphisms and migraine have been mixed, but a meta-analysis of 26 studies suggested that they may be a risk factor for migraine in Caucasians, but not Asian populations.¹⁵⁰ Folate, vitamin B6 and vitamin B12 (as well as riboflavin and choline)

lower elevated homocysteine, and individuals with MTHFR polymorphisms may be uniquely susceptible to adverse effects related to low dietary intake of these vitamins.

In a review of five studies assessing supplementation with folate, vitamin B6 and/or vitamin B12, most studies reported good outcomes for migraine prevention.¹⁵¹ Genotype may modify treatment response. In an open-label study ($n = 16$), children with migraine, hyperhomocysteinaemia and MTHFR polymorphisms responded well to folic acid (5 mg once daily) for 6 months.¹⁵² In a subsequent clinical trial ($n = 52$), people with migraine and the MTHFR C677T genotype who were carriers of the C allele experienced a greater treatment response compared with TT genotypes in a 6-month clinical trial of folic acid, vitamin B6 and vitamin B12 supplementation (2 mg of folic acid, 25 mg of vitamin B6 and 400 mcg of vitamin B12).¹⁵³ Similarly, women who were C allele carriers of the MTHFR C677T variant showed a higher reduction in homocysteine levels and severity of pain in migraine in response to the same dose of folic acid, vitamin B6 and vitamin B12 supplementation in another study ($n = 206$).¹⁵⁴ Related to diet, a higher dietary intake of folate has been associated with reduced migraine frequency, particularly in individuals with the CC genotype for the MTHFR C677T.¹⁵⁵

Vitamin E

Vitamin E has antioxidant activity in the central nervous system that may be relevant to the pathophysiological role of redox stress in migraine.¹⁵⁶ A double-blinded trial in women with menstrual migraine ($n = 72$) found that vitamin E supplementation at a dose of 400 IU daily for 5 days, 2 days before to 3 days after menstruation, for two cycles significantly reduced pain severity, photophobia, phonophobia, nausea and functional disability when compared with placebo.¹⁵⁷ In a clinical

trial ($n = 35$), a vitamin E-containing antioxidant formula (providing N-acetylcysteine 1200 mg, vitamin C 1000 mg and vitamin E 500 IU per day) reduced the number of headaches per month (by 3 per month), migraine duration, headache pain scores, and acute headache medication use after 3 months of treatment.¹⁵⁸

Vitamin D

Vitamin D deficiency or insufficiency has a higher prevalence in migraine sufferers compared with controls, and vitamin D supplementation might reduce the frequency of attacks. It has been estimated that vitamin D deficiency or insufficiency is present in 45–100% of people with migraine, and serum vitamin D level has been negatively correlated with frequency of headaches.¹⁵⁹ In people with migraine, vitamin D supplementation has been shown to exert a number of biological effects relevant to migraine pathophysiology, including improved Th17/Treg related cytokines balance,¹⁶⁰ lowering calcitonin gene-related peptide (CGRP),¹⁶¹ and reducing nitric oxide synthase and interleukin (IL)-6.¹⁶²

Several clinical studies have assessed the effect of vitamin D in people with headache or migraine, and generally showed a decrease in headache frequency after vitamin D supplementation.¹⁶³ For example, children with migraine ($n = 53$) who were given vitamin D (400 IU, 800 IU or 5000 IU daily if not deficient, mildly deficient, or very deficient, respectively) plus amitriptyline for 6 months had a significantly lower number of migraine attacks when compared with amitriptyline alone.¹⁶⁴ Adults ($n = 165$) with migraine who received vitamin D (4000 IU daily) for 24 weeks had significantly raised serum 25(OH)D levels and reduced frequency of migraine attacks.¹⁶⁵ Vitamin D may also improve medication treatment response, as noted in a report describing a positive interaction with pregabalin.¹⁶⁶

Magnesium

Magnesium deficiency adversely affects neurological function and could contribute to the development of migraine.¹⁶⁷ Magnesium's blockade of the glutamatergic *N*-methyl-D-aspartate receptor, a receptor known to be a contributor to pain transmission, and its role in mitochondrial functioning are some mechanisms considered particularly relevant.¹⁶⁸

Low serum, saliva and brain levels of magnesium are present in people with migraine, are exaggerated during an acute migraine attack, and significantly predict migraine intensity.^{169,170,171} In a population study, lower dietary intake of magnesium increased risk of migraine, while attainment of the Recommended Dietary Allowance through food and supplements was associated with reduced risk.¹⁷²

A review of five clinical trials found that magnesium, when used as a prophylactic treatment against migraine, resulted in a favourable reduction in migraine attacks ranging between 22% and 43%.¹⁷³ Evidence of efficacy was more compelling for a dose of > 600 mg daily and for magnesium as magnesium citrate when compared with other types of magnesium.

IV magnesium sulphate has been studied as a treatment for migraine in emergency department settings and is effective, comparable to other IV medications (metoclopramide, prochlorperazine, caffeine citrate), well tolerated and has a good safety profile.^{174,175,176,177}

Iron

Iron-deficiency anaemia could contribute to migraine, and there is some evidence to suggest that treatment of iron-deficiency anaemia can greatly reduce the rate of migraine attacks suggesting it may be an underlying cause of migraine in some people.

Headache or migraine is not considered a typical symptom of iron-deficiency anaemia but may be overlooked. In a group of patients ($n = 127$) with iron-deficiency anaemia, 79.5% reported headaches and 36.2% met the criteria for migraine.¹⁷⁸ A case-control study found an association between iron-deficiency anaemia and migraine, especially in women and girls.¹⁷⁹ Iron-deficiency anaemia has also been significantly associated with menstrual migraine.^{180,181}

Treatment of children ($n = 98$) with iron deficiency and migraine with iron (4 mg per kg per day of ferrous sulphate) for 3 months significantly reduced migraine frequency, severity, duration and disability.¹⁸² Iron supplementation has also been reported to reduce monthly frequency and severity of migraine headache in adults ($n = 183$) with migraine and iron deficiency.¹⁸³ Dietary iron intake has been inversely associated with severe headache or migraine in women aged 20–50 years, suggesting optimising iron intake via diet may also be important for migraine prophylaxis.¹⁸⁴

Zinc

Zinc serum levels have been observed as lower in people with migraine,^{185,186} and this may have clinical relevance as zinc is essential for a wide range of neurological functions relevant to migraine.¹⁸⁷ Clinical studies suggest zinc may be a useful therapy for migraine. A randomised clinical trial ($n = 80$) of zinc sulphate (50 mg zinc daily) for 8 weeks resulted in a reduction in headache severity and migraine attack frequency, although this was not statistically significant.¹⁸⁸ A second study, also a randomised clinical trial ($n = 60$), assessed zinc gluconate (15 mg of zinc daily) over 12 weeks, and reported significantly reduced frequency and severity of migraine attacks.¹⁸⁹

Coenzyme Q10 (CoQ10)

CoQ10 deficiency, as measured by serum CoQ10, is common in patients with migraine and can be used to personalise treatment.¹⁹⁰ It is important to note that low serum CoQ10 is a biomarker of mitochondrial dysfunction, and that CoQ10 supplementation can improve mitochondrial function.¹⁹¹ CoQ10 also has well-documented anti-inflammatory effects, and has been shown to reduce the inflammatory markers CGRP and TNF- α in people with migraine.¹⁹²

In a meta-analysis of six clinical studies, CoQ10 reduced the duration and frequency of migraine attacks.¹⁹³ A dose-response analysis of CoQ10 in migraine suggested a non-linear association with maximal efficacy at 300 mg daily regardless of variation in bioavailability of different formulations.¹⁹⁴ CoQ10 may be synergistic with curcumin, as one study ($n = 100$) found that a combination of curcumin (80 mg) plus CoQ10 (300 mg) was significantly more effective than either therapy alone for migraine prevention.¹⁹⁵

Alpha-lipoic acid

Alpha-lipoic acid (ALA) has potential for the management of migraine, in part because it improves insulin sensitivity. Disordered glucose and insulin metabolism is a key feature of migraine, although it is not clear if alterations in glucose metabolism are risk factors for or consequences of migraine.¹⁹⁶ Patients with migraine and insulin resistance who received ALA (400 mg twice daily) for 6 months experienced a reduction in the number of migraine attacks and days of treatment, although there was no improvement in insulin sensitivity in this study.¹⁹⁷

ALA has antioxidant and anti-inflammatory effects, independent of effects on insulin metabolism, that may play a role in its therapeutic effect. In women with episodic

migraine ($n = 92$), ALA (300 mg twice daily) for 3 months significantly decreased serum levels of malondialdehyde and C-reactive protein (CRP), and clinical symptoms of depression, anxiety and stress when compared with placebo.¹⁹⁸

Improvements in mitochondrial and endothelial function have also been observed. In women with episodic migraines ($n = 92$), ALA (300 mg twice daily) for 12 weeks significantly reduced migraine severity and frequency, and reduced serum lactate and vascular cell adhesion molecule-1, suggesting improvement in mitochondrial and endothelial function, respectively.¹⁹⁹

Other reports also suggest a therapeutic role for ALA. An open-label study ($n = 54$) reported a beneficial effect of ALA (600 mg daily) for migraine prophylaxis after just 1 month.²⁰⁰ When ALA (300 mg daily) was added to topiramate therapy, treatment was more effective and better tolerated than topiramate alone.²⁰¹

Carnitine

Carnitine and acetyl-L-carnitine (ALC) have well-established neurological effects relevant to migraine, including mitochondrial enhancing, antioxidant and analgesic activity, but whether these translate to clinical value is less understood.²⁰² The few studies assessing carnitine as a monotherapy have produced mixed results. A 12-week study ($n = 72$) of ALC (3 g daily) found no benefit for migraine prophylaxis in adults.²⁰³ In contrast, paediatric patients ($n = 56$) with episodic migraine treated with L-carnitine (50 mg per kg per day) experienced a reduction in migraine frequency, severity and duration that was comparable to the study arm receiving propranolol.²⁰⁴ Carnitine and ALC have been used as components of multi-ingredient nutritional formulations for migraine, and studies in which they

have been administered with other nutrients are discussed below. Carnitine palmitoyltransferase II (CPT2) or carnitine deficiency should be considered in treatment refractory migraine. Case reports have described cases of migraine discovered to be related to CPT2 or carnitine deficiency, and successfully managed with carnitine in adolescents^{205,206} and young adults.²⁰⁷ In these cases, patients had chronic and often daily headache, additional diverse symptoms (e.g. chronic constipation, abdominal pain and constant extreme fatigue) and were refractory to multiple medications.

5-Hydroxytryptophan (5-HTP)

5-HTP has been investigated for migraine based on its role as a precursor to serotonin and the potential contribution of alterations in serotonin in the pathophysiology of migraine.²⁰⁸ Other potential mechanisms of 5-HTP in migraine include analgesic effects mediated by elevations in plasma beta-endorphins,²⁰⁹ and reaction in cortical spreading by serotonin-oestrogen interactions.²¹⁰ However, studies of 5-HTP are few and were mostly conducted over 30 years ago with little interest in 5-HTP for migraine since this time, which coincides with the approval of the first selective serotonin reuptake inhibitor (SSRI) drugs.²¹¹ In a clinical study ($n = 40$), 5-HTP (300 mg daily for 40 days) was reported to reduce migraine frequency and severity compared with placebo.²¹² In patients with headache ($n = 31$), including migraine and other types of chronic headache, 5-HTP (400 mg daily) for 2 months showed that 48% of participants had a greater than 50% average reduction in headache symptoms.²¹³ A study in patients with migraine ($n = 124$) assessed 5-HTP (600 mg daily) over 6 months with a significant improvement in 71% of patients, particularly for intensity and duration of attacks.²¹⁴ In contrast, a 12-week study in a paediatric cohort with migraine found no benefit of 5-HTP (5 mg per kg of body weight daily) when compared with placebo.²¹⁵ However, it should be noted that both 5-HTP

and placebo significantly reduced migraine frequency and severity.

Clinical studies suggest that 5-HTP may be a useful therapy for migraine. It should also be noted that 5-HTP has been reported to benefit other types of headaches, including paediatric headaches,²¹⁶ fibromyalgia-related migraine,²¹⁷ chronic primary headaches²¹⁸ and chronic tension-type headaches.²¹⁹

Omega-3 fatty acids

Low dietary intake of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) increases the risk for headaches²²⁰ and migraine.²²¹ An adequate dietary supply of EPA and DHA is critical for neurological health, and low levels, as measured by the percentage of EPA/DHA in erythrocytes [the Omega-3 Index (O3I)], have been associated with impaired brain function, atrophy of key brain regions and diverse neurological diseases.²²²

A systematic review and meta-analysis of 10 randomised-controlled trials of EPA/DHA in migraine found a significant reduction of approximately 3.44 hours in the duration of migraine, but no effect on frequency or severity.²²³ However, it was noted that there were several limitations that may have confounded results, including: lack of adequate placebo (olive oil was sometimes used); not controlling for omega-3:6 ratio (which may influence EPA/DHA efficacy); a masking effect by migraine medications; and lack of personalisation (e.g. not testing baseline omega-3 status or response). Subsequent to the publication of this meta-analysis, a clinical trial was published in which 66% of patients with chronic migraine who received omega-3 (1500 mg EPA/DHA daily) for 60 days in conjunction with amitriptyline had an 80.0% reduction in the number of headache days per month, compared with 33% with amitriptyline alone.²²⁴

In general, the evidence is suggestive for the benefits of EPA/DHA in migraine, but until better quality clinical trials are available that account for the limitations mentioned above the clinical benefit remains unclear. In practice, an exploratory therapeutic trial of 1000–2000 mg EPA/DHA daily for at least 8 weeks could be considered, and personalised based on testing of the O3I.²²⁵

Palmitoylethanolamide (PEA)

PEA is an endocannabinoid-like bioactive lipid mediator used as a nutritional supplement primarily for its neurological, anti-inflammatory and analgesic effects.²²⁶ Preclinical evidence suggests that modulation of the endocannabinoid system by PEA could relieve migraine pain.²²⁷ For pain management, case studies, clinical trials and meta-analyses of PEA have demonstrated good evidence of efficacy and excellent tolerability at typical doses of 600–1200 mg daily.²²⁸

In patients with migraine with aura ($n = 20$), PEA (1200 mg daily) for 90 days resulted in a statistically significant and time-dependent reduction in pain, as a composite of severity and frequency, at the 60- and 90-day time points.²²⁹ In addition, PEA reduced non-steroidal anti-inflammatory drug (NSAID) use compared with controls. An open-label study in patients with episodic migraine ($n = 25$) assessed a PEA-containing nutraceutical (Calmux®, Bioksan, Spain; providing PEA 800 mg, *Scutellaria baicalensis* 800 mg, *Boswellia serrata* extract 500 mg and *Harpagophytum procumbens* root extract 400 mg per day) over 3 months and reported a significant reduction in pain intensity.²³⁰ A paediatric cohort with migraine without aura ($n = 70$) who received PEA (600 mg daily) for 3 months experienced a significant reduction in pain intensity and attack frequency as well as a reduction in medication requirement.²³¹

Melatonin

Melatonin, although a hormone, is available as a non-prescription over-the-counter dietary supplement in the USA, Canada and some EU countries. As a dietary supplement, melatonin is considered very well tolerated and safe at typical doses of 1–20 mg daily, and even safe when used at very high doses of up to 1000 mg daily in the short term.²³² Relevant to migraine, serum melatonin may be lower in a sub-group of patients,²³³ and alterations in melatonin could play an important role in migraine pathophysiology via modulation of several neural pathways involved in the generation of migraine attacks.²³⁴ In addition, melatonin supplementation can exert analgesic effects independent of endogenous melatonin status.²³⁵ It is also possible that by improving sleep, melatonin may prevent migraine attacks,²³⁶ and help resolve acute attacks by encouraging sleep, at least in children.²³⁷

Studies suggest melatonin may be useful for migraine prevention, and for acute management of migraine headache attacks. In a systematic review of seven studies, melatonin was generally found to be effective for migraine prevention with comparable efficacy to other preventive medications. In adults, doses of 3 mg daily appeared to be more effective than 2 mg doses, and a treatment duration of 3 months was more likely to be related to a beneficial outcome.²³⁸

A novel study explored the use of melatonin for acute treatment of migraine attacks.²³⁹ Children and adolescents ($n = 84$) aged 4–17 years with episodic migraine were prescribed ‘high-dose’ or ‘low-dose’ melatonin (< 40 kg: 4 mg versus 1 mg; ≥ 40 kg: 8 mg versus 2 mg) as an edible milk-chocolate-based melatonin formulation (Good Day Chocolate, USA). Acute treatment of a migraine attack with melatonin reduced pain intensity and reduced migraine duration with a 2-hour pain-relief rate (defined as mild or no

headache) of 94% and 80% in the high- and low-dose groups, respectively. Napping occurred in 67% and 47% in the high- and low-dose groups, respectively. Both higher dose and napping after treatment predicted greater benefit.

Ginger

Ginger (*Zingiber officinale*) has well-established clinical use as an anti-inflammatory and analgesic in addition to nausea, a common feature of migraine.²⁴⁰ A meta-analysis of three randomised-controlled studies ($n = 227$) in which ginger monotherapy (two studies) or feverfew (*T. parthenium*; one study) had been explored as an intervention for migraine prevention and acute treatment found ginger effective for reducing migraine pain, nausea and vomiting.²⁴¹ The studies attributed to positive effects were trials in which ginger was used as an acute abortive treatment while, in contrast, ginger used as a daily prophylactic over 1 month did not perform better than placebo.²⁴² The first study assessing ginger (with feverfew) as an abortive treatment was in fact a homeopathic remedy, and not a herbal product.²⁴³ In the second, patients treated with ginger (a single dose of 400 mg of extract providing 5% gingerols) in addition to IV ketoprofen showed significantly better clinical response after 1 hour, 1.5 hours and 2 hours compared with medication alone.²⁴⁴ Also, ginger reduced pain and improved functional status. Ginger appears to have promise as an acute abortive treatment, but this requires validation with further research. Clinically, a therapeutic trial of ginger at the first sign of headache could be considered.

Curcumin

Curcumin, an anti-inflammatory polyphenol derived from turmeric (*Curcuma longa*) rhizome, has been explored as a possible therapeutic intervention in patients with migraine, alone and in combination with other nutrients. In a

clinical trial of nano-curcumin alone, patients with episodic migraine ($n = 44$) were randomised to nano-curcumin (80 mg daily) or placebo for 2 months.²⁴⁵ Nano-curcumin was reported to significantly reduce the frequency, severity and duration of headaches. The same research group have explored mechanisms of action in study participants, demonstrating modulation of the Th2/T regulatory cell axis,²⁴⁶ and reduction in gene expression and plasma levels of IL-17.²⁴⁷ Another research group studied a different curcumin extract ($n = 44$) for a period of 8 weeks at a dose of 500 mg twice daily (providing 95% curcuminoids), administered after lunch and dinner to improve absorption.²⁴⁸ In this study, participants ($n = 44$) receiving curcumin had a significant reduction in headache severity and duration, with a marginal reduction in frequency. There was also a significant reduction in CGRP and IL-6.

A series of studies have examined the clinical effect of a nano-curcumin and omega-3 fatty acid formulation. A clinical trial ($n = 74$) comparing nano-curcumin (80 mg daily), omega-3 fatty acids (1200 mg of EPA and 600 mg of DHA daily), a combination of them, or placebo found a significant reduction in migraine attack frequency in the nano-curcumin and omega-3 fatty acids combination, while curcumin or omega-3 fatty acids alone were not effective.²⁴⁹ In addition, they demonstrated a significant downregulation of TNF- α gene expression with the combination only. The same research group have also reported downregulation of IL-6 gene expression, a decrease in the serum concentration of high-sensitivity (hs)-CRP,²⁵⁰ reduction of serum intercellular adhesion molecule 1 (ICAM-1)²⁵¹ and serum IL-1 β ,²⁵² with the effect generally more pronounced for the combination.

A combination of nano-curcumin and CoQ10 has also been investigated. Patients with episodic migraine ($n = 91$) received either a combination of nano-curcumin (80 mg) plus CoQ10 (300 mg), nano-curcumin, CoQ10, or placebo for 8 weeks. The curcumin and CoQ10 combination was more effective than all the

other interventions for reducing migraine attack frequency, severity and duration, suggesting a synergistic or additive effect.¹⁹⁵

Overall, it appears curcumin alone or in combination with omega-3 fatty acids or CoQ10 may be useful for migraine, and both more commonly available 95% curcuminoid extracts and nano-formulations (e.g. liposomal) may be effective albeit at significantly different doses of 1000 mg (total extract) or 80 mg (curcumin) daily, respectively.²⁵³

Phytoestrogens

Based on the oestrogen withdrawal hypothesis of migraine aetiology, phytoestrogens have been explored as a therapeutic for migraines with some evidence of potential benefit. The oestrogen withdrawal hypothesis is based on the observation that migraine is more prevalent in women and tends to be related to fluctuations in oestrogen during menarche, menstruation, pregnancy and menopause, with migraine attacks being twice as common in the perimenstrual period when oestrogen levels decline.²⁵⁴ Oestrogen directly influences several pathways involved in migraine in the central nervous system.²⁵⁵ A higher rate of oestrogen decline in the late luteal phase and 2 days post-peak

may represent a neuroendocrine vulnerability pattern in migraineurs versus controls.²⁵⁶ Stabilising oestrogen with hormone replacement therapy can help mitigate migraine.²⁵⁷ A possible alternative to hormone replacement therapy for the management of migraine is phytoestrogens; non-steroidal phytonutrients that selectively modulate oestrogen receptors.²⁵⁸

Three clinical trials have assessed the effect of phytoestrogens in menstrual migraine, including soy isoflavones with other hormone-modulating herbs,²⁵⁹ soy isoflavones alone,²⁶⁰ and resveratrol (Table 1).²⁶¹

These studies suggest that soy isoflavone extract with additional herbs or the soy isoflavones genistein and daidzein alone may be useful for menstrual migraine, while resveratrol has no benefit. The reason for this difference in efficacy may be due to differences in ability to selectively modulate oestrogen receptors between soy isoflavones and resveratrol. Soy isoflavones are oestrogen receptor β -specific, while resveratrol modulates both α and β oestrogen receptors.²⁶² Therefore, if trialling phytoestrogens, soy isoflavones at a dose of > 76 mg daily for at least 3 months should be considered.

Table 1: Clinical trials assessing phytoestrogens for migraine prophylaxis

Study	Subjects	Intervention	Outcome
Burke <i>et al.</i> (2002)	<i>n</i> = 49 women with menstrual migraine	Combination of 60 mg soy isoflavones, 100 mg dong quai and 50 mg black cohosh extracts, or placebo, daily for 24 weeks	Migraine frequency during weeks 9–24; 10.3 in placebo-treated and 4.7 in patients treated with the phytoestrogen preparation
Ferrante <i>et al.</i> (2004)	<i>n</i> = 10 women with menstrual migraine	56 mg of genistein and 20 mg of daidzein daily, for 3 months	Average number of days with migraine decreased significantly after 3 months of therapy
Dzator <i>et al.</i> (2022)	<i>n</i> = 62 women with menstrual migraine	75 mg of resveratrol, or placebo, twice daily for 3 months	Resveratrol did not affect number of days with migraine, the migraine-related disability, or quality of life

Probiotics

Digestive disorders have frequently been associated with migraine headaches, and may play a contributory or causal role through a variety of mechanisms, including alterations in the enteric immune and nervous systems by intestinal bacteria and gut-derived inflammatory and vasoactive mediators entering circulation.²⁶² In one study, migraine sufferers were found to have significantly higher levels of nitrate, nitrite and nitric oxide reductase bacterial genes in samples collected from the oral cavity, and slight but significant differences in faecal samples as well.²⁶³ Modification of gastrointestinal health and ecology could be a treatment target, with a number of clinical examples that support the importance of identifying and managing gastrointestinal dysfunction in migraine sufferers. Eradication of *Helicobacter pylori*,^{264,265,266} improvement of IBS with an IgG-based elimination diet, and treatment of coeliac disease with a gluten-free diet have resulted in improvement in migraine. In fact, many nutritional interventions discussed above describe dietary changes and nutritional supplements (e.g. vitamin D and omega-3 fatty acids) that may improve gastrointestinal health and ecology.²⁶⁷ Interestingly, an uncontrolled study suggested possible benefit in migraine sufferers who were managed with a nutritional plan focused on improving gastrointestinal assimilation and elimination using a combination of probiotics, nutrients and herbs.²⁶⁸

Probiotics have been investigated in patients with migraine. A 12-week pilot study ($n = 27$) of a multi-strain probiotic (Ecologic Barrier, Winclove Probiotics, Netherlands) at a dose of 2.5 billion CFU daily reported a significant reduction in migraine frequency and intensity; however, this study lacked a control group.²⁶⁹ In a subsequent randomised placebo-controlled trial ($n = 63$) of the same probiotic at a dose of 5 billion CFU for 12 weeks, the intervention did not reduce migraine, failing

to support the previous open-label study.²⁷⁰ In addition, there was no impact of the probiotic on intestinal permeability or inflammation compared with placebo. In contrast, a different probiotic was associated with clinical benefit. A 10-week randomised placebo-controlled trial ($n = 79$) assessed a multi-strain probiotic (Bio-Kult, ADM Protexin Limited, UK) at a dose of 4 billion CFU daily.²⁷¹ Compared with placebo, the probiotic significantly reduced migraine frequency, severity, duration and abortive drug use.

It is plausible that improvements in gastrointestinal health such as those associated with clinical management of *H. pylori*, IBS or coeliac disease may coincide with improvement in migraine through shared pathophysiological mechanisms. Dietary changes and nutritional supplements also impact microbial ecology and gastrointestinal health and function, which may, at least in part, provide one mechanism by which they exert beneficial effects. Probiotics have limited evidence in migraine, with only one study of a specific multi-strain probiotic suggesting benefit, while another was not effective. Microbiome testing, although widely available, cannot identify probiotic treatment responders so a 10-week therapeutic trial could be considered.

Nutrient combinations

In addition to the monotherapies described above, some clinical trials have studied the effects of multi-component nutrient formulations (nutrient combinations). These are summarised below (Table 2). Most of these studies have suggested clinically relevant reductions in migraine frequency and severity, but are limited by lack of placebo control (four out of seven studies). Few compared nutrient combinations with individual nutrients to determine if there is an additive or synergistic advantage to a multi-component formula over individual components. Tarighat Esfanjani *et al.*²⁷³

did report a slightly better effect of magnesium and carnitine versus either nutrient alone, but Maizels *et al.*²⁷² found that a relatively low dose of riboflavin that was intended as the control was as effective as a combination of high-dose riboflavin, magnesium and feverfew. And no studies personalised interventions to pathophysiological

sub-groups, such as mitochondrial dysfunction or oxidative stress, or examined biological characteristics of treatment responders, which would be informative. Despite these limitations, nutrient combinations appear to have promise for the management of migraine.

Table 2: Clinical trials of nutrient combinations for migraine

Study	Subjects	Intervention	Outcome
Maizels <i>et al.</i> (2004) ²⁷²	<i>n</i> = 49 patients with migraine	Combination (riboflavin 400 mg, magnesium 300 mg and feverfew 100 mg), or riboflavin 25 mg, daily for 3 months	Both groups showed a significant reduction in number of migraines, migraine days and migraine severity
Tarighat Esfanjani <i>et al.</i> (2012) ²⁷³	<i>n</i> = 133 patients with migraine	Combination (magnesium oxide 500 mg, L-carnitine 500 mg), or magnesium oxide 500 mg, or L-carnitine 500 mg for 12 weeks	All interventions significantly reduced migraine frequency and severity, but the combination was associated with a greater reduction in severity
Gaul <i>et al.</i> (2015) ²⁷⁴	<i>n</i> = 130 patients with migraine	Combination (Migravent®, Germany; Dolovent®, USA; riboflavin 400 mg, magnesium 600 mg, CoQ10 150 mg with multivitamin and minerals) or placebo for 3 months	Significant reduction in migraine severity and non-significant reduction in frequency
Guilbot <i>et al.</i> (2017) ²⁷⁵	<i>n</i> = 62 patients with migraine	Combination (feverfew 100 mg, CoQ10 100 mg, magnesium 112.5 mg) for 3 months	Significant reduction in days with migraine, migraine severity Reductions in depression, anxiety and improved quality of life
Hajihashemi <i>et al.</i> (2019) ²⁷⁶	<i>n</i> = 56 patients with migraine	Combination (CoQ10 30 mg, L-carnitine 500 mg) or placebo for 8 weeks	Significant reduction in migraine severity, duration, frequency and serum lactate
Vikelis <i>et al.</i> (2020) ²⁷⁷	<i>n</i> = 113 patients with episodic migraine	Combination (magnesium 281.25 mg, vitamin B2 4.8 mg, CoQ10 20 mg, feverfew 150 mg, <i>Andrographis paniculata</i> 100 mg) for 3 months	Significant reduction in number of migraine days, headache severity and medication use
Visser <i>et al.</i> (2020) ⁶⁵	<i>n</i> = 35 patients with migraine	Combination (N-acetylcysteine 1200 mg, vitamin C 1000 mg, vitamin E 500 IU) or placebo for 3 months	Significant reduction in number of headaches per month, migraine duration, headache pain scores and acute headache medication use

Table 3: Clinical summary of nutritional supplements for migraine

Nutrient	Clinical indications	Duration	Dose
Riboflavin	Consider a routine therapeutic trial in patients with migraine	> 3 months	Adults: 400 mg daily; children: 50–200 mg daily
Niacin	Limited evidence suggests benefit as an abortive Consider a therapeutic trial	Single dose	500 mg
Vitamin B12	Screen patients for B12 deficiency	> 3 months	If deficient, 1000 mcg daily Monitor B12 status to avoid excess or toxicity
Homocysteine-lowering vitamins	Screen patients for elevated homocysteine Some MTHFR-genotypes may respond better to B vitamins	> 6 months	If indicated, B vitamin complex Monitor folate, B6 and B12 status to avoid excess or toxicity
Vitamin E	Assess dietary intake for deficiency Consider a routine therapeutic trial in patients with migraine	> 3 months	400 IU daily
Vitamin D	Screen patients for vitamin D deficiency	8 weeks	If deficient, 6000 IU/day for at least 6 weeks to achieve serum 25(OH)D > 30 ng/ml ²⁷⁸ Monitor vitamin D status to avoid excess or toxicity
Magnesium	Assess dietary intake and risk factors for deficiency Screen patients for magnesium deficiency Consider a routine therapeutic trial in patients with migraine	> 3 months	> 600 mg daily, in divided doses, as magnesium citrate
Iron	Screen patients for iron-deficiency anaemia	2 months	If iron-deficiency anaemia, management should be holistic and personalised ²⁷⁹
Zinc	Assess dietary intake and risk factors for deficiency Screen patients for zinc deficiency	> 2 months	If deficient, > 15 mg daily

CoQ10	Assess serum CoQ10 Consider a therapeutic trial regardless of serum levels	> 6 weeks	300 mg daily, in divided doses, with food
Alpha-lipoic acid	Assess insulin resistance/blood glucose metabolism Assess redox stress Consider a therapeutic trial regardless of test results	> 3 months	300–400 mg twice daily
Carnitine	Screen for CPT2 or carnitine deficiency in treatment refractory migraine	Indefinitely	660–1650 mg daily in divided doses
5-HTP	Consider a routine therapeutic trial in patients with migraine	> 40 days	> 300 mg daily
EPA/DHA	Assess dietary intake Screen patients with the O3I test	> 60 days	> 1500 mg daily combined EPA + DHA (and depending on O3I status)
PEA	Consider a therapeutic trial in patients with migraine May be useful for reducing drug requirements	> 60 days	Adults: 1200 mg daily; children: 600 mg daily
Melatonin	May be useful as a preventative in some cases Limited evidence suggests benefit as an abortive	> 3 months (prevention) 1–2 doses (at onset of an attack)	Adults: > 3 mg daily (prevention); children and adolescents: > 8 mg in divided hourly doses (at onset of attack), possibly higher for adults
Ginger	Limited evidence suggests benefit as an abortive	> 3 months (prevention) 1 dose (at onset of an attack)	Prevention: > 400 mg of extract (5% gingerols) daily, in two divided doses Treatment: > 400 mg of extract (5% gingerols) at onset of attack
Curcumin	Consider a therapeutic trial in patients with migraine May be useful for reducing drug requirements	> 2 months	1000 mg turmeric extract providing 95% curcuminoids daily 80 mg nano-curcumin (e.g. liposomal) daily

Phytoestrogens	May be useful for menstrual and hormone-related migraines	> 3 months	> 76 mg soy isoflavones daily
Probiotics	May be useful if gastrointestinal involvement	> 10 weeks	4 billion CFU daily of a multi-strain probiotic (Bio-Kult) daily
Nutrient combinations	Consider a therapeutic trial in patients with migraine	> 3 months	Multiple options available (see Table 2 above)

A wide range of nutritional interventions have been studied clinically and could be considered when managing migraine in clinical practice (Table 3). ‘Clinical indications’ include clinical history, symptoms and biomarkers that may help guide personalisation. Treatment duration and dose are based on clinical studies cited and discussed in this review, and are generally indicative of effective dose and time to see a significant clinical response. Importantly, clinical studies typically have indiscriminately tested interventions and have rarely utilised biomarkers or clinical symptoms to identify treatment responders, so the ‘clinical indications’ are in some cases based on the author’s opinion regarding the rationalisation of different management options.

Discussion

Migraine headaches have complex relationships to food and nutrition related to pathogenesis and opportunities for clinical management. Dietary interventions can be broadly divided into three major categories that may also be indications for their clinical use: healthy diet; identify aggravating foods or intolerances; and modify underlying pathophysiology or dysfunction. Clinical indications, such as dietary history, and biomarkers or investigations, such as the positive confirmation of coeliac disease, may help identify which dietary interventions are best suited to an individual (Figure 1).

Nutritional intervention with vitamins, minerals, amino acids and other nutrients have shown considerable promise for the management of migraine. A broad range of nutritional interventions is possible, so a pragmatic model that rationalises their indications and use may be helpful in clinical practice (Figure 2). Suboptimal intakes or deficiencies of vitamins, minerals and fatty acids can be assessed through dietary recall and/or laboratory testing, although both have limitations and may not accurately identify treatment responders, and nutrients may have pharmacological effects independent of deficiency or low dietary intake. Other nutrients have more specific indications like improving mitochondrial function, blood glucose metabolism, oestrogen stability or gut microbiome ecology; however, it should be emphasized that nutritional compounds have diverse mechanisms of action so this may be an oversimplification. Additionally, currently accessible laboratory testing may not be a reliable way to direct treatment, as in the cases of mitochondrial function, oestrogen stability and gut microbial ecology, for which there are few, if any, well-established clinical assessments relevant to migraine. Until reliable assessment tools are available, a therapeutic trial with a nutritional intervention, and subsequent positive or null symptomatic response, may be the most pragmatic assessment.

There is a need for clinical guidelines, treatment algorithms and a greater number of validated

biomarkers that could help clinicians match nutritional and lifestyle medicine-based interventions to patients mostly likely to benefit.²⁸⁰ In the meantime, patient symptoms, health history, genetics, environment, lifestyle, diet and behaviour, amongst other considerations, can be leveraged in a clinical setting and inform personalised management plans.²⁸¹ Nutritional approaches for migraine management can be used in a personalised and pragmatic way to improve patient outcomes.²⁸²

Conclusion

Chronic migraine headaches are a prevalent and debilitating disease that would benefit from better management options. A diverse range of therapeutic nutritional options have been explored for migraine headache, with varying degrees of benefit. The wide range of therapeutic options may make it challenging to approach nutritional management of migraine in a clinical setting, so a pragmatic model that helps personalise interventions from clinical signs and symptoms and reliable biomarkers would be useful. There is a need for clinical guidelines, treatment algorithms and a greater number of validated biomarkers that could help clinicians match nutritional and lifestyle-medicine-based interventions to patients most likely to respond to different interventions. Although a greater understanding of the role of nutritional medicine for migraine is needed, a considerable body of clinical evidence already exists, and could inform clinical practice in a way that improves patient outcomes and reduces suffering associated with the disease.

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