**Nervous System - Migraine**

Category: Health Condition/ Disease
Exported: July 31, 2015

Keywords: headache migraine attack migrainous head pain aura neurological disorder nervous system

***Practice Questions***

**Q1: What dietary components, if any, are triggers for migraine among migraineurs?**

Subcategory: Intervention
Last Updated: 2014-03-11
Keywords: trigger alcohol red wine beer tyramine sulphites sulfites histamine phenols flavonoids chocolate cocoa theobromine cheese phenylethylamine biogenic amine aspartame sucralose artificial sweetener monosodium glutamate (MSG) hydrolyzed vegetable protein hydrolyzed plant protein citrus octopamine processed meat nitrate nitrite dehydration fatty foods fasting monoamine oxidase (MAO) inhibitor precipitating factor

[Search Strategy](#dietarycomponents)

**Key Practice Point**

**Evidence Synthesis**

While research into migraine triggers is not new, only recently have studies taken an experimental or quasi-experimental rather than a descriptive approach. The following triggers have been self-reported by migraineurs in cross-sectional studies and have been positively associated with migraines in experimental studies:

* Aspartame (reported by 8.2-9% of participants) – evidence from a small RCT and two case-reports. {grade\_c}
* Caffeine withdrawal (reported by 22% of participants) – evidence from a retrospective cohort study. {grade\_c}
* Fasting (reported by 40-82% of participants) – evidence from an RCT, prospective cohort study and case-control study. {grade\_c}
* Lipids (reported by 17% of participants) – evidence from an RCT and case-control study. {grade\_c}
* Meat and Fish (reported by 3.6% of participants) – evidence from a cross-sectional study. {grade\_c}
* Sucralose – evidence from three case reports. {grade\_c}

The following triggers have been self-reported by migraineurs in cross-sectional studies, but have not been associated with the migraines in experimental studies:

* Tyramine – evidence from four double-blinded RCTs. {grade\_b}
* Chocolate (reported by 0-22.5% of participants) – evidence from a double-blinded RCT and a prospective cohort study. {grade\_c}
* Dairy (milk reported by 2.3-2.5% of participants, cheese reported by 0-18.2% of participants) – evidence from a prospective cohort study. {grade\_c}
* Vegetables (reported by 0-11.1% of participants) – evidence from a cross-sectional study. {grade\_c}
* Eggs (reported by 2- 7.4% of participants) – evidence from a case-control study. {grade\_d}
* Monosodium glutamate (MSG) (reported by 2.5-12.9% of participants) – no other evidence. (grade­\_d}

The following triggers have been self-reported by migraineurs in cross-sectional studies, but are associated with conflicting research evidence that both supports and refutes its status as a migraine trigger:

* Alcohol (reported by 17-76% of participants) – evidence from a prospective cohort study and cross-sectional study found a decreased risk of migraine with moderate alcohol intake, two cross-sectional studies and an experimental study found an increased risk of migraine with alcohol intake (wine specifically, for the experimental study), and one cross-sectional study found no relationship between alcohol and migraines. {grade\_d}
* Caffeine – (reported by 6.4-14.5% of participants) – four cross-sectional studies included participants who reported caffeine as a trigger but two retrospective cohort studies failed to identify it as a precipitating factor. Additionally, three population studies found an increased prevalence of migraine in adults and adolescents who drank coffee/tea, but one population study found no association. {grade\_d}
* Citrus fruits (reported by 0-11.1% of participants) – evidence from two cross-sectional studies. {grade\_d}
* Cold Foods – (reported by 1.4-4.6% of adult participants and 55.4% of adolescent participants) – evidence from three experimental studies, two that showed a relationship with headaches in migraineurs and one that did not. {grade\_d}
* Dehydration (reported by 31-91.4% of participants) – evidence from an RCT and cross-sectional study. {grade\_d}

**Practice Guidance**

Migraineurs may find it worthwhile to experiment with identifying and avoiding potential dietary triggers and should not be dissuaded from doing so. The most commonly reported dietary triggers by research participants include fasting (up to 82%), alcohol (up to 76%), dehydration (up to 91.4%), and cold foods (up to 55.4% of adolescents). However, additional evidence supporting alcohol, dehydration, and cold foods as dietary triggers for migraines is conflicting.

Other dietary triggers have been reported by less than a quarter of research participants, but with varying levels of support from additional research.

* Positive association with migraines: aspartame, caffeine withdrawal, lipids, meat, fish and sucralose.
* No association with migraines: tyramine, chocolate, dairy, vegetables, eggs and MSG.
* Unclear (conflicted) association with migraines: excess caffeine and citrus fruits.

Elimination of specific foods should be harmless unless entire food groups are eliminated from the diet. In that case, consultation with a registered dietitian may be necessary to ensure all nutrient needs are being met.

**Grade of Evidence: B, C & D**

**Evidence**

1. A systematic review evaluated the frequency with which heterogeneous populations of migraineurs identified migraine triggers in 25 studies published between 1987 and 2013 (1). Most included studies were cross-sectional in nature and relied on self-report. Fasting (either intentionally or unintentionally by skipping a meal) was the third most commonly reported migraine trigger (44%, n=3374) after stress (58%) and auditory triggers (56%). In the publication, however, fasting was erroneously reported as the fourth most common trigger (confirmed with author by PEN evidence analyst via personal communication). Alcohol was the10th most commonly named trigger and was identified by 27% (n=3695). According to the author, ‘foods’ were listed as triggers approximately 20% of the time (n not provided). Chocolate was specifically mentioned as the most common trigger within the ‘foods’ group, but no further information was provided. The author concluded that identifying and mitigating migraine triggers might help migraineurs (1). In addition to the risks of bias associated with self-reported, cross-sectional studies, the methods in this review were poorly reported, which made it difficult to assess the review’s quality.
2. In an effort to evaluate the evidence on migraine dietary triggers, authors of a good-quality critical review analyzed studies published between 1980 and 2010 (2). There were no age or gender restrictions, but case reports were excluded and studies needed to link a dietary factor specifically to migraines rather than a variety of headache types that included migraine. Of the 45 included studies, 33 were cross-sectional or case-control studies and 12 were experimental or prospective cohort studies. The study populations were highly varied and participants included children, adolescents and adults, males and females, and individuals living on every continent except Antarctica and in both urban and rural areas. The results for different dietary triggers are below:
* Fasting (n=18): The frequency with which fasting was reported as a migraine trigger ranged from 40% to 82% in the majority of studies, which made it the most significant dietary trigger. In addition to evaluations of trigger frequency, a case-control study found that migraineurs were significantly less likely than control subjects to eat meals on a regular schedule (*P*=0.046) and consume three meals/day (*P*=0.001). When hunger was induced experimentally in an RCT of people who reported hunger as a migraine trigger, there was a significant increase in both migraine occurrence and intensity (*P*<0.01).
* Alcohol (n=26): Alcohol was reported as a trigger with a frequency between 17% and 76%, although the evidence supporting it as a trigger is conflicted with some population studies finding that moderate intake of wine and alcohol decreased migraine prevalence, some finding they increased symptoms (especially with high intake), and one study finding no association. A small, non-blinded, experimental study of migraineurs who reported red wine as a trigger found that individuals who drank red wine were significantly more likely to have developed migraine symptoms than those who consumed a vodka drink of equal alcohol content. However, a prospective cohort study that tracked dietary intake for 90 days found no negative impact of alcohol on migraine attacks even though it was consumed on 7% to 10% of the days by 60% to 80% of participants.
* Chocolate (n=14): For the general population of migraineurs, chocolate had a triggering frequency that ranged from 0% to 6%, but frequencies increased in populations who believed chocolate was a trigger (19.2% to 22.5%). A prospective cohort study that tracked dietary intake for 90 days found no negative impact of chocolate on migraine attacks even though it was consumed on half of the study days by the majority of participants. Furthermore, a double-blinded RCT (n=63, 100% women) that controlled for diet found that participants were less likely to experience a migraine when they consumed a chocolate sample than when they consumed a carob sample.
* Caffeine (n=12): Four studies reported coffee as a trigger with a frequency between 6.4% and 14.5%, but two studies failed to identify it as a trigger altogether. Three population studies found an increased prevalence of migraines in adolescents and adults who consumed coffee or tea than in those who did not, but another population study found no association. Caffeine withdrawal, however, has been widely associated with headaches, and was identified as trigger by 22% of migraineurs with aura in a retrospective cohort study.
* Citrus Fruits & Vegetables (n=7): The evidence for citrus fruits and vegetables as precipitating factors for migraines is mixed with one population study finding no association between fruits and vegetables and migraines and another population study describing citrus fruit as a significant predictor of migraines (RR=1.80; 95% CI, 1.00-3.05; *P*=0.047). The frequency with which citrus fruits were described as migraine triggers ranged from 0% to 11.1%.
* Lipids (n=3): Among individuals who considered fatty or oily foods to be a migraine trigger, the frequency with which they precipitated migraines was 17% in one cross-sectional study. Additionally, in a case-control study migraineurs consumed more lipids in their diets than non-migraineurs and in an intervention study that limited fat intake in 54 individuals (78% female), migraine frequency, intensity and duration were significantly reduced from baseline (*P*<0.0001).
* Dehydration (n=4): Although a population study found no association between insufficient liquid intake and migraine symptoms, dehydration has been listed in the literature as a triggering factor with frequencies ranging between 31% and 91.4%, depending on the population. Additionally, a small RCT (n=18) found that an increased fluid intake of 1.5 L per day significantly decreased migraine duration and intensity.
* Ice Cream & Ice Water (n=7): In the literature, these foods triggered migraines with a frequency of 1.4% to 4.6% in adults and 55.4% in adolescents. One experimental study found that temperature-induced headaches were more likely among non-migraineurs, but two others found that direct exposure to ice cubes and ice water increased migraineurs’ susceptibilities to headaches.
* Dairy (n=12): Although a prospective cohort study using a 90 day food diary found no negative impact of dairy on migraines, cheese and milk have been listed as triggering factors with frequencies of 0% to 18.2% and 2.3% to 2.5%, respectively.
* Meat, Fish & Eggs (n=3): A population study reported that migraineurs consumed less fish than controls and another study reported that 4.1% of participants identified fish as a migraine trigger. Meat was listed as a trigger with a frequency of 3.6% and the combination of pork and dairy was listed 3% of the time. No association was found between egg consumption in migraineurs versus non-migraineurs in a case-control study, but eggs were reported as triggers by 2.0% to 7.4% of study participants.

The following foods (and their frequencies) were self-reported as triggers in ≤2 studies: monosodium glutamate (2.5% and 12.9%), aspartame (9%), sausage (6%), salami (4.5%), Chinese food (3.5%), soda, walnuts, and sugary foods (1.5% each), pizza (1%). Additionally, one small experimental study in children (n=39) found a decreased occurrence of migraines when a diet rich in fibre was consumed. The authors concluded, “Despite the vast literature, there are relatively few data on potential precipitating factors” and that “analyses involving population studies, prospective studies with and without interventions, and research investigating the interactions between various factors have only recently been emerging”. The evidence base was limited by the high number of cross-sectional studies that used self-report, the frequent use of convenience samples and wording differences that may account for variations in frequency.

1. A small, prospective cohort study of adult migraineurs (n=34, 97% female) used a six-week electronic diary completed twice daily to analyze the relationship between night time eating and migraine symptoms (3). Stress was controlled for using the validated Daily Stress Inventory. In the mornings, participants recorded whether they had eaten no food, a snack, a late dinner, or breakfast since their last entry. The exact timing of the food intake as well as the amount and type of food were not recorded and these were noted as limitations. In an analysis of diary days that followed a non-headache day, participants who had eaten a snack since their previous diary entry were 40% less likely to have experienced a headache (HR=0.6; 95% CI, 0.4 to 0.9; *P*=0.013) than those who had not eaten, but there was no significant effect for those who had eaten a late dinner (HR=0.79; 95% CI, 0.55 to 1.15; *P*=0.22) or early breakfast (HR=0.92; 95% CI, 0.65 to 1.47; *P*=0.98). The authors concluded that night time eating and headache symptoms are associated but that personal characteristics unmeasured in this study likely confound the relationship and more research is needed.
2. In a 2003 narrative review, authors evaluated experimental trials on the physiological response to ingestion of dietary biogenic amines such as tyramine (4). They identified 12 studies, six of which were from the same research group in the 1960s and 1970s that were not entirely separate trials. Hence, the review authors evaluated those six publications as one study with 45 subjects and reported on six additional published trials. In the majority of the studies, children and adults ingested capsules with 100-200 mg of tyramine or lactose (placebo) and reported migraine incidence by questionnaire in the 24 hours after ingestion of the capsule. In the results from the one research group, the rate of headaches with tyramine was markedly greater than with lactose (80% versus 8% of participants), but unfortunately most of these studies were not blinded. However, in four other double-blinded, placebo-controlled studies (described below), tyramine was not associated with migraine any more than the placebo.
	* Among 59 child migraineurs given either 100 mg of tyramine or lactose; 16/59 developed migraine after tyramine and 14/59 after placebo and among another 38 child migraineurs given the same; 9/38 developed migraine after tyramine and 15/38 after placebo (5).
	* Among 80 adult migraineurs given either 200 mg of tyramine or lactose; 20/80 developed migraine after tyramine and 23/80 after placebo (6).
	* Among 25 adult female migraineurs given either 125 mg of tyramine or lactose; there were nine headaches after tyramine and nine headaches after lactose-placebo (7).
	* Among three more groups of migraineurs given 125 mg of tyramine or lactose placebo; 19/27 developed headache (type of headache not described) after tyramine while 14/27 developed headache on placebo, 10/35 developed headache after tyramine and 12/35 on placebo, and another 2/13 after tyramine and 7/13 after placebo (8).
3. A narrative review reported the evidence for a relationship between monosodium glutamate (MSG) and migraine headache and concluded that there is no research evidence to support a relationship (9). Of the reports the authors could locate on the topic, one was advice from a headache clinic suggesting that MSG could trigger migraine and the other (written in Spanish) provided theory for a relationship but cited the first report as evidence of a relationship between MSG and migraine.
4. A 2002 safety review of aspartame reported that headache was the most common aspartame-associated adverse effect reported by the general population to the U.S. FDA (Food and Drug Administration) and CDC (Centers for Disease Control) (10). Additionally, in a survey of 171 migraineurs attending a headache clinic, 8.2% reported aspartame as a dietary trigger of their migraine attacks (11). In additional case reports, three female migraine sufferers (aged 26, 32 and 40 years) reported that chewing sugarless gum with aspartame triggered migraine attacks (12). It is not known if confounders such as the repetitive chewing action may have mediated this response. Two other case reports described significant worsening of migraine headache pain following ingestion of an aspartame-containing formulation of rizatriptan (a medication used to treat migraine) by a 14-year old male and a 36-year old female who regularly avoided aspartame because they felt it triggered their migraines (13). When taking the aspartame-containing formulation (they did not realize it contained aspartame), migraine pain increased in intensity instead of being alleviated. The amount of aspartame in the medication was 1/10th that of a typical aspartame packet.
5. In a small, double-blinded, crossover study 25 migraineurs who believed aspartame was a trigger for their migraines (therefore not representative of the migraineur population as a whole) were randomized to ingest aspartame (300 mg) or placebo capsules daily for four-week periods (14). A total of eight subjects withdrew from the study and six were removed from data analysis due to non-compliance, resulting in data analysis on only 11 (nine female, two male) of the 25 participants. Six of these migraineurs had statistically significantly greater frequency of migraine when on aspartame. The mean number of migraines per month was 1.72±1.42 (both groups combined) at baseline, 1.55±0.93 on the placebo, and 3.55±2.58 on aspartame. However, the statistics performed in this study have been criticized as inappropriate for a crossover design (10). Additionally, the success of the blinding was not described (if the migraineurs were able to taste the intensely sweet contents of the aspartame capsules, the blinding would have been lost) and the study might suffer from attrition bias, where the reasons for dropping out and/or noncompliance may have been relevant to the results.
6. A limited number of case reports have identified sucralose as a possible trigger for migraines (15-17). In one instance an individual who had experienced menstrual related migraines began experiencing increased frequency of migraines after changing sweeteners from aspartame to sucralose (15). Dietary trigger questionnaires revealed that sucralose had been used between 30 minutes to three hours prior to a migraine in nine of ten instances. Following a time of discontinued use, the individual experienced a recurrence of migraine after a blinded sucralose challenge. In another case report, an individual experienced a migraine after consumption of diet soda sweetened with sucralose (17). On repeated challenge, the individual experienced migraines only when consuming soda sweetened with sucralose. Critiques of these reports have cautioned against drawing case and effect inferences in light of potential confounding factors (18).
7. The Canadian Headache Society’s Guideline for Migraine Prophylaxis notes that “although much of the literature on migraine triggers and the effects of lifestyle factors on migraine lacks scientific rigour, lifestyle and trigger management remains an important aspect of migraine treatment” (19). They list skipping meals and excessive caffeine as factors that may increase migraine frequency and provide a worksheet to help identify triggers that includes 19 foods and beverages.

**Comments**

Attributing the onset of a migraine to dietary triggers is problematic because the connection is easily biased and the onset of a migraine may be related to other modifying variables or triggers that occur simultaneously (20). A problem with many of the experiments on food triggers is that subjects were often selected if they believed that the food or ingredient in question was a migraine trigger for them. This latter component of subject selection increases the likelihood of placebo or expectancy effects (2).

Little is known about the cause of migraines and as this condition can be debilitating, migraineurs may find it worthwhile to experiment with avoiding potential triggers and should not be dissuaded from doing so (2, 3, 19).

**Rationale**

A number of mechanisms have been proposed to be involved in the onset of a migraine. Specifically, depolarization of cortical neurons and sensitization of trigeminal nerve ganglia have been suggested to be involved (20). Vasoconstriction, vasodilation and vascular inflammation with involvement of neurotransmitters and serotonin receptors may also be involved. It has been suggested that dietary triggers may impact any of the above. Specifically, tyramine, tyrosine, aspartame and phenylalanine, monosodium glutamate (MSG), hydrolyzed vegetable protein (HVP) and hydrolyzed plant protein (HPP) are either neurotransmitter precursors or may modulate neurotransmitter activity. Tyramine, a biogenic amine, is normally metabolized by monoamine oxidase (MAO) and other enzymes in the gastrointestinal tract and liver before entering circulation. It is theorized, however, that migraine sufferers may lack these enzymes, which would result in tyramine entering the circulation and stimulating the release of norepinephrine and resultant vasoconstriction. Red wine, beer and cheese are implicated because of their tyramine content (20).

Another hypothesis as to how dietary triggers are involved in precipitating a migraine is an immune-mediated reaction through IgE and IgG antibodies (21). There is some evidence that migraineurs more frequently have antibodies against foods than non-migraineurs, and preliminary research in the form of a randomized, double-blinded, crossover trial where participants followed individualized provocation and elimination diets for six weeks found that the elimination diet significantly decreased the number of migraine days and attacks, but did not change attack severity or duration. Further research is needed in this area to elucidate possible mechanisms for migraine onset (21).

Other theories for purported dietary triggers include:

* Alcohol - suspected migraine triggers in various types of alcoholic beverages include sulphites, tyramine, histamine, which may increase nitric oxide release and stimulate vasodilation, and phenols or flavonoids, which may induce a release of serotonin from platelets (20).
* Chocolate - phenylethylamine (a biogenic amine also metabolized by MAO enzymes), theobromine, caffeine, and catechins are components of chocolate that have been theorized to play a role in migraine by changing cerebral blood flow and increasing release of norepinephrine (20).
* Citrus - the phenolic amines and octopamine in citrus content may modulate neurotransmitters (20).
* Processed meats - nitrates and nitrites are potential triggers via stimulation of the release of nitric oxide, a vasodilator (20).
* Fasting - One proposed mechanism is that fasting may be a trigger for migraine by affecting release of serotonin, norepinephrine, or stress hormones or because of caffeine withdrawal or hypoglycemia (20). Another theory is that fasting decreases the availability of glycogen-derived glucose, which may in turn create an excitatory-inhibitory imbalance that causes mass depolarization of neural networks (22).
* Fatty foods/high fat diet - it is theorized that because there is a significant rise in serum free fatty acids during migraine and because it is thought that high levels of serum free fatty acids will affect serotonin levels, platelet aggregability, or production of prostaglandin E and vasodilation; ingestion of fatty foods which also has these effects may be implicated as a dietary trigger of migraine (20, 23, 24).

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**Q2: Are there any nutrients or dietary supplements that decrease the frequency of migraines (migraine prophylaxis) or acutely treat them?**

Subcategory: Intervention
Last Updated: 2008-06-12
Keywords: prophylaxis magnesium feverfew Tanacetum parthenium L parthenolide riboflavin vitamin B2 butterbur petasites Petadolex omega-3 fatty acids gamma-linolenic acid GLA alpha-linolenic acid ALA niacin coenzyme Q10 soy isoflavones phytoestrogen menstrual migraine safety

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**Key Practice Point**

**Evidence Synthesis**

Results from evidence-based reviews suggest that oral magnesium supplementation may help prevent migraines. Dose of 600 mg/day of trimagnesium dicitrate for adults or 9 mg/kg/day of magnesium oxide divided into three times a day for children and adolescents were found to be effective in preventing migraines. Side effects are minimal and most commonly include gastrointestinal upset. {grade\_c}

A systematic review of four experimental studies on adult migraineurs in emergency settings found no evidence to support the use of intravenous magnesium sulfate as an acute treatment for migraine and, as a result, the Canadian Headache Society recommended against its use despite minimal adverse side effects (flushing). {grade\_c}

**Practice Guidance**

Published guidelines on migraine prophylaxis from the Canadian Headache Society, the American Headache Society, and the European Federation of Neurological Societies all support the magnesium supplementation to prevent migraines. Recommended doses for oral magnesium supplementation are 600 mg/day for adults and 9 mg/kg/day for children and adolescents. Such doses may help prevent migraine attacks but are well in excess of the UL described by some countries in their Dietary Reference Values (350 mg/day of supplemental magnesium for Australia, Canada, and New Zealand) and should be used under medical supervision. Due to the debilitating effects of migraine attacks and the limited adverse effects of magnesium supplementation among patients with healthy renal function, magnesium supplementation may be an option for migraineurs to consider, but only after consultation with their doctor. Self-medication with such high doses is not recommended.

**Grade of Evidence: C**

**Evidence**

1. An evidence-based review of studies published between 1990 and 2015 examined the relationship between adult migraineurs (≥18 years) and magnesium (1). Of the 20 included studies, 16 observational studies assessed magnesium status in blood, saliva, hair and/or tissue samples and generally found, regardless of measurement technique, that migraineurs had significantly lower magnesium levels than non-migraineurs. The remaining four studies were placebo-controlled, double-blinded RCTs (n=35 to 81; study duration of three to four months; magnesium dose of 243 to 600 mg/day). Three studies found significant decreases in migraine frequency for both the experimental and the control groups. The study with the largest sample size, however, found a significant decrease in migraine frequency and duration in the group that was supplemented with 600 mg/day of trimagnesium dicitrate (*P*=0.03) and an inverse relationship between initial serum magnesium and migraine attack frequency. Two studies noted adverse gastrointestinal events in the experimental groups. None of the studies controlled for dietary magnesium (which, despite randomization, may have been affected by the small sample size) or used magnesium status as an inclusion or exclusion criteria. The authors concluded there is strong evidence supporting an association between magnesium status and migraine, but limited evidence that supports oral supplementation as a migraine prophylaxis (1). Significant decreases in migraine frequency in the control groups suggest a strong placebo effect in this population.
2. An evidence-based review summarized the literature published before March 2013 and provided recommendations on the use of nutraceuticals in preventing migraines in children and adolescents ≤18 years of age (2). The review authors found a placebo-controlled, double blinded RCT (n=118) with a four-month treatment period of 9 mg of magnesium oxide/kg/day (divided tid) found that both groups experienced fewer headache days and there was no significant difference between groups (*P*=0.088). A nonblinded, uncontrolled study in which children with periodic syndromes (n=40, including 25 whose primary presentation was migraines) were given 122 to 266 mg of elemental magnesium found that 72.5% of participants reduced their migraine frequency to ≤33% of baseline within a month of treatment. The studies noted important adverse effects that were more significant in the experimental group (soft stools/diarrhea). Using the GRADE system of evidence analysis the authors weakly recommended the use of magnesium to prevent pediatric migraines based on low quality evidence.
3. A comparison of migraine-related clinical practice guidelines published between 2008 and 2012 found that all guidelines agreed that magnesium could be used as a prophylaxis, but had separate views on how strongly magnesium was recommended (3). The American Headache Society/American Academy of Neurology Guidelines concluded that evidence for magnesium was Level B: “probably effective” and “should be considered for patients requiring migraine prophylaxis”. In the Canadian Headache Society Guidelines, however, 600 mg of magnesium citrate was strongly recommended based on low quality evidence and minimal side effects. Finally, the European Federation of Neurological Societies Guidelines categorized magnesium as a ‘drug of third choice’ (3). Discrepancies in how strongly magnesium was recommended appeared to arise from differences in study quality assessment.
4. A systematic review on the efficacy of migraine treatments in emergency settings in adult populations included 44 double-blinded RCTs published before March 2013, four of which examined intravenously administered magnesium sulfate (4). Using the GRADE system of evidence analysis, one good and one poor quality trial found no evidence that magnesium sulfate was superior to a placebo in treating migraines. A fair quality trial found some improvement in secondary outcomes and subgroup differences and a small, poor quality trial found magnesium sulfate was effective. The most common side effect was flushing, a temporary reddening of the neck and face. The authors weakly recommended against intravenous magnesium sulfate use on the basis of moderate quality evidence.

**Comments**

Dietary reference intakes for magnesium vary between countries and the International Dietary Reference Values Collection should be consulted for the most up-to-date information. Of note, the UL for supplemental magnesium in Canada, Australia, and New Zealand is 350 mg/day based on risk of diarrhea. The U.K., however, has not set a safe upper level due to insufficient evidence (5).

A simple, accurate, and inexpensive way to assess magnesium status does not exist (1). The most common assessment is serum magnesium but this test has poor sensitivity to detect deficiency because serum magnesium is buffered by skeletal magnesium. Magnesium loading, whereby magnesium levels (serum and/or urine) are determined before and after large magnesium doses, is considered more accurate, but is also time and labour intensive (1). Because of limitations in assessing magnesium status, it is not clear from the literature whether magnesium status moderates the relationship between supplementation and migraine prevention (2).

**Rationale**

Magnesium has a role in many of the physiological processes that have been theorized to be involved in migraine onset including neuroinflammation, calcium homeostasis, the creation of glutamate and nitric oxide, altered serotonin receptor activity, and altered mitochondrial metabolism, the latter of which has been associated with aura in migraine (1). As several studies have noted that migraine sufferers tend to have suboptimal magnesium levels, supplementation has been suggested as a way to decrease one’s susceptibility to migraine attacks.

**References**

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**Key Practice Point**

**Evidence Synthesis**

Evidence from RCTs suggest that riboflavin doses of 50 to 200 mg per day are not more effective than a placebo at reducing migraine frequency in children and adolescents. {grade\_c}

In adults, the evidence for riboflavin as a migraine prophylaxis is more convincing. Consistent results from a well-controlled RCT and several lower-quality trials suggest 400 mg of riboflavin can reduce migraine frequency. These results are also reflected in the clinical practice guidelines for both Canada and the United States. {grade\_b}

A conclusion regarding the use of riboflavin as an acute migraine treatment in either children or adults is not possible at this time due to the lack of available evidence. {grade\_d}

**Practice Guidance**

Published guidelines on migraine prophylaxis from the Canadian Headache Society, the American Headache Society, and the European Federation of Neurological Societies all support riboflavin supplementation in adults to prevent migraines. The recommended dose is 400 mg/day to help decrease migraine attack frequency. Riboflavin supplementation in children and adolescents, however, is not supported by evidence.

Even though a UL has not been established for riboflavin, medication with such high doses should only be considered and undertaken in consultation with one’s doctor because the long-term health effects of such high doses are not known (i.e. longer than four months of treatment).

**Grades of Evidence: B, C & D**

**Evidence**

1. An evidence-based review summarized the literature published before March 2013 and provided recommendations on the use of nutraceuticals in preventing migraines in children and adolescents ≤18 years of age (1). There were three small studies that evaluated the use of riboflavin as a migraine prophylaxis. The first was a nonblinded, uncontrolled study where participants (n=41) given 200 or 400 mg riboflavin daily over a period of six months experienced a significant reduction in headache frequency from baseline at three and four months, but not six months. The usefulness of these results is complicated by the study population, which included children with tension-type headaches and benign paroxysmal vertigo in addition to those with migraine. The second study was a double-blinded RCT (n=48) in which there was no significant difference in the percentage of children whose migraine attacks had been reduced by at least 50% in the third month of treatment between those receiving 200 mg riboflavin and those receiving a placebo. The final study was a double-blinded crossover RCT (n=42). Again, there was no significant difference between 50 mg of riboflavin daily and the placebo in terms of the mean migraine frequency over four months, but the treatment dose may have been too low. Using the GRADE system of evidence analysis, the authors made a weak recommendation based on low quality evidence against the use of riboflavin as a migraine prophylaxis in pediatric populations.
2. The aforementioned evidence-based review also summarized the literature on the use of riboflavin in preventing migraines in adults, but did not provide a final recommendation (1). The best available research, a double-blinded, placebo-controlled RCT (n=55), found that 400 mg of riboflavin daily resulted in significantly fewer migraines over four months than the placebo (*P*=0.0001). A second double-blinded RCT (n=49) found no significant difference between groups in the number of participants who had reduced their migraine frequency by at least 50% in the third month of treatment, but these results are limited because the intervention group received a mix of riboflavin (400 mg), magnesium (300 mg) and feverfew (100 mg), and the control group received 25 mg of riboflavin. Additionally, there have been four nonblinded, uncontrolled trials (n=23 to 64), each of which provided a riboflavin dose of 400 mg and found an improvement in migraine frequency or severity.
3. A comparison of migraine-related clinical practice guidelines published between 2008 and 2012 found that all guidelines agreed that riboflavin could be used as a prophylaxis, but had separate views on how strongly it was recommended (2). The American Headache Society/American Academy of Neurology Guidelines concluded that evidence for riboflavin, at a dose of 400 mg/day was Level B: “probably effective” and “should be considered for patients requiring migraine prophylaxis”. In the Canadian Headache Society Guidelines, 400 mg of riboflavin was strongly recommended based on low quality evidence of benefit and minimal side effects. Finally, the European Federation of Neurological Societies Guidelines categorized riboflavin as a ‘drug of third choice’ (2). Discrepancies in how strongly magnesium was recommended appeared to arise from differences in study quality assessment.

**Comments**

Dietary reference intakes for riboflavin vary between countries and the International Dietary Reference Values Collection should be consulted for the most up-to-date information. Of note, an upper limit for riboflavin has not been set due to insufficient evidence of adverse effects at high doses. The most common side effect is a yellow discolouration in urine (3).

Riboflavin has a short half-life of about one hour and therefore supplementation using smaller doses throughout the day is theorized to be more effective than a single large dose, though this remains to be tested in the literature (1).

**Rationale**

The rationale behind the use of riboflavin in migraine prophylaxis is due to its role as a component of flavin mononucleotide (FMN), which is involved in electron transport in the Krebs cycle (oxidative phosphorylation) and is essential in the production of mitochondrial energy (1). Studies have shown that migraineurs have decreased mitochondrial energy and it has therefore been theorized that riboflavin supplementation may help prevent migraine.

**References**

1. Orr SL, Venkateswaran S. Nutraceuticals in the prophylaxis of pediatric migraine: Evidence-based review and recommendations. Cephalagia. 2014 Jan 17;34(8):568-83. Abstract available from: <http://www.ncbi.nlm.nih.gov/pubmed/24443395>
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3. Expert Group on Vitamins and Minerals, Committee on Toxicity. Safe upper levels for vitamins and minerals. 2003. Available from: <http://cot.food.gov.uk/sites/default/files/vitmin2003.pdf>

**Key Practice Point**

**Evidence Synthesis**

A systematic review of RCTs showed that feverfew (*Tanacetum parthenium L*.) was mildly effective in preventing migraines (a decrease of 0.6 migraines per month), though there was heterogeneity among studies and some inconsistency in the results. Therefore it cannot be concluded with confidence that feverfew is an effective migraine prophylaxis. {grade\_b}

A small RCT indicated that feverfew and ginger extract taken sublingually at the onset of a migraine may be an effective acute migraine treatment. {grade\_c}

Multiple RCTs and clinical practice guidelines have concluded that feverfew is not associated with significant adverse effects and is safe for use in most populations. The most commonly noted side effect is gastrointestinal upset. {grade\_a}

**Practice Guidance**
Feverfew may be helpful in preventing and treating migraine attacks and has been recommended by American and European clinical practice guidelines as a migraine prophylaxis, but not by Canadian guidelines. Although the Canadian Neurological Society acknowledged there is no safety risk observed from the literature, they felt the evidence suggested feverfew offered no advantage over a placebo.

At this time there is insufficient information to recommend a specific dose, though 6.25 mg of a CO2-extract feverfew tid decreased migraine frequency. Dose recommendations are further complicated by variations in commercial feverfew processing methods and evidence of incorrectly identified amounts of the active ingredient, parthenolide, on product labels in Canada.

Feverfew has not been shown to have significant adverse effects in the general population but is not recommended for pregnant women or anyone who is allergic to plants in the *Asteraceae* family. Additionally, anyone who is breastfeeding or taking blood-thinner medication should consult a physician prior to supplementation.

**Grades of Evidence: A, B, C**

**Evidence**

1. In a Cochrane review on the efficacy and safety of feverfew for migraine prevention, the authors identified six double-blinded, placebo-controlled RCTs (n=561) published before January 2015 (1). There was a wide range in sample size (n=17 to 218), participant age (9 to 72 years) and study duration (2 to 8 months). Half of the studies used a crossover design and half used parallel groups; four studies used feverfew as a treatment and two examined the effects of feverfew withdrawal. A meta-analysis could not be conducted due study heterogeneity. Feverfew had a positive effect in four studies, three of which had small sample sizes. The fourth, however, was a large (n=218), methodologically sound study where participants randomized to receive 6.25 mg of a CO2-extract feverfew tid experienced a significant reduction in the number of monthly migraine attacks over those taking a placebo (1.9 migraines/month versus 1.3). However, there were no differences in attack intensity or duration. Feverfew had no effect in two well-controlled studies, one of which tested 143 mg/day of an alcoholic feverfew extract for two months and the other of which used 100 mg/day of powdered, dried feverfew for three months. An analysis of adverse events found no significant differences between those receiving feverfew and the placebo, with the most common complaints being gastrointestinal upset and mouth ulcers. Although the studies were well controlled and methodologically sound, the small sample size of all but one study cause the authors concluded “there is low quality evidence that feverfew is effective in migraine prevention”.
2. Feverfew has also been tested in combination with other alternative migraine treatments. In a double-blinded RCT of 59 migraineurs (76.6% female, 12 to 60 years), participants used either a liquid, sublingual feverfew and ginger extract or a placebo to treat migraine attacks in their early stages over a one-month period (2). Two-hours after treatment, those in the intervention group had a significantly lower pain four-point scale than those in the control group (-0.24 versus -0.04, *P*=0.006). Additionally, in the intervention group 63.7% experienced no or mild pain two hours after treatment compared with only 38.6% in the control group (*P*=0.003). No significant adverse effects were detected in the group using feverfew. The authors concluded that feverfew and ginger was an effective, acute treatment for migraines. The study’s statistical approach drew criticism because it assumed each migraine attack was independent when, in reality, one participant could experience multiple attacks during the study period (3). Therefore, the results of the study were reanalyzed using a repeated-measures analysis and the authors concluded, “the efficacy of sublingual feverfew/ginger (LipiGesic M) appears robust”.
3. In a double-blinded, placebo-controlled trial 52 adult migraine sufferers completed a four-week baseline run-in period and then were randomized to receive a supplement delivering 400 mg of riboflavin, 300 mg of magnesium and 100 mg of feverfew or a placebo (containing 25 mg of riboflavin) daily for three months for migraine prevention (4). Data analysis was performed when 49 patients had completed the trial. The primary outcome measure of a 50% reduction in migraine frequency from baseline to month three was achieved by a similar number of patients in the placebo and treatment groups, 44% and 42% respectively. It is important to note that both groups improved by the third month compared to baseline (a decrease in approximate mean migraine attacks per month from five to three) indicating a powerful placebo effect in this study.
4. A comparison of migraine-related clinical practice guidelines published between 2008 and 2012 found divergence in feverfew recommendations (5). The American Headache Society/American Academy of Neurology Guidelines concluded that evidence for feverfew was Level B: “probably effective” and “should be considered for patients requiring migraine prophylaxis”. In the Canadian Headache Society Guidelines, however, feverfew was listed as “do not use” based on one moderate quality and one poor quality study that showed no effect, two poor quality studies that showed a positive effect and clinical experience. No safety risk was observed in the literature. Finally, the European Federation of Neurological Societies Guidelines categorized feverfew as a ‘drug of third choice’ (5). Discrepancies in guideline recommendations appeared to arise from differences in primary study quality assessment.

**Comments**

Feverfew is a plant in the *Asteraceae* family and its leaves have been used historically to treat a variety of ailments including fever (1). Commercially it is available fresh, dried and powdered or as an alcoholic or CO­­2 extract.

A laboratory analysis of approximately 30 different commercially available feverfew products (capsules, tablets and tinctures) from the Canadian marketplace discovered significant variability in parthenolide content (6). Parthenolide is considered the primary active constituent of feverfew and was often found to vary significantly from product claims. While some products contained 100% of that declared, others had parthenolide contents that ranged from 8% to 446% of product claims. The authors noted that the active constituents in feverfew plant leaves (the main plant constituent used in supplements) vary naturally as a function of growing and harvesting conditions and from location to location and year to year. However, they also noted that it is the responsibility of the manufacturer to take steps to standardize their products.

Health Canada's monograph on feverfew indicates companies should include on feverfew product labels the recommendation to consult a health care practitioner if taking blood thinners, if breastfeeding or if symptoms persist or worsen. The monograph also indicated that feverfew should not be used if one is pregnant or allergic to plants of the Asteraceae/Compositae/Daisy family (7).

**Rationale**

It has been suggested that feverfew, which contains parthenolide, may inhibit production of prostaglandins, mediate vasoconstriction and vasodilation, and/or decrease serotonin release from platelets (1).

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**Key Practice Point**

**Evidence Synthesis**

Data from case reports (based on four adult migraineurs in total) suggests that oral intakes of 300-500 mg of niacin taken at the onset of symptoms may decrease migraine pain and that 375 mg/day taken prophylactically twice daily may decrease the frequency of attack. However, there is no clinical research to support this. {grade\_d}

**Practice Guidance**

Self-medication with such high doses of niacin (10-15 times the UL in Australia, New Zealand and Canada) is not recommended unless otherwise directed by a physician.

**Grade of Evidence: D**

**Evidence**

1. In a 2005 systematic review, authors reviewed literature published before February 2004 on the efficacy of niacin as an acute treatment for headaches, including migraine and tension-type headaches (1). Nine articles met inclusion criteria, five focused on migraine and all consisted of case series and case reports. No controlled trials were found. Two case series (n=36) involved intramuscular or intravenous injection of niacin and were found to be effective for most patients. Unfortunately, whether "effective" meant decreased frequency, duration and/or pain severity was not described. In two case reports, three patients took niacin orally (300-500 mg) at onset of symptoms and had their migraine pain alleviated. Another patient took 375 mg of niacin twice daily for one month followed by once daily for two months and reported a notable reduction in frequency of migraine attack. From their review, the authors concluded that the literature on oral niacin intakes for migraine is extremely limited, uncontrolled and confounded and that more research is warranted.

**Comments**

The UL for niacin in Australia, New Zealand and Canada is a chronic intake of 35 mg/day and is based on symptoms collectively referred to as the "niacin flush"; redness, burning, itching and tingling of the face, neck, and arms (2, 3). The U.K. has not established a safe upper level for either nicotinic acid or nicotinamide due to insufficient evidence (4). For more information, consult the International Dietary Reference Values Collection.

**Rationale**

Theories as to how niacin could potentially prevent or alleviate migraine are based upon the vasodilatory effects of niacin and its role in mitochondrial energy metabolism, a defect in the latter of which has been proposed to play a role in migraine (1). It has also been proposed that niacin may increase serotonin levels indirectly by facilitating conversion of tryptophan to serotonin by decreasing tryptophan's conversion to kynurenines (5).

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**Key Practice Point**

**Evidence Synthesis**

In children and adolescents, there is conflicting evidence in support of coenzyme Q10 as a migraine prophylaxis with a single RCT with a high dropout rate finding no difference between 100 mg/day supplementation and a placebo, and an open-label study showing reduced headache days when coenzyme Q10-deficient participants were supplemented with 1-3 mg/kg of body weight daily. {grade\_c}

A small RCT and a lower quality trial found supplementation with 300 mg/day of coenzyme Q10 (CoQ10) decreased the frequency of migraine attacks in adults. {grade\_c}

A conclusion regarding the use of coenzyme Q10 as an acute migraine treatment is not possible at this time due to the lack of available evidence. {grade\_d}

**Practice Guidance**

While there is some research that indicates coenzyme Q10 supplementation may help prevent migraines in children, adolescents and adults, overall there is insufficient evidence to conclude with confidence that coenzyme Q10 is an effective migraine prophylactic. However, because of the lack of side effects reported with its use, supplementation with coenzyme Q10 is something migraineurs may wish to consider in consultation with their doctor.

Clinical practice guidelines from Canada, United States, and Europe agree that coenzyme Q10 may be tried as a migraine prophylaxis at a dose of 100 mg tid.

**Grade of Evidence: C & D**

**Evidence**

1. An evidence-based review summarized the literature published before March 2013 and provided recommendations on the use of nutraceuticals in preventing migraines in children and adolescents ≤18 years of age (1). There were two studies that evaluated the use of coenzyme Q10 as a migraine prophylaxis. The first was a non-blinded, uncontrolled study (n=252), where participants with migraine and an identified coenzyme Q10 deficiency were given a 1-3 mg/kg body weight supplement daily. After an average of three months of treatment, participants experienced significantly fewer headache days per month. The second study was a double-blinded, placebo-controlled, crossover RCT (n=120). Participants experienced significant decreases in migraine frequency after four months of treatment when receiving both 100 mg coenzyme Q10 and the placebo, with no difference between groups. This study was limited by a high dropout rate (58%), which limited statistical power. Using the GRADE system of evidence analysis, the authors made a weak recommendation based on low quality evidence for the use of coenzyme Q10 as a migraine prophylaxis in pediatric populations.
2. The aforementioned evidence-based review also summarized the literature on the use of coenzyme Q10 in preventing migraines in adults, but did not provide a final recommendation (1). The best available research, a double-blinded, placebo-controlled RCT (n=50), found that 100 mg of coenzyme Q10 tid resulted in fewer migraines over four months than the placebo (*P*=0.05). A second, non-blinded, uncontrolled study (n=32) found that 61.3% of participants supplemented with 150 mg of coenzyme Q10 experienced at least a 50% reduction in migraine frequency over the four-month treatment period. Neither study assessed coenzyme Q10 levels at baseline and only a single adverse event (cutaneous allergy) was noted.
3. A comparison of migraine-related clinical practice guidelines published between 2008 and 2012 found agreement in the coenzyme Q10 prophylaxis recommendations, with all three guidelines acknowledging the low quality of available evidence (2). The American Headache Society/American Academy of Neurology Guidelines concluded that evidence for coenzyme Q10, at a dose of 100 mg/day tid was Level C: “possibly effective” and “may be considered for patients requiring migraine prophylaxis”. In the Canadian Headache Society Guidelines, the same dose was strongly recommended based on low quality evidence of benefit and minimal side effects. Finally, the European Federation of Neurological Societies Guidelines categorized coenzyme Q10 as a ‘drug of third choice’ (2).

**Rationale**

It has been proposed that mitochondrial dysfunction may be involved in the etiology of migraine and it has therefore been hypothesized that supplementation with coenzyme Q10 (CoQ10) may help prevent migraine due to its role as an electron carrier in the electron transport chain (1).

**References**

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**Key Practice Point**

**Evidence Synthesis**

Based on evidence from two RCTs and the American clinical practice guidelines, supplementation with omega-3 or gamma-linolenic acid is not supported as an effective way of preventing migraine in adolescents or adults. {grade\_c}

A conclusion regarding the use of omega-3 or gamma-linolenic acid as an acute migraine treatment is not possible at this time due to the lack of available evidence. {grade\_d}

**Practice Guidance**

Supplementation with omega-3 or gamma-linolenic acid is not recommended as a migraine prophylaxis or treatment at this time and is only distantly related to current theories of migraine precipitation. However, due to the limited amount of published research in this area, more well-designed, controlled trials may be warranted.

**Grade of Evidence: C & D**

**Evidence**

1. An evidence-based review summarized the literature published before March 2013 and provided recommendations on the use of nutraceuticals in preventing migraines in children and adolescents ≤18 years of age (1). A single, double-blinded, crossover, RCT in adolescents (n=27, 12- to 21-years-old) provided 1 g capsules of omega-3 fatty acids bid for two months, followed by a month washout period and then two months of 1 g capsules of olive oil bid. Both the treatment and the placebo groups experienced a significant reduction in migraine pain and frequency, with no difference between groups. The study authors concluded that the olive oil may not have been a true placebo and the unsaturated fatty acids could have also been helpful in preventing migraine. Using the GRADE system of evidence analysis, the authors made a strong recommendation based on low quality evidence against the use of omega-3 fatty acids as a migraine prophylaxis in pediatric populations.
2. The aforementioned evidence-based review also summarized the literature on the use of omega-3 fatty acids in preventing migraines in adults, but did not provide a final recommendation (1). The best available evidence, a double-blinded RCT (n=196), found no difference in the mean number of migraine attacks over the last four weeks of a four month treatment period between those receiving a 6 g omega-3 supplement daily and those receiving a placebo. A second, non-blinded, uncontrolled trial that coupled omega-3 and gamma-linolenic fatty acid supplementation with vitamin supplementation (niacin, vitamin B6, vitamin E, and β-carotene) and lifestyle interventions found that 86% of participants experienced a significant reduction in yearly migraine attack frequency after 6 months of treatment. In addition to the weak design of this trial, the multi-faceted intervention makes it impossible to specifically attribute any positive migraine prophylaxis effect to fatty acid supplementation.
3. In a comparison of migraine-related clinical practice guidelines published between 2008 and 2012, the authors found only one guideline that assessed the evidence for omega-3 fatty acids (2). The American Headache Society/American Academy of Neurology Guidelines concluded that evidence for omega-3 supplementation was Level U (analogous to PEN evidence grade D): “conflicting or inadequate evidence” and that there was “insufficient evidence to support of refute use for migraine prophylaxis”.

**Rationale**

An “outdated and overly simplistic” theory hypothesized that migraine auras were caused by constriction of key blood vessels in the brain (1). Consequently, omega-3 fatty acids, which have well-established anti-vasopressor properties, were suggested as a migraine aura prophylaxis. They have also been theorized to play a role in preventing inflammation in the brain due to their anti-inflammatory properties (1).

**References**

1. Orr SL, Venkateswaran S. Nutraceuticals in the prophylaxis of pediatric migraine: Evidence-based review and recommendations. Cephalagia. 2014 Jan 17;34(8):568-83. Abstract available from: <http://www.ncbi.nlm.nih.gov/pubmed/24443395>
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**Key Practice Point**

**Evidence Synthesis**

Evidence from a small RCT and a low-quality pilot study suggest that phytoestrogen supplementation may decrease the frequency of migraines, including menstrual migraines. {grade\_c}

A conclusion regarding the use of phytoestrogens as an acute migraine treatment is not possible at this time due to the lack of available evidence. {grade\_d}

**Practice Guidance**

Two small studies have suggested that supplementation with a combination of three phytoestrogen compounds (soy isoflavones, dong quoi and black cohosh) or two isoflavones (genistein and diadzein) may decrease menstrual migraine frequency. More research is needed to conclude with confidence that such supplementation is safe and effective for acute and prophylactic migraine treatment.

**Grade of Evidence: C & D**

**Evidence**

1. A systematic review of articles published between 1990 and August 2014 evaluated the effectiveness of different compounds in both preventing and treating menstrual migraines (1). Two of the included studies assessed the use of phytoestrogens as a migraine prophylaxis. The best available evidence was a double-blinded, placebo-controlled study; investigators randomized 49 premenopausal menstrual and non-menstrual migraineurs to receive a placebo or phytoestrogen supplement (60 mg soy isoflavones, 100 mg dong quoi and 50 mg black cohosh daily) for 24 weeks while keeping daily diaries. Between weeks nine to 24, the mean number of menstrual migraine attacks was significantly less among the phytoestrogen group compared to the placebo group (4.7±1.8 versus 10.3±2.4). A second, non-blinded, uncontrolled trial (n=11) found that the average number of migraines was significantly decreased from baseline (*P*<0.005)after supplementation with 56 mg of genistein and 20 mg of diadzein (isoflavones) daily for three months.

**Rationale**

In adults, migraine occurs more frequently in women and fluctuations in the hormones estrogen and progestin have been associated with migraine (2). Migraine has been reported to be more common around the time of menses among some women. This is commonly referred to as "menstrual migraine". It is theorized that soy isoflavones (genistein and daidzein) and other phytoestrogens such dong quoi and black cohosh may modulate a proposed estrogen effect on migraine incidence (2).

**References**

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**Key Practice Point**

**Evidence Synthesis**

Limited evidence from a small RCT and a lower quality trial suggest that butterbur (*Petasites hybridus*) extract, in the form of Petadolex®, is well tolerated and may be an effective prophylaxis for migraines in children. {grade\_c}

For adults, there is fair evidence from two well-controlled RCTs suggest that 75 mg bid of Petadolex® is effective at reducing migraine frequency. {grade\_b}

A conclusion regarding the use of butterbur extract as an acute migraine treatment is not possible at this time due to the lack of available evidence and long-term use safety issues?. {grade\_d}

**Practice Guidance**

There is some controlled research that supports 100-150 mg/day of butterbur root extract as a way of decreasing the frequency of migraine attack, particularly in adults, and butterbur has been suggested as a migraine prophylaxis by Canadian, American and European clinical practice guidelines.

However, safety concerns have been raised regarding the use of butterbur root extract because of naturally existing plant compounds called pyrrolizidine alkaloids that are toxic to the liver and need to be removed during supplement manufacture and processing. Petadolex® is the name of a purified butterbur extract that has been tested in research studies and is safe for short-term use. Given the aforementioned safety concerns, caution is necessary, especially with regards to children.

Few side effects have been reported in human trials using butterbur extract for migraine relief, including gas, nausea, stomach pain, rash and dislike of the supplement’s smell.

**Grades of Evidence: B, C & D**

**Evidence**

1. An evidence-based review summarized the literature published before March 2013 and provided recommendations on the use of nutraceuticals in preventing migraines in children and adolescents ≤18 years of age (1). There were two studies that evaluated the use of butterbur extract as a migraine prophylaxis. The first was a non-blinded, uncontrolled study (n=108), where participants with migraine were given 50 to 150 mg daily of Petadolex® (a standardized butterbur extract purified of toxins). After four months of treatment, 77.2% of participants had reduced migraine frequency by at least 50%. The second study was a three-armed RCT (n=63) that compared the effect of Petadolex® (50 mg to 150 mg bid based on age and treatment response) to music therapy and to a placebo over a treatment period of 8 weeks. Both the Petadolex® and placebo groups experienced a significant decrease in migraine frequency, with no difference between them. There were no significant differences in adverse effects between the Petadolex® and placebo groups; the most common complaints were gastrointestinal upset and cutaneous symptoms. Using the GRADE system of evidence analysis, the authors made a weak recommendation based on low quality evidence for the use of butterbur extract (in the form of Petadolex®) as a migraine prophylaxis in pediatric populations.
2. The aforementioned evidence-based review also summarized the literature on the use of butterbur extract in preventing migraines in adults, but did not provide a final recommendation (1). The best available research, a three-armed, double-blinded, RCT (n=245), found that the group that received 75 mg of Petadolex® bid reduced their migraine frequency by 45% over the four month treatment period. This reduction was significant when compared to the groups that received 50 mg bid (*P*=0.04) and the placebo (*P=*0.005). A second double-blinded RCT (n=60) also found that participants who received 50 mg of Petadolex® bid experienced a significant decrease in migraine attack frequency over three months (3.3±1.5 attacks at baseline to 1.7±0.9) when compared to those who received a placebo (*P*<0.05). In both studies, the Petadolex® had few adverse effects (minor gastrointestinal upset).
3. A comparison of migraine-related clinical practice guidelines published between 2008 and 2012 found that all guidelines agreed that butterbur extract could be used as a prophylaxis, but had separate views on how strongly it was recommended (2). The American Headache Society/American Academy of Neurology Guidelines concluded that evidence for butterbur, at a dose of 50 to 75 mg bid was Level A: “established as effective” and “should be offered to patients requiring migraine prophylaxis”. In the Canadian Headache Society Guidelines, 75 mg bid of butterbur was strongly recommended based on moderate quality evidence of benefit and minimal side effects. Finally, the European Federation of Neurological Societies Guidelines categorized butterbur as a ‘drug of second choice’ (2). Discrepancies in how strongly butterbur extract was recommended appeared to arise from differences in study quality assessment.

**Comments**

Butterbur (*Petasites hybridus*) is a member of the *Asteraceae* family with a long history of use in medicine (1). Human trials using butterbur extract for migraine relief have reported few side effects with gas, rash, and dislike of the supplement’s smell reported most frequently (3). Based on data from adverse event reports, nausea, gas and stomach pain were most frequently reported. The authors concluded that, overall, butterbur is safe for humans, but cautions that butterbur naturally contains hepatotoxic pyrrolizidine alkaloids that need to be removed upon processing and manufacturing (3).

The primary form of butterbur root extract used in trials was Petadolex®, which has been processed to remove the pyrrolizidine alkaloids. In Germany, where some of the research was conducted, Petadolex® is regulated as a drug, while in the US it is regulated as an herbal preparation (3). Petadolex® is available in the Canadian marketplace and has a license from Health Canada's Natural Health Product Directorate (4). However, the long-term safety of this product has not been definitively established.

**Rationale**

The mechanism of action of butterbur extract is not known, although it has been suggested that it may have anti-inflammatory or vasodilatatory properties (1).

**References**

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4. Health Canada. Search Licensed Natural Health Products. [cited 2015 4 Sept]. Available from: <http://webprod5.hc-sc.gc.ca/lnhpd-bdpsnh/index-eng.jsp>

**Key Practice Point**

**Evidence Synthesis**

From very small, non-blinded, uncontrolled trials where ginkgolide B was investigated in combination with other nutraceuticals, the supplement was shown to decrease migraine attack frequency in children and adolescents without aura and to decrease migraine attach frequency and aura duration in adults with aura. {grade\_c}

A ginkgolide B compound combined with other nutraceuticals was also found to be an effective treatment in adults with migraines associated with aura in a single, low quality, uncontrolled trial. {grade\_d}

**Practice Guidance**

Although there are few adverse effects associated with ginkgolide B, the quality of the research supporting its use is limited and of poor quality. Until more research is available, migraineurs wishing to experiment with ginkgolide B should carefully weigh the cost of the supplement against possible benefits in conjunction with their healthcare providers.

**Grade of Evidence: C & D**

**Evidence**

1. An evidence-based review summarized the literature published before March 2013 and provided recommendations on the use of nutraceuticals in preventing migraines in children and adolescents ≤18 years of age (1). There were three trials, all non-blinded and uncontrolled, that evaluated the use of ginkgolide B as a migraine prophylaxis in individuals with migraine without aura. All trials provided the ginkgolide B as part of a compound that also included coenzyme Q10, riboflavin, and magnesium. In the first trial (n=24), mean monthly migraine frequency decreased significantly over the three month treatment period from 7.4±5 attacks at baseline to 2.2±2.8 attacks (*P*=0.0015). Likewise, in the second trial (n=119), attacks decreased from 9.71±4.33 to 4.53±3.96 (*P*<0.001) over three months. In the third trial (n=374), mean monthly attack frequency decreased significantly from 9.13±2.84 to 1.73±1.23 over six months (*P*-value not provided), which was a significantly greater reduction than a second group that received a compound that included tryptophan, niacin and vitamin B6. The low-quality study designs and the combination of ginkgolide B with other nutraceuticals led review authors to weakly recommend against the use of ginkgolide B in pediatric populations based on low quality evidence.
2. A small non-blinded, uncontrolled trial evaluated the use of ginkgolide B as a migraine prophylaxis in adult migraineurs with aura (n=45, 76% female) (2). After a two-month run-in period, participants were given Migrasoll® capsules (combination of ginkgolide B, coenzyme Q10 and riboflavin) bid for four months. Over the course of the study migraine attack frequency and aura duration decreased significantly (*P*<0.0001), and no adverse effects were reported. The authors concluded that Migrasoll® was safe and effective in both preventing migraine attacks and reducing aura symptoms, but that these results need to be confirmed by larger, better controlled studies (2). Without a control group, any benefit cannot be attributed to the supplement because of the placebo effect.
3. In a non-blinded, uncontrolled trial of 22 adults with aura, with or without migraine (64% female), were instructed to take two capsules of Migrasoll® (a multi-ingredient supplement containing ginkgolide B, coenzyme Q10 and riboflavin) at the onset of aura symptoms for a single aura attack (3). Compared to a single baseline measurement of aura duration, Migrasoll® significantly decreased aura duration (*P*<0.001) from 33.6±11.5 minutes to 21.9±11.8 minutes. The authors concluded that Ginkgolide B is an effective acute treatment for aura, but that these results need to be confirmed by larger, more rigorous studies (3). However, this conclusion is likely premature considering the confounding effects of the other nutraceuticals present in Migrasoll® and the lack of a control group.

**Rationale**

During a migraine attack, levels of platelet-activating factor increase and induce serotonin secretion (1). Ginkgolide B, a diterpene derived from *Ginkgo biloba*, is theorized to have a role in migraine prophylaxis because it blocks the receptor to which platelet-activating factor binds, thereby preventing its activity.

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**Key Practice Point**

**Evidence Synthesis**

A single, small RCT showed that vitamin E supplementation of 400 IU taken daily around the time of menstruation significantly improved migraine pain severity and duration, light and sound sensitivity and nausea. {grade\_c}

A conclusion regarding the use of vitamin E as a migraine prophylaxis is not possible at this time due to the lack of available evidence. {grade\_d}

**Practice Guidance**

There is very limited evidence to support vitamin E supplementation as a treatment for menstrual migraines. The dose used in the only published study, 400 IU daily, is below the upper limits for vitamin E established by Canada, Australia, New Zealand, and the U.K (see the International Dietary Reference Values collection). It may be useful for the patient and her or his health care providers to weigh the financial cost of the supplement against any potential benefits.

**Grade of Evidence: C & D**

**Evidence**

1. A double-blinded, placebo-controlled, crossover RCT (n=67) investigated the effectiveness of vitamin E supplementation for treating migraines associated with menstruation (1). Participants were university students, 20- to 30-years-old, with a history of regular menstrual cycles and a migraine that started on day one of menstruation in at least two of their last three cycles. For two menstrual cycles each, participants first took a daily placebo and then a 400 IU vitamin E supplement from two days before menstruation until three days after, with a one cycle washout period in between placebo and supplement. As compared to baseline, migraine severity and duration were significantly decreased for both groups, though the magnitude of reduction was significantly larger after vitamin E supplementation. Additionally, vitamin E significantly improved light and sound sensitivity and nausea when compared to the placebo (*P*<0.05). The authors concluded that vitamin E may be a useful treatment option, but that larger studies are needed (1). Based on the study design, in which all participants first received the placebo rather than half being randomly assigned to receive the treatment first, internal threats to validity include the threats of history and maturation. Additionally, vitamin E status was not assessed at baseline. Finally, the PEN evidence analyst has concerns about the accuracy of the published statistical results.

**Rationale**

Prostaglandin release has been proposed as key contributor to the precipitation of menstrual migraines because of the high levels associated with menstruation (1). If this is true, vitamin E is hypothesized to be a useful treatment for women because it inhibits the release of prostaglandin precursors and their conversion into prostaglandins.

**References**

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# Search Strategy

**Q1: What dietary components, if any, are triggers for migraine among migraineurs?**

|  |
| --- |
| **List the SEARCH TERMS** |

(PubMed MeSH Database to help and any additional terms used)

1. Headache

2. Migraine Disorders

3. Precipitating Factors

4. Migraine headache trigger

5. Alcoholic Beverages

6. Sulfites

7. Tyramine

8. Cacao

9. Tannins

10. Sodium Glutamate

11. Nitrites

12. Nitrates

13. Nutritive Value

14. Trichlorosucrose

15. Cheese

16. Aspartame

17. Fasting

18. Dehydration

Limits: Humans

|  |
| --- |
| **List DATABASES and GREY LITERATURE Sources Searched** |

(Consider PubMed and international government and organizational guidelines)

PubMed

Cochrane

NHMRC

NICE

Health Canada

National Guideline Clearinghouse

|  |
| --- |
| **Other Methods used to Find Information** |

Looking through the reference list of articles obtained through other means.

**DATE of Search (any date restrictions)**

**August 10-11, 2015 (restricted to Jan. 1, 2013 – Dec. 31, 2015)**

# Search Strategy

**Q2: Are there any nutrients or supplements (natural health products) that are effective for either decreasing the frequency of migraine (migraine prophylaxis) or for acutely treating a migraine?**

|  |
| --- |
| **List the SEARCH TERMS** |

(PubMed MeSH Database to help and any additional terms used)

* 1. Migraine disorders
	2. Dietary supplement
	3. Magnesium
	4. Feverfew
	5. Niacin
	6. coenzyme Q10
	7. fatty acids, omega-3
	8. riboflavin
	9. Tanacetum parthenium
	10. Phytoestrogens
	11. Petasites
	12. Ginkgo biloba

|  |
| --- |
| **List DATABASES and GREY LITERATURE Sources Searched** |

(Consider PubMed and international government and organizational guidelines)

PubMed

Cochrane Library

NHMRC

NICE

Health Canada

National Guideline Clearinghouse

Google Scholar

|  |
| --- |
| **Other Methods used to Find Information** |

Looking through the reference list of articles obtained through other means.

**DATE of Search (any date restrictions) Aug 20, 2015 (Jan 1, 2007 – Present)**

***Background***

**Migraine Background**
Last Updated: 2008-06-06
Keywords: headache migraine attack migrainous head pain aura neurological disorder nervous system

**Prevalence**

Worldwide, an estimated 14% of the population has experienced at least one migraine, with more female migraineurs than males (Ramage-Morin, 2014). Migraine prevalence, however, appears to vary geographically. In Canada, based on evidence from 2010/2011, 8.3% of Canadians had been diagnosed with migraines and prevalence was more than twice as likely in females than males over the age of 12 years (Ramage-Morin, 2014). A similar difference in prevalence between females and males has also been observed in England, with 18.3% of females having experienced a migraine in 2014 as compared to 7.6% of males (BMJ, 2014). In the U.K., estimated migraine prevalence is 5.85 million people 16- to 65-years-old (BMJ, 2014), which is approximately 9.1% of the total population (UK Office for National Statistics, 2014). Australian data from 2007 suggests a higher overall migraine prevalence (11.5% of the population) than in Canada or the U.K., with the previously observed spread between females (14.9%) and males (6.1%)(Stark et al 2007).

**Diagnosis**

Migraine is a complex chronic neurological condition that is characterized primarily by recurrent episodes of severe head pain that are often associated with nausea and sensitivity to light and sound (Pietrobon). The intensity of the head pain and other commonly associated symptoms can result in significant time lost from work, school and activities of daily living. The negative impact both on the individual’s quality of life and the cost to society through loss of productivity can be severe and the World Health Organization has listed it as the world’s 19th most disabling disease (Leonardi, 2005).

A number of mechanisms have been proposed to be involved in the onset of a migraine. Specifically, activation of the trigeminovascular system has been implicated by a large body of indirect evidence (Pietrobon). Activation of this system is thought to trigger the release of neurotransmitters associated with vasoconstriction and vasodilation, which can lead to painful inflammation (Merck). The mechanism that activates the trigeminovascular system, however, is still unknown (Pietrobon). In migraine with aura, the aura is thought to be facilitated by cortical spreading depression in the brain, which is associated with altered mitochondrial metabolism (Teigan).

The International Headache Society has created the following diagnostic criteria for migraines without aura (IHS):

1. At least five attacks that fulfill criteria B through D below:
2. Headache that lasts four to 72 hours (untreated or unsuccessfully treated).
3. Headache has a minimum of two of the following characteristics:
         unilateral location
         pulsating quality (throbbing)
         moderate or severe intensity pain (inhibiting/prohibiting daily activity)
         pain aggravated by movement (e.g. walking or climbing stairs).
4. One of the following symptoms during the headache:
         nausea and/or vomiting
         sensitivity or aversion to:
    o        light (photophobia)
    o        noise (phonophobia).
5. There is no evidence that any other underlying disease is the cause of the headache.

Migraine with aura is diagnosed by visual (e.g. loss of vision or seeing lights, spots or lines), sensory (e.g. numbness or tingling) and/or dysphasic speech disturbances that last between five minutes and 24 hours (see ICHD-II for more information, IHS). Most often, aura occurs in conjunction with migraine headache, but there are two subtypes of migraine with aura that are not associated with head pain (IHS). Prodrome may also occur among many migraine patients, often before a migraine attack occurs. This condition can be characterized by such symptoms as increased irritability, hyperactivity, change in mood or emotions, difficulty thinking and food cravings or hyperosmia (an exaggerated or abnormally acute sense of smell) (Pryse-Phillips).

Migraine occurrence is also hormonally related, with the drop in estrogen levels associated with menstruation thought to be a migraine trigger (Silberstein). Migraine is more common among women and more common around the time of menstruation with an estimated 50% of women migraineurs having an increased risk of migraine in the days leading up to menses. Previously, researchers believed that oral contraceptives were a migraine trigger, but now the relationship appears to exist due to the periodic cessation of the pills (and therefore estrogren) every 21 days. Rather than being a migraine trigger, oral contraceptives that decrease the frequency of menses are beginning to be considered as a treatment for migraineurs who experience severe menstrual migraines (Silberstein).

**Triggers**

A number of different migraine triggers have been hypothesized and tested including those arising from psychosocial, sensory, environmental, physiological and dietary stimuli. There is noted individual variability in response to potential triggers; a trigger may cause no response in one individual and a severe reaction in another (Millichap). A 2014 review of the top ten most frequently reported migraine triggers included (Peroutka):

1. Stress (reported by 58% of respondents)
2. Auditory (56%)
3. Fasting (44%)
4. Hormones (44%)
5. Fatigue (43%)
6. Sleep (43%)
7. Weather (39%)
8. Visual (38%)
9. Olfactory (38%)
10. Alcohol (27%).

In addition to fasting and alcohol, a number of other dietary components have been reported by migraineurs as triggers of their migraine attacks. These commonly include (Rockett)

* chocolate
* caffeine and/or caffeine withdrawal
* citrus fruits
* fatty foods
* dehydration
* cold foods like ice water and ice cream
* dairy products especially aged and fermented cheeses
* meat products
* eggs.

Additionally, aspartame, sucralose, processed meats like sausage and salami, Chinese food, soda, walnuts, sugary foods, and pizza have been reported infrequently as migraine triggers (Rockett). Although many food triggers have been identified within the literature, it is important to keep in perspective that food triggers are only identified by about one third of migraineurs; non-food triggers are far more common (Pringsheim, 2012).

Avoiding the aforementioned potential triggers should generally be a harmless endeavour as long as no major food groups are completely excluded from the diet. Due to the incapacitating nature of migraine attacks, migraineurs should not be discouraged from experimenting with their diet. However, consultation with a registered dietitian can help ensure that nutrient needs continue to be met.

**Treatments**

Management consists of treating acute migraine attacks and, in some cases, reducing migraine frequency (migraine prophylaxis) (Pringsheim, 2012). Avoiding suspected triggers, including dietary triggers, falls into the latter category. The treatment used will depend on patient preferences, migraine severity, concurrent medical conditions, evidence of treatment efficacy and the side-effect profile (Prinsheim, 2012).

Treatment is generally divided into two categories:

1. Acute treatment – symptom management with the overall goal of helping patients to be pain-free within two hours of treatment (Worthington, 2013). The main categories of medication for acute migraine treatment are (Worthington, 2013):
	* triptans
	* analgesics and/or anti-inflammatory medications
	* anti-emetics (metoclopramide or domperidone) if nausea and vomiting co-occur
	* ergotamine (recommended less frequently).
2. Prophylaxis - medication is often taken for at least two months with the goal of decreasing migraine frequency by at least 50%, realizing it will not likely eliminate migraine attacks altogether (Pringsheim, 2012). The main categories of prophylactic medication for migraine include the following (Pringsheim, 2012):
	* antihypertensives (including beta-blockers and calcium channel blockers)
	* antiepileptics
	* antidepressants
	* serotonin receptor antagonists
	* nutraceuticals (vitamins, minerals, herbal supplements).

Non-pharmacological treatments have also been used by migraineurs with varying degrees of success. In particular, behavioural therapies that address stress and blood pressure reduction have been shown to be effective (Pringsheim). Tested therapies include (Pringsheim):

* relaxation techniques
	+ meditation
	+ abdominal breathing
	+ progressive muscle relaxation
	+ visualization and guided imagery
	+ autogenics training
* biofeedback training
	+ hand temperature biofeedback
	+ electromyograph biofeedback
	+ temporal pulse amplitude biofeedback
* cognitive behavioural therapy.

Additionally, migraineurs seem to benefit from regular sleep and exercise and from learning skills that help them to self-monitor, effectively communicate their pain, and manage their time. Migraineurs are also often encouraged to keep a diary of the frequency, severity and duration of their attacks, the circumstances that precede them (to identify potential triggers) and their response to treatment (Pringsheim).

**References**

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# Diagnosis and Treatment of Childhood Migraine.

[Merison K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Merison%20K%5BAuthor%5D&cauthor=true&cauthor_uid=27704257)1, [Jacobs H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jacobs%20H%5BAuthor%5D&cauthor=true&cauthor_uid=27704257)2.

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# O017. Cortical functional correlates of responsiveness to short-lasting preventive intervention with ketogenic diet (KD) in migraine: a multimodal evoked potentials study.

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***Related Practice Questions***

**Q:**What is the evidence on the safety of sweeteners (e.g. nonnutritive, artificial, intense, low calorie, sugar substitutes)?

*Last Updated: 2013-10-29*

*Keywords: sweeteners intense sweetener sugar substitute artificial non-nutritive nutritive alternative bulk compound polyols food additive safety*

#### Key Practice Point

Acesulfame potassium, aspartame, D-tagatose, neotame, stevia glycosides, sucralose and thaumatin have been approved in Australia, Canada, New Zealand, and the European Union for use and are considered safe for daily use in moderation at or below their Acceptable Daily Intake.

Cyclamate and saccharin have also been approved for use in Australia, New Zealand and the European Union. Alitame has been approved for use in Australia and New Zealand.

Saccharin and cyclamate have been approved in Canada as table-top sweeteners but are not permitted for use in food products at present. However, Health Canada is considering relisting saccharin in the Food and Drug Regulations to allow its use as a sweetener in certain foods.

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[Evidence](https://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&pqcatid=144&pqid=1295&kppid=1296&book=Evidence#Evidence) | [References](https://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&pqcatid=144&pqid=1295&kppid=1296&book=Evidence#References)

#### Evidence

1. The following sweeteners are approved for use in Australia and New Zealand by Food Standards Australia New Zealand: alitame, acesulfame potassium (Ace K), aspartame, cyclamate, D-tagatose, neotame, saccharin, sucralose, steviol glycosides and thaumatin (1).
2. The following sweeteners are approved for use by Health Canada: acesulfame potassium, aspartame, D-tagatose, neotame, stevia glycosides, sucralose, and thaumatin (2,3).
3. Cyclamate and saccharin are approved by Health Canada as table-top sweeteners but are not permitted for use in food products (2). However, Health Canada is considering relisting saccharin in the Canadian Food and Drug Regulations to allow its use as a sweetener in certain foods as a result of a review of the evidence relating to its safety (4).
4. The following sweeteners are approved for use in the European Union (EU): aspartame, acesulfame potassium, D-tagatose, neotame, sucralose, saccharin, thaumatin and sodium cyclamate (5).
5. EU Regulation 1131/2011, which came into effect in 2011, permits steviol glycosides to be used in certain specified foods at permitted maximum levels (expressed as steviol equivalents (6).

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#### Key Practice Point

Acesulfame potassium is considered safe for human consumption in moderation at or below the Acceptable Daily Intake (ADI). The ADI for acesulfame potassium is 15 mg/kg body weight.

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#### Evidence

1. The Joint FAO/WHO Expert Committee on Food Additives has evaluated the effects of acesulfame potassium across several animal models (1). This analysis examined the sweetener’s metabolism and absorption, acute toxicity testing, reproductive and antigenicity effects and carcinogenicity and found that acesulfame potassium was neither metabolized nor exhibited carcinogenicity. In pharmacology tests in a small number of healthy human subjects, acesulfame potassium was found to be excreted in the urine unchanged. The ADI for acesulfame potassium is 15 mg/kg body weight.
2. A more recent study of acesulfame potassium, which used a specialized model of rat, exposed animals to doses of up to 5,700 mg/kg body weight for 40 weeks and found no effect on body weight, carcinogenesis or survival (2).

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#### Key Practice Point

Alitame is considered safe for human consumption in moderation at or below the Acceptable Daily Intake (ADI). The ADI for alitame is 0-1 mg/kg body weight.

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#### Evidence

1. The Joint FAO/WHO Expert Committee on Food Additives evaluated the effects of alitame across several animal models (1) to assess safety and establish an ADI. In rodent studies no evidence of genotoxicity, teratogenicity or carcinogenicity was found (2,3).
2. In their review of alitame, the Joint FAO/WHO Expert Committee on Food Additives notes the following three studies (3):
	* A 14-day trial involving eight individuals who consumed 15 mg/kg body weight/day of alitame in the form of capsules and then assessed saliva, urine and plasma contents found no evidence of changes or hepatic enzymes in response to alitame use.
	* A, 90-day double-blind trial involving 80 control subjects receiving placebo and 77 subjects receiving 10 mg/kg body weight/day of alitame in the form of capsules and measured blood pressure, weight, eye health and cardiac parameters noted that four of the treated subjects and two control subjects discontinued participation due to side-effects (primarily rash, dry eyes and abdominal cramps). A repeat challenge of alitame with the same subjects six months later did not result in any side-effects.
	* A 90-day double-blind trial of alitame involving individuals with type 1 or type 2 diabetes administered 10 mg/kg body weight/day of alitame capsules to 75 individuals and placebo capsules to 80 control subjects. Gastrointestinal side-effects were reported by 29% of treated participants and 25% of those in the control group. Participants were then followed for two years with yearly physical assessments and interviews. After one year five of the treated subjects, but no control subjects, had experienced an MI. Further analysis found that this result could be explained by chance. After year two of follow up no evidence of adverse health effects were found in this study group.
3. The ADI for alitame is 0-1 mg/kg body weight (1).

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#### Comments

Alitame is 2,000 times sweeter than sucrose and is composed of L-aspartic acid, D-alanine and a novel amine (1). It is water soluble, stable at high temperatures and over a broad range of pH levels.

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#### Key Practice Point

Aspartame is considered safe for human consumption in moderation at or below the Acceptable Daily Intake (ADI) with the exception of individuals with phenylketonuria (PKU). The ADI for aspartame is 40 mg/kg body weight.

See Additional Content:  [What dietary components, if any, are triggers for migraine among migraineurs?](http://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&pqcatid=146&pqid=9068)

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#### Evidence

1. Two studies were identified that examined the effects of aspartame-containing products on the health of those with phenylketonuria (PKU). In one randomized double-blind, placebo-controlled cross-over study 48 adults, heterozgyotes for PKU, received 12-week treatments of placebo, 15 mg/kg/day or 45 mg/kg/day of aspartame. Although plasma phenylalanine levels increased in the 45 mg/kg/day treatment group, no significant difference in EEG analysis, urinary organic acid levels or adverse effects were reported (1). In a second smaller study, plasma phenylalanine levels were measured after five homozygous PKU subjects consumed a 354 mL diet soda. The increases in plasma phenylalanine levels between subjects varied between 0.26 mg/dL to 1.77 mg/dL two to three hours after ingestion and were not considered to be clinically significant (2).
2. Anecdotal and theoretical concerns have been raised about the safety of aspartame. In one case that was analyzed by regulatory authorities, groups of 100-150 rodents were fed varied concentrations of aspartame until their natural death. Upon examination the research team reported an increased incidence of lymphoma, leukemia and carcinoma of the renal pelvis in the test rodents (3). The European Food Safety Authority (EFSA) identified concerns with the study design in their review of the findings and concluded that the increased rates of malignancy could not be attributed directly to aspartame intake. As a result the EFSA concluded that there was no need to further review the safety of aspartame or to revise established ADI levels (4). Following its own analysis of the study data, Health Canada concluded that the study did not provide conclusive evidence linking the ingestion of aspartame to any adverse health effects. Based on the evaluation of that study, Health Canada maintained its position on the general safety of aspartame (5).
3. In a critical review of available scientific literature on aspartame Magnuson, et al. examined toxicity studies across a variety of animal models and found no adverse effects with doses of up to 4000 mg/kg body weight per day nor evidence that aspartame is carcinogenic (6).
4. In a five-year study of the records and food frequency questionnaires of 473,984 individuals aged 50-71 years enrolled in the NIH-AARP Diet and Health Study higher aspartame intake was not associated with increased risk of hematopoietic or brain cancers (7).
5. The dietary assessment questionnaires of participants enrolled in the Nurses Health Study and the Health Professionals Follow up Study over a 22-year follow-up period were examined for a possible association between regular and diet (containing aspartame) soda consumption and lymphoma, myeloma, and leukemia (8). Compared to men who did not drink diet soda, those who drank >1 diet soda per day had a relative risk (RR) of 1.31, 95% CI, 1.01 to 1.72 of non-Hodgkin's lymphoma and a RR of 2.02, 95% CI, 1.20 to 3.40 of multiple myeloma while men and women had a RR of 1.42, 95% CI,1.0 to 2.02 of leukemia. Researchers concluded that because of inconsistent observations between sexes and an observed association between the consumption of regular soda and non-Hodgkins lymphoma in men, these findings might be explained as chance observations.
6. The Joint FAO/WHO Expert Committee on Food Additives has determined that the ADI for aspartame is 40 mg/kg body weight (9).

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#### Comments

Phenylketonuria (PKU) is an inherited genetic disorder in which the body cannot metabolize phenylalanine. Since aspartame contains phenylalanine, the European Food Safety Authority, Food Standards Australia New Zealand and Health Canada require that products having aspartame as an ingredient must be labelled to alert consumers to the presence of phenylalanine (10-12).

The European Food Safety Authority has also been directed to re-evaluate the use of all intense sweeteners that were approved prior to 2009. The target date for completion of this work is 2020 with the exception of the review of aspartame, which is scheduled for completion in 2013.

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#### Key Practice Point

D-tagatose is considered safe for human consumption in moderation at or below the Acceptable Daily Intake (ADI). The ADI for D-tagatose is 125 mg/kg body weight.

D-tagatose is metabolized through the same biochemical pathway as fructose therefore individuals with disorders in fructose metabolism should be advised to avoid products containing D-tagatose.

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#### Evidence

1. In Australia and New Zealand D-tagatose has been assessed and approved as a novel food as the proposed applications of the product exceeded usual dietary consumption patterns (1). In Canada D-tagatose has been assessed and approved as a non-medicinal sweetening agent in natural health products (2).
2. The Joint FAO/WHO Food Additives Committee has set the ADI for D-tagatose at 125 mg/kg body weight (3), an increase from 80 mg/kg body weight after additional data from human studies was provided by the applicant (4). A challenge in establishing an ADI for this sweetener arises because intakes of >30 g/day results in gastrointestinal symptoms (nausea, diarrhea) in some individuals.
3. D-tagatose is metabolized through the same biochemical pathway as fructose therefore individuals with disorders in fructose metabolism should be advised to avoid products containing D-tagatose (5).

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#### Comments

D-tagatose is a monosaccharide that is naturally occurring in some fruits and dairy products and may also be produced through isomerization after enzymatic hydrolysis of lactose to galactose (1). The resultant sweetener is 92% as sweet as sucrose but poorly absorbed and eventually fermented in the large intestine providing approximately 11 kJ/g.

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#### Key Practice Point

Neotame is considered safe for human consumption in moderation at or below the Acceptable Daily Intake (ADI). The ADI for neotame is 0-2 mg/kg body weight.

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#### Evidence

1. Alhough neotame is a derivative of phenylalanine and aspartic acid, during metabolism <20% of phenylalanine is released into the plasma. It is the position of the Academy of Nutrition and Dietetics that this amount is not clinically significant for those with PKU (1).
2. Studies across a variety of animal models indicate that neotame is not carcinogenic, or associated with reproductive toxicity (2).
3. The U.S. Food and Drug Administration reviewed data from five trials in healthy adults and one trial in adults with type 2 diabetes analyzing the effect of doses of neotame on laboratory measures, vital signs and subjects’ self reported adverse effects and found no impacts on the parameters measured (3).
4. The Joint FAO/WHO Food Additives Committee has set the ADI for neotame at 0-2 mg/kg body weight (2).

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#### Comments

Neotame is produced by adding a t-butyl group to the free amine group of aspartic acid. The resultant product is 7,000 to 13,000 times sweeter than sugar. In Canada, neotame is approved as a table-top sweetener and in products including cereals, beverage mixes, toppings, yogurt, chewing gum, nut spreads, sweetened coatings for snack foods and unstandardized baked products, mixes and condiments (4). Unlike aspartame-containing products, neotame does not require cautionary labelling as the chemical structure of this compound blocks the ability of peptidases to break the bond between aspartic acid and phenylalanine thereby reducing the availability of phenylalanine. In addition, because of the intense sweetness of neotame, much lower amounts of phenylalanine are consumed compared with aspartame. Neotame is metabolized and eliminated in the urine and feces (5).

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#### Key Practice Point

Sucralose is considered safe for human consumption in moderation at or below the Acceptable Daily Intake (ADI). The ADI for sucralose is 0-15 mg/kg body weight.

See Additional Content:  [What dietary components, if any, are triggers for migraine among migraineurs?](http://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&pqcatid=146&pqid=9068)

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#### Evidence

1. In its evaluations of the safety of sucralose, the Joint FAO/WHO Expert Committee on Food Additives examined study results across a series of animal models and healthy human subjects (1). The studies observed the metabolism, neurotoxicity, reproductive effects and carcinogenicity of sucralose and found no adverse effects. The sweetener was observed to be poorly absorbed and excreted unchanged in the urine. The ADI for sucralose set by the Joint FAO/WHO Expert Committee on Food Additives is 0-15 mg/kg body weight.
2. Tolerance studies in healthy human volunteers exposed to increasing doses of sucralose up to 5 mg/kg/day for 13 weeks and single dose 10 mg/kg/day challenges revealed no adverse effects on EKG tracings, urinalysis, hematology results or changes in ophthalmology exams (2).
3. A study of the effects of sucralose on satiety and glucose levels in eight healthy women who received either sucrose and/or sucralose in water followed by a standard breakfast found sucralose exerted no significant effect on perceptions of hunger, short-term glucose concentrations or triglyceride levels in blood samples tested at 30, 60, 90 and 120 minutes after the standard meal (3). Effects on insulin, glucose, and ghrelin concentrations were observed only after the consumption of the sucrose drinks.
4. A series of studies examining the effects of sucralose on the health of various animal models have demonstrated no adverse effects (4-8).

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#### Comments

Sucralose is produced by replacing three hydroxyl groups in sucrose with chlorine, which produces a sweetener that is 600 times sweeter than sugar yet not hydrolyzed in the small intestine (9). Sucralose is heat stable.

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#### Key Practice Point

Thaumatin is considered safe for human consumption. An acceptable daily intake (ADI) for thaumatin has not been set by the Joint FAO/WHO Expert Committee on Food Additives.

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[Evidence](https://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&pqcatid=144&pqid=1295&kppid=1301&book=Evidence#Evidence) | [Comments](https://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&pqcatid=144&pqid=1295&kppid=1301&book=Evidence#Comments) | [References](https://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&pqcatid=144&pqid=1295&kppid=1301&book=Evidence#References)

#### Evidence

1. In its evaluations of the safety of thaumatin, the Joint FAO/WHO Expert Committee on Food Additives examined results of in vivo and in vitro studies and studies across a series of animal models examining mutagenicity, allergenicity and overall exposure effects (1). No treatment effects were observed.
2. An ADI for thaumatin has not been set by the Joint FAO/WHO Expert Committee on Food Additives (1).
3. As thaumatin is a protein extract, the majority of human studies have focused on tolerance and allergy testing. In studies reviewed by the Joint FAO/WHO Committee on Food Additives, 30 healthy human subjects received 280 mg capsules of thaumatin for a 12-week period (1). This amount represents a cumulative dose that was estimated to be 140 times maximum consumer intake. No hematological or cellular changes were observed in subjects consuming thaumatin.
4. A report of laboratory personnel exposed to thaumatin intermittently over a seven-year period, who responded positively to skin prick tests, did not demonstrate oral sensitivity when exposed to thaumatin in challenge tests (2).

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#### Comments

Thaumatin is a mixture of intensely sweet proteins extracted from the fruit of the West African perennial Thaumatococcus daniellii(1).

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#### Key Practice Point

Saccharin is considered safe for human consumption in moderation at or below the Acceptable Daily Intake (ADI). The ADI for saccharin is 0-5 mg/kg body weight.

Saccharin has been approved for use in Australia, New Zealand and the European Union.

Saccharin has been approved in Canada as a table-top sweetener but is not permitted for use in food products at present. However, Health Canada is considering relisting saccharin in the Food and Drug Regulations to allow its use as a sweetener in certain foods.

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#### Evidence

1. The Joint FAO/WHO Expert Committee on Food Additives analyzed the health effects of saccharin in response to reports of increased incidence of bladder tumours in rodents fed high doses of saccharin. This group concluded on the basis of two generation feeding studies that rats, predominantly males, appear to be the only species that exhibit increased incidence of bladder tumours (1,2). The development of these tumours also appears to be predicated on exposure to high levels of saccharin during the neonatal period. Examination of epidemiological data did not demonstrate an association between saccharin and incidence of bladder cancer in humans (2).
2. Health Canada has not relisted saccharin as an approved food additive, pending regulatory amendments (3).
3. The European Food Safety Authority has approved the use of saccharin (E954) as a sweetener in food products under Directive 94/35/EC (4).
4. Food Standards Australia New Zealand has approved the use of saccharin as a sweetener (5). Information regarding the amounts permitted in specific food products is available in standard 1.3.1 at <http://www.comlaw.gov.au/Series/F2008B00614>.
5. The Joint FAO/WHO Expert Committee on Food Additives has set the ADI for saccharin at 0-5 mg/kg body weight (1).

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#### Comments

Saccharin is heat stable and not metabolized in the body (6).

In the 1970s, studies raised concerns that saccharin could be carcinogenic in laboratory rats. On this basis, saccharin was delisted as a food additive in Canada, although access to saccharin as a table-top sweetener was maintained. Recent data has demonstrated that the carcinogenic effect of saccharin in rats is not relevant for humans.

Following these reviews, the International Agency for Research on Cancer (IARC) concluded that saccharin is no longer considered a "possible carcinogen in humans." In May 2000, the U.S. National Toxicology Program removed saccharin from its list of suspected cancer-causing chemicals and the Joint Expert Committee on Food Additives (JEFCA) of the World Health Organization and the Food and Agriculture Organization of the United Nations established an ADI for saccharin (1).

Although Health Canada has deemed that saccharin is safe for use, a warning regarding its use for women who are pregnant must still be included on the sweetener’s label until the regulation regarding its use is amended (7).

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#### Key Practice Point

Cyclamate is considered safe for human consumption in moderation at or below the Acceptable Daily Intake (ADI).

It is approved for use in Australia and New Zealand at ADI levels of 0-11 mg/kg body weight.

Cyclamate is approved for use by the European Union at ADI levels of 0-7 mg/kg body weight.

Cyclamate is approved by Health Canada as a table-top sweetener and as a non-medicinal ingredient in natural health products but it is not permitted for use as a food additive. In Canada it is approved for use at ADI levels of 0-11 mg/kg body weight.

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#### Evidence

1. Cyclamate is considered acceptable for use within ADI levels, based on historic use and lack of reported adverse effects. It should be noted that while the Joint FAO/WHO Expert Committee on Food Additives has approved use of cyclamates at 0-11 mg/kg body weight, in 2000 the European Union Scientific Committee on Food approved cyclamate use at 0-7 mg/kg body weight based on a reassessment of data that indicated that unabsorbed cyclamate could be metabolized by microflora in the lower gut of some individuals to cyclohexylamine (1,2).
2. Cyclamate and its metabolite cyclohexylamine have been investigated for their effects on fertility, cardiovascular health and as a potential carcinogen. Although cyclamate has been observed to affect male fertility in high dose cyclamate animal studies, an epidemiological study of 405 infertile men and 379 case control subjects found no association between cyclamate consumption and infertility (3).
3. The effects of cyclamate on cardiovascular indices (heart rate, blood pressure) were studied in 194 individuals with diabetes given 1 g/day cyclamate for seven days and 20 of these individuals restudied while receiving 2 g/day of cyclamate for two weeks. Despite inter-subject variability in plasma measurements of cyclohexylamine following ingestion of cyclamate the authors concluded that metabolism of 2 g/day of cyclamate to cyclohexylamine would not affect heart rate or blood pressure (4).
4. In a study of the metabolism of cyclamate to cyclohexylamine in 14 healthy participants given calcium cyclamate three times a day for 13 weeks, the maximum metabolism of cyclamate to cyclohexylamine was not maintained for extended periods supporting the current ADI of 0-11 mg/kg body weight per day (5).
5. Food Standards Australia New Zealand has approved the use of cyclamate as a sweetener (6,7). Information regarding the amounts permitted in specific food products is available in standard 1.3.1 at <http://www.comlaw.gov.au/Series/F2008B00614>.
6. Cyclamate is approved by Health Canada as a table-top sweetener and as a non-medicinal ingredient in natural health products but it is not permitted for use as a food additive (8). In Canada it is approved for use at ADI levels of 0-11 mg/kg body weight.

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#### Comments

Cyclohexylamine is a metabolite of cyclamate. Researchers have noted inter-subject variability in the ability to metabolize cyclamate to cyclohexylamine. Cyclohexylamine is an indirectly acting sympathomimetic amine, meaning that it may have an effect similar to that observed with the stimulation of the sympathetic nervous system (4).

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#### Key Practice Point

Steviol glycosides are considered safe for human consumption in moderation at or below the Acceptable Daily Intake (ADI). The ADI for steviol glycosides is 4 mg/kg body weight.

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#### Evidence

1. Steviol glycosides are approved for use as a sweetener or flavour enhancer in natural health products/dietary supplements and as a table-top sweetener in Australia, New Zealand, Canada and the European Union in quantities that do not exceed ADI of 4 mg/kg/day steviol content (1-4). This amount is the equivalent of 50 mg/kg/day (~3550 mg/day for an adult) of stevia leaf or 10 mg/kg/day (~710 mg/day for an adult) of stevioside or mixed steviol glycosides or 12 mg/kg (~850 mg/day for an adult) of rebaudioside A (1).
2. The Joint FAO/WHO Expert Committee on Food Additives has concluded from recent studies, of 16 weeks duration, that there are no adverse effects associated with the use of steviol glucosides in quantities of 4 mg/kg/day in individuals with type 2 diabetes (5). No adverse effects associated with steviol glucosides in quantities of 4 mg/kg/day in individuals with low or normal blood pressure.
3. In evaluating the safety of steviol glycosides, the Joint FAO/WHO Expert Committee on Food Additives has concluded that stevioside and rebaudioside A are not genotoxic in vitro or in vivo (6,7).

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#### Comments

Steviol glycosides is a group of chemical sweeteners derived from the stevia plant, Stevia rebaudiana Bertoni. The leaves of S. rebaudiana contain eight different steviol glycosides, the largest component in the form of stevioside representing about 5-10% in dry leaves (3). Stevioside has a sweetening potency 250-300 times that of sucrose and is stable to heat. S. rebaudiana also contains rebaudioside A, rebaudioside C, and dulcoside A.

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***Related Tools and Resources***

### [Fr: Régime alimentaire à teneur réduite en sulfites (Sulphite-Restricted Diet)](http://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&trcatid=ALL&trid=15884)

***Resource Type:****Handout*

A french resource for consumers and health professionals that provides guidance on the sulphite-restricted diet for the management of sulphite sensitivity. Note: This handout can be shared but not customized.

*Last Updated: 2013-05-23     Target Audience: Consumer*

*Keywords: sulphate allergy allergen restricted hypersensitivity food list restaurant substitutions recipes asthma symptoms test preservative fruits vegetables potatoes grapes label additives ingredient label french*

### [Fr: Régime alimentaire à teneur réduite en glutamate monosodique (MSG) (Monosodium Glutamate(MSG) Restricted Diet)](http://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&trcatid=ALL&trid=15890) http://www.pennutrition.com/img/flag_Canada.gif

***Resource Type:****Handout*

A french resource for consumers and health providers that provides guidance on the MSG-restricted diet for the management of MSG sensitivity. Note: This handout can be shared but not customized.

*Last Updated: 2013-05-23     Target Audience: Consumer*

*Keywords: allergy allergen free hypersensitivity food list restaurant substitutions recipes additive symptoms Chinese restaurant syndrome Kwok's flavourings sources HPP HVP hydrolysed vegetable protein plant label ingredient french*

### [Healthy Eating Guidelines for People with Migraine Headaches](http://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&trcatid=ALL&trid=22570) http://www.pennutrition.com/img/flag_Canada.gif

***Resource Type:****Handout*

A client handout providing healthy eating guidelines for people who suffer migraine headaches.

*Last Updated: 2014-08-18     Target Audience: Consumer*

*Keywords: headache migraine attack migrainous head pain aura neurological disorder nervous system handout eating guidelines*

### [Migraine](http://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&trcatid=ALL&trid=9073)

***Resource Type:****Topic Overview*

This section from the Merck Home Health Handbook describes what a migraine is, its symptoms, diagnosis, prevention, treatment and medication options. The writing level is advanced and it is written for the health care professional.

*Last Reviewed: 2012-05-15     Target Audience: Professional*

*Keywords: headache migraine attack migrainous head pain aura neurological disorder nervous system*

### [Migraine Headache](http://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&trcatid=ALL&trid=9074)

***Resource Type:****Audio/Visual*

This is an interactive tutorial by the Patient Education Institute produced for the patient. It provides a link to an audio and slide show tutorial with accompanying text written in plain language. Clients can play the tutorial and listen to learn about the different types of migraine and treatment and prevention options.

*Last Reviewed: 2013-06-11     Target Audience: Consumer*

*Keywords: headache migraine attack migrainous head pain aura neurological disorder nervous system*

### [Monosodium Glutamate (MSG) Restricted Diet](http://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&trcatid=ALL&trid=2526) http://www.pennutrition.com/img/flag_Canada.gif

***Resource Type:****Handout*

A resource for consumers providing guidance on a MSG-restricted diet for the management of a MSG sensitivity. Note: This handout can be shared but not customized.

*Last Updated: 2012-12-20     Target Audience: Consumer*

*Keywords: food list restaurant substitutions recipes additive Chinese restaurant syndrome Kwok's flavourings sources HPP HVP hydrolysed vegetable protein plant label ingredient list allergen allergies atopy atopic food sensitivity anaphylaxis anaphylactic intolerances*

### [Sulphite-Restricted Diet](http://www.pennutrition.com/KnowledgePathway.aspx?kpid=11148&trcatid=ALL&trid=2525) http://www.pennutrition.com/img/flag_Canada.gif

***Resource Type:****Handout*

A resource for consumers providing guidance on a sulphite-restricted diet for the management of a sulphite sensitivity. Note: This handout can be shared but not customized.

*Last Updated: 2012-12-20     Target Audience: Consumer*

*Keywords: sulphate restrict restricted food list restaurant substitutions recipes asthma test preservative fruits vegetables potatoes grapes label additives ingredient label list allergen allergies atopy atopic food sensitivity anaphylaxis anaphylactic intolerances sulphites*