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Role of Herbal Medicine for Prevention and Treatment of Migraine.

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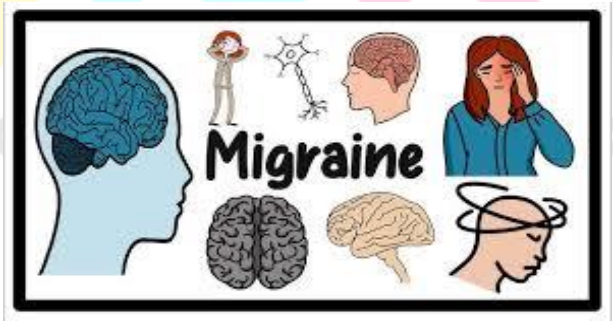
2. Introduction

Migraine affects more than one billion individuals each year across the world, and is one of the most common neurologic disorders, with a high prevalence and morbidity, especially among young adults and females. Migraine is associated with a wide range of comorbidities, which range from stress and sleep disturbances to suicide. The complex and largely unclear mechanisms of migraine development have resulted in the proposal of various social and biological risk factors, such as hormonal imbalances, genetic and epigenetic influences, as well as cardiovascular, neurological, and autoimmune diseases. This review presents a comprehensive review of the most up-to-date literature on the epidemiology, and risk factors, as well as highlighting the gaps in our knowledge.



Migraine is a common neurological disorder that is caused by the stimulation of a mechanism in the brain that leads to release of pain-producing inflammatory substances around the nerves and blood vessels of the head. This disorder usually begins at puberty and mostly affects people aged from 35 to 45 years. Migraine headaches are more common in women, with a ratio of 2:1, due to hormonal factors. (World Health

Organization 2016.) People with migraines report experiencing symptoms such as nausea, vomiting, unilateral head pain, pulsating or throbbing pain, photophobia, phonophobia, blurring of vision, presence of shimmering lights, circles, other shapes, or colors before the eyes, and the presence of numbness of lips, tongue, fingers, legs before the start of the headache. (Buse et al. 2017.) "Migraine is ranked among the world's leading causes of years lived with disability" (Frederick et al. 2014 675-685). Headache disorders tend to occur in about 50% among adults worldwide. Of those 50% of people with headache disorder, 30% or more have reported migraine. (World Health Organization 2016.) There are no known causes of migraines that are consistent for all patients. However, there are some common causing factors that are found amongst migraineurs. Some of those factors are depicted as hyperexcitable brain that reacts stronger to stimuli, which happens due to an inflammation of the lining of the brain. Another factor is genetics, where people are more predisposed to changes in estrogen levels, weather changes, a disrupted sleep pattern, or red wine. (Evans & Evans 2009.) As of today, there is no known cure for migraine headaches. However, there are a few possible treatments for the symptoms of this disorder. These include pharmacological and nonpharmacological methods. For pharmacological approach, some medications such as antipsychotics, antihypertensives, and triptans are known to treat the migraine attack. Nonpharmacological methods include acupuncture, supplements and herbs. (Guldiken 2009.) The purpose of this literature review was to collect and integrate the information about causes and treatments of migraines.

Migraine is defined as "an episodic headache associated with certain features, such as sensitivity to light, sound, or movement" or "a recurring syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures" (1). Migraines can be placed into two categories, which are resistant migraines (i.e., "having failed at least 3 classes of migraine preventatives and suffer from at least 8 debilitating headache days per month for at least 3 consecutive months without improvement") and refractory migraines (i.e., "having failed all of the available preventatives and suffer from at least 8 debilitating headache days per month for at least 6 consecutive months") (2). Migraines can also be associated with different syndromes like somnambulism, cyclic vomiting, abdominal migraine, benign paroxysmal vertigo, benign paroxysmal torticollis and confusional migraine, which have different clinical presentations, duration and prevalence (3). Migraine is a cyclic disorder which has different phases, including a premonitory phase, transient neurological symptoms (i.e., migraine aura), intense headache attack and postdrome phase (4). Furthermore, migraine is a burdensome disease which has an impact on the individual's economic situation, family relationships, as well as work and school activities (5). Globally, migraine was the second largest contributor to the disability-adjusted life-years (DALYs) lost due to neurological disorders in 2016, accounting for 16.3% [95% uncertainty interval (UI): 11.7–20.8] of the attributable DALYs (6). The global age-standardized prevalence of migraine increased by 1.7% (0.7–2.8) from 1990 to 2019, and in 2019 there were 1.1 billion (0.98–1.3) prevalent cases and 525.5 (78.8–1,194) years lived with disability (YLDs) per 100,000 population (7). In the United States, the economic burden of migraine was significantly higher in patients with migraine, than among those without migraine ($11,010 vs. $4,436; $p < 0.01$) (8).

Based upon several proposed mechanisms for migraine (9), various risk factors have been identified, such as: advanced age, head trauma, lower socioeconomic status, caffeine or medication overuse, stress, sleep problems (e.g., snoring), obesity, pain syndrome, and pro-inflammatory or pro-thrombotic states (10). In addition to the above mentioned risk factors, several other risk factors have been suggested for chronic migraine, a subtype of migraine, including ineffective treatment of acute migraine and the overuse of medication (11). Demographic (e.g., sex and race) and lifestyle factors (e.g., caffeine misuse, body weight gain and sleep disorders) are also additional risk factors (10, 12).

Methods

Any type of primary or secondary studies that evaluated the relationship between different disorders or agents with migraine in humans were included in this study, but there were no filters on publication date, article type, or sex. Studies were excluded if they were not in English, were *in-vitro* or were conducted on animal, or evaluated the risk factors for other types of headaches (i.e., other than migraine). Firstly, independent author screened the title and/or abstract of the identified studies and then full-texts were obtained for all articles that made it through the first screening process and these were also screed by the authors. At both steps, any discrepancies between the reviewers were resolved by discussion or through consultation with a teacher..

3.Aim And Objective:

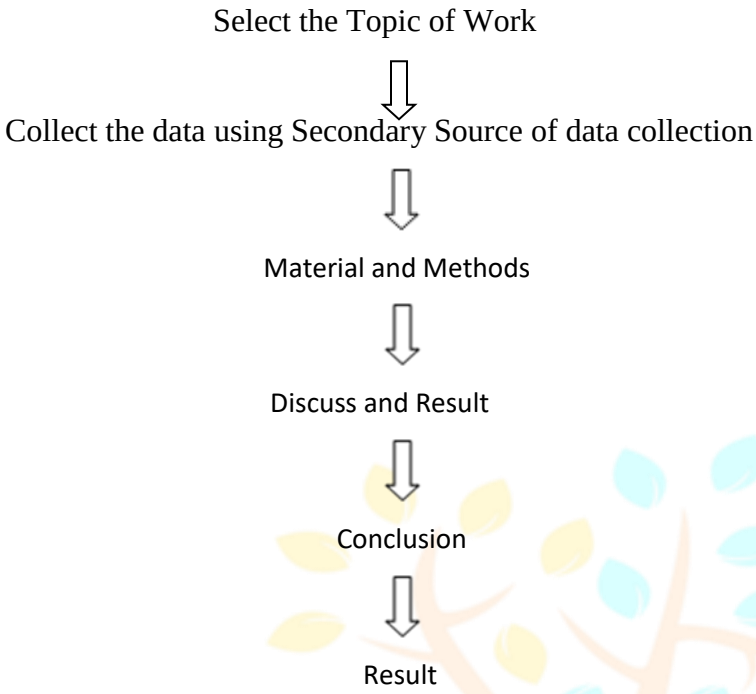
Aim:

A Brief Review on Role of Herbal Medicine For Prevention And Treatment Of Migraine.

Objective of the study:

1. To Known about Migraine disease.
2. To Study Brief history of Migraine.
3. To Study risk factors in Migraine.
4. To Study Herbal medicine for prevention and treatment of migraine.

4.Plan of Work



A Brief History of Migraine

Review Of Literature

Migraine, and the associated pain, has long plagued humans (14). Many people have suffered from migraines, including Julius Caesar, St. Paul, Thomas Jefferson, and Charles Darwin (15). Three thousand years BC, an anonymous Sumerian poet described a state of illness in which the headache was so severe that the patient wished to be relieved of the pain by death (14, 16). In Mesopotamia, it was believed that the evil spirit of Ti'e was attacking its victims, leading to terrible headache symptoms (14, 15). Skulls have been found in archeological excavations, which indicate that doctors recommended removing parts of the patient's skull to relieve severe headaches (14, 15). In ancient Egyptian medicine (From 3,000 BC), migraines and nerve pain, as well as sudden and severe pain, were clearly described (17). Hippocrates (460 – 370 BC), the father of medicine, was the first to scientifically document his clinical observations about migraine, freeing the disease from superstition (18, 19). Hippocrates described a bright light in the right eye, followed by the onset of severe pain in the head, which eventually extended to the entire area (18, 19). Aretaeus of Cappadocia (30–90 A.D.) provided one of the first formal classifications for headaches (20, 21). He divided headaches into three main types: (a) cephalalgia, a mild and short-term headache, (b) cephalea, a type of headache that is chronic and more severe, and (c) heterocrania, a paroxysmal headache on one side of the head, often accompanied by nausea, vomiting, photophobia, symptoms of the eyes, sweating and changes in the perception of fragrances (20, 21).

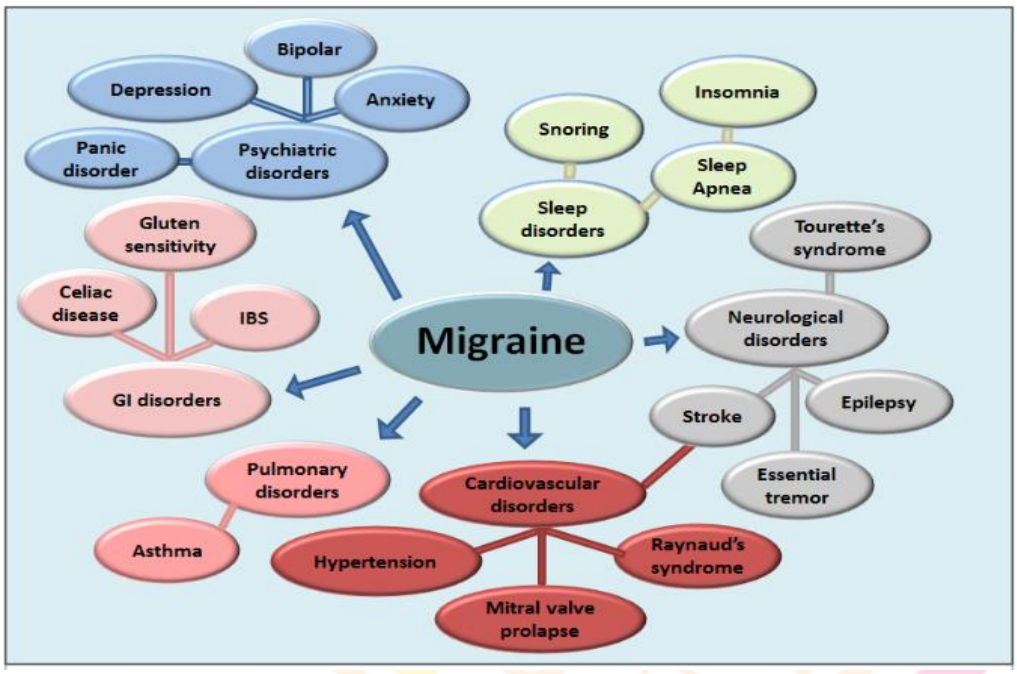
Galen (129–216 AD) wrote about a severe pain that affected almost half of the head (22, 23). Galen, like Hippocrates, believed that migraines were caused by vapors rising from the stomach into the head (22, 23). Razi (also known by his Latinized name Rhazes, 854–925 CE), a famous Iranian physician (24), devoted an entire chapter to headaches in his book, in which he wrote about the symptoms and treatment of migraine. His work

described in detail one of the different types of headaches, now known in modern medicine as migraine clusters, and he also suggested that severe and sudden headaches may be a preliminary sign of a stroke (25). Ibn Sina, also known in the West as Avicenna (980–1,037), another famous Iranian physician (26, 27), wrote a chapter on headaches in his book "Canon of medicine," which described different types of headaches, including one type which covered the entire head. This type of headache was severe, intensified by activity and was also characterized by photophobia and noise phobia (28–30). In the 17th century, Thomas Willis (1,621–1,675) published his hypothesis that "megrim" was due to the dilatation of blood vessels within the head (the first enunciation of a vascular theory) (31). In 1,873, Edward Liveing proposed that migraine was due to "nerve storms evolved out of the optic thalamus" (32). In 1,898, Moebius stated that "parenchyma is the master, circulation the servant," and that both brain and blood vessel dysfunctions were necessary to produce a migraine attack (32, 33).

Global Epidemiology and Trends

Migraine is one of the most common neurological diseases worldwide, with the global prevalence of migraine being estimated to be 1.1 billion [95% uncertainty interval (UI): 0.98–1.3] cases in 2019 (7). In that same year, the national age-standardized point prevalence of migraine ranged from 8,277 to 22,400.6 cases per 100,000 (7). The highest age-standardized point prevalence rates were found in Belgium [22,400 (95% UI: 19,305.2–26,215.8)] and Italy [20,337.7 (95% UI: 17,724.7–23,405.8)], while the lowest rates were found in Ethiopia [8,277 (95% UI: 7,226.2–9,527.5)] and Djibouti [8,915.3 (95% UI: 7,629.9–10,476.6)] (7). In 2019, the national age-standardized incidence rates of migraine ranged from 692.6 to 1,528.4 cases per 100,000, with Italy [1,528.4 (95% UI: 1,345.4–1,709.3)] and Norway [1,515.7 (95% UI: 1,333.8–1,693.4)] having the highest rates. In contrast, the lowest rates were observed for Ethiopia [692.6 (95% UI: 605.2–776.7)] and Djibouti [737.2 (95% UI: 623.5–848.9)] (7). The global prevalence of migraine has increased substantially over the last three decades (7). According to the Global Burden of Disease (GBD) 2019 study, the estimated global prevalence of migraine increased from 721.9 million (95% UI: 624.9–833.4) in 1990 to 1.1 billion (95% UI: 0.98–1.3) in 2019 (7). The percentage change in the global age-standardized prevalence rate and years lived with disability (YLDs), from 1990 to 2019, were 1.7 (95% UI: 0.7–2.8) and 1.5 (95% UI: −4.4 to 3.3), respectively (7). During this period, the highest increases in the age-standardized prevalence per 100,000 population were in East Asia (7.9% (95% UI: 4.3–12%) and Andean Latin America [6.7% (95% UI: 2.1–11.9%)], while the largest decreases were in High-income North America [−2.2% (95% UI: −5.3 to 1.1%)] and Southeast Asia [−2.2% (95% UI: −3 to −1.4%)] (7). Furthermore, the age-standardized YLD rate of migraine also increased from 517.6 (95% UI: 82.0–1169.1) in 1990 to 525.5 (95% UI: 78.8–1194.0) in 2019 (7). The prevalence of migraine was higher in females, than in males, across all age groups. In 2019, the global age-standardized prevalence rate in females and males were 17,902.5 (95% UI: 15,588.3, 20,531.7) and 10,337.6 (95% UI: 8,948.0, 12,013.0) per 100,000 populations, respectively (7). The highest incidence rate and number of incident cases of migraine were in the age group 10–14 years, in both females and males (7).

Risk Factors and Comorbidities



Large-scale epidemiological studies have identified several risk factors for migraine attacks. For instance, a web-based survey of 15,133 patients with migraine and 77,453 controls showed that insomnia, depression, anxiety, gastric ulcers and/or gastrointestinal bleeding, angina and epilepsy were significantly higher among migraineurs than among the control group ($p < 0.001$) (34). Also, the intensity and frequency of pain are both related to biological and psychological disorders, as well as due to inflammation (34). In accordance with the complex nature of migraines, differentiating between migraine risk factors, triggers, and outcomes is difficult (13). Informing patients about the causes and exacerbating factors can reduce the frequency and severity of attacks (13). Furthermore, some interventions, such as aerobic exercise, can reduce migraine attack duration, pain intensity and decrease the number of migraine days/month (35). Table 1 shows the different risk factors associated with migraine development and progression.

Table 1

Risk factors for migraine.

Biological factors	Hormonal imbalances	Estrogen dysregulation Demographic factors Metabolic factors Genetic and epigenetic factors	Cortisol dysregulation Advancing age Female sex Obesity Dyslipidemia Diabetes Hypertension *MTDH* gene *MEF2D* gene *PRDM16* gene

Psychological factors	Psychological factors	Anxiety	Phobia Panic Stress
Miscellaneous*	Miscellaneous*	Lower level of education	Lower socioeconomic status

*These conditions need to be furtherly assessed by future studies.

Biological Risk Factors and Comorbidities

Hormonal Imbalances

Migraine attacks are often associated with fluctuating hormone levels (36, 37). Hormones control chemicals in the brain that affect the sensation of pain, so any hormonal imbalances can influence the pain-processing networks in the brain (36, 37). Hormones have a potential connection to the pathophysiology of migraines (36). Of the hormones investigated, most of the attention has been directed to researching the level and fluctuations of sex hormones (37). In this section, we review the role of hormones in migraines.

Estrogen

Females suffer from migraines at about twice the rate of men (38). In addition to the prevalence rate, sex-based differences in migraine attacks have been validated by studies using structural and functional magnetic resonance imaging (MRI) of the brain (39). Alterations in the posterior insula and the thickness of the precuneus cortices have been identified in female migraineurs, in comparison to males and healthy controls from both sexes, using structural MRI scans (39). Functional MRI studies have also found evidence of gender differences in pain sensitivity and pain processing pathways (40). Although, both biological and psychosocial factors contribute to the sex differences in migraine, it seems that sex hormones are the most important (41). Migraine occurrence can be affected by menstruation, pregnancy, and menopause, in addition to the use of hormonal contraceptives and hormone replacement therapies (39). In this regard, a recent systematic review of 12 studies showed that high-estrogen levels, high estrogen fluctuations, and hormonal replacement therapy were associated with the worst migraine outcomes (42). Menstrual migraine is a specific condition when the timing of the attacks are associated with drops in estrogen levels a few days before menstruation (40, 43). There are close interrelationships between estrogen and several neurotransmitters, including serotonin, norepinephrine, dopamine, catecholamines, and endorphins (40, 43). The results from positron emission tomography (PET) scans show that fluctuations in estrogen have a powerful influence on the balance of the previously mentioned

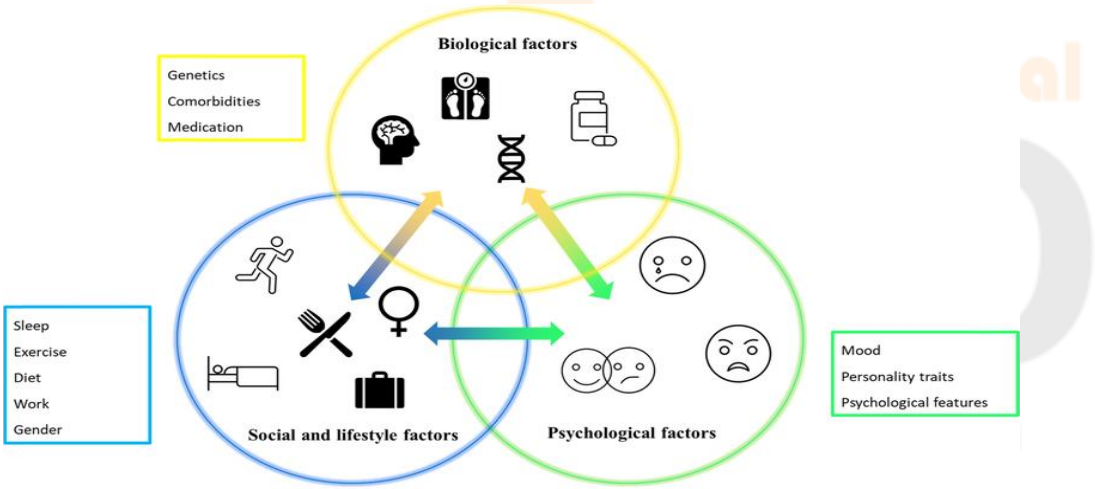
neurotransmitters, which all play a crucial role in the communication between nerve cells (40, 44). Therefore, estrogen administration to premenstrual and menopausal women can decrease the occurrence of migraine headaches (40, 45, 46).

Cortisol

Cortisol is a steroid hormone produced by the adrenal gland in response to stress (47). Elevated cortisol levels create physiological changes and effects a wide range of processes, such as body metabolism, blood pressure, and the immune system (47). One likely hypothesis is that the increased levels of cortisol can cause migraines (47). Another hypothesis is that the increased levels of the stress hormone cortisol, during the early morning, may be responsible for the circadian variation in migraine attacks (48). Surprisingly, these findings were not confirmed in the latest systematic review of the research (47, 48), which found no significant association between cortisol levels and the pathogenesis of migraine (47) or between circadian variations and the onset of migraine attacks (48).

Thyroid Hormones

A bidirectional relationship between migraine and hypothyroididsm has been suggested (49). Migraines may be as a result of high thyroid stimulating hormone (TSH) levels which can lead to pituitary growth and the compression of intrasellar structures (50). Furthermore, a systematic review of case-control studies showed that the weighted overall standardized mean difference for serum levels of TSH, T3, and T4 in migraineurs, compared with non-migraineurs, were 0.80 (95% CI: 0.04, 1.56), −0.27 (95% CI: −0.66, 0.12), and 0.09 (95% CI: −0.08, 0.26), respectively (51). Therefore, migraine and hypothyroidism can be considered to be comorbid (49).



Metabolic Factors

Metabolic syndrome (MetS) is a cluster of metabolic disorders that includes abdominal obesity, diabetes, dyslipidemia, and hypertension (52). Increasing urbanization, hypernutrition, sequential abdominal fat accumulation, and sedentary life styles are the greatest known risk factors for MetS (52). However, a number of studies in different populations have made conflicting findings about the associations migraine has with obesity, diabetes, hypertension, and hypothyroidism (49, 53–59). While obesity is considered a risk factor for episodic

and chronic migraines, this association is most commonly observed in women under the age of 55 years old (53). Therefore, it seems that the association between obesity and migraine is dependent upon gender and age (53). Moreover, several studies have investigated the relationship that migraines have with adipocytokines (i.e., cell signaling proteins that participate in glucose, lipid, and energy homeostasis), but their conflicting findings preclude any solid conclusions (54). The results of a systematic literature review have shown the protective effect of type 1 diabetes on migraines, but there was no significant relationship between migraine and type 2 diabetes (55). The association between migraine and the risk of developing type 2 diabetes was evaluated in a prospective cohort study, which found that the development of type 2 diabetes was reduced in women with active migraines (56). The bilateral association between diabetes and migraine has also been shown in a systematic review and meta-analysis (57).

Genetic and Epigenetic Factors

Epidemiological research has found that genetic factors play a substantial role in the development of both migraine with aura and migraine without aura (65, 66). The concordance rate in monozygotic twins is higher than in dizygotic twins. The evidence also implies that migraine is a heritable trait and data indicates 42% heritability (95% CI: 36–47%) (67). This finding was also supported by the analysis of polygenic risk scores (PRS), which confirmed the familial aggregation of migraine (68, 69). The severity of migraines, and early age of onset, are associated with high PRS in familial cases (68, 69). Familial hemiplegic migraine (FHM) is a monogenic autosomal dominant subtype of migraine with aura, which is caused by mutations in three genes, which are *CACNA1A*, *ATP1A2*, and *SCN1A* (70–72). All three are ion transport-related genes, which control neuronal activity via the modulation of glutamate availability at the synaptic terminals (73). The polygenic nature of complex traits and disorders explains the small, but additive effect of many genetic loci in the pathophysiology of migraine (74). Over the past decade, genome-wide association studies (GWAS) have used high-throughput genotyping technologies to identify the associated loci and variants with migraine risk. The first GWAS on migraine was conducted in 2010, which identified rs1835740 as the first genetic risk factor for migraine (74). In the GWAS conducted to date, increasing the sample size and international collaborations has led to remarkable progress in the identification of the novel genetic variants associated with migraine (75–78). The results of 22 GWAS from the International Headache Genetics Consortium (IHGC) were combined to identify new susceptibility loci for migraine (79). Thirty-eight distinct genomic loci were identified, 28 of which had not been previously reported (79). Expression analysis of the identified genes demonstrated the two most strongly enriched tissues, which included the aorta and tibial artery in the cardiovascular system, and the smooth muscles of the esophagus and the esophageal mucosa in the digestive system (79).

Smoking, Alcohol, and Substance Abuse Disorder

Previous research has identified an association between migraine and the increased risk of substance abuse and addiction (85). Compared to major depression and anxiety disorders, the comorbidity between

substance abuse and migraine is weaker and the findings are sometimes contradictory (86). Since substance abuse also has high comorbidity with BD (bipolar disorder), it is possible that the apparent relationship between migraine and substance abuse could potentially be accounted for by the comorbidity between migraine and BD (86). Alcohol is one of the top 10 migraine triggers, and has been shown to increase the risk of migraine development by up to 51% (87). However, there is also evidence which has found no link between alcohol and migraines (85) and there remains some uncertainty about the mechanisms by which alcohol triggers migraine attacks (88).

Age and Sex

Age, female sex, and low educational status are the most important demographic risk factors for migraine chronification, while higher education can act as a protective factor against migraines (11). Migraines can develop at any age, but the prevalence rate appears to be highest before the age of 45 (89). The prevalence rate rises throughout early adult life, peaking during middle age and then falls gradually (89). Multiple epidemiological studies have found significant sex differences in the prevalence of migraines, with three times as many women affected as men (7, 90). The findings from structural and functional brain MRIs have confirmed sex-related differences in migraine attacks (41). The higher prevalence of migraines in women could be related to several biological and psychological differences between men and women, such as sex hormones, genetic factors, exposure to environmental stressors, as well as the level and response to stress and pain (90, 91). However, the increased prevalence of migraines with the onset of puberty and menarche, during menstruation, pregnancy, and menopauses suggests that fluctuations in sex hormones, especially estrogen, play a critical role in the higher prevalence of migraines in women (90, 92).

Sleep Disorders

There is a strong and significant relationship between sleep and migraines, in which sleep disturbances are associated with migraine type and severity (34, 91). Migraine is associated with different types of sleep problems, like insomnia, sleep-related breathing disorders (e.g., obstructive sleep apnea), sleep-related movement disorders (e.g., restless-leg syndrome), central disorders of hypersomnolence (e.g., narcolepsy), circadian rhythm-related sleep-wake disorders and parasomnia (93). Furthermore, sleep complaints occur with greater frequency among chronic, rather than episodic, migraineurs (94). Sleep problems are also one of the most common factors precipitating migraines (8.3–64%) (87, 95).

Fatigue

Fatigue and chronic fatigue syndrome (CFS) are common in patients with chronic migraines (98). Physical fatigue is often associated with the precipitation of migraine attacks (87). Although the relationship between fatigue, stress, and migraines is complex, migraineurs often report feeling a significant decrease in what they perceive to be a normal degree of physical strength and/or energy (87).

Eating Disorders

Eating disorders have also been found to be associated with migraines (99). Eating disorders may be characterized by specific behaviors, such as avoidance fasting and skipping meals, that may trigger a migraine (88). Eating disorders, including anorexia nervosa (AN) and bulimia nervosa (BN) are severe psychiatric and somatic conditions that occur mainly among young women (88). However, whether eating disorders are linked to migraine, remains somewhat controversial (88). Although the causes of eating disorders are largely unknown, there is evidence to suggest that biological and psychological factors play an important role in the pathogenesis, along with monoamine, indole, and same hypothalamic centered hormonal disorders (89, 100). Migraine is characterized by similar metabolic and psychological anomalies, suggesting that a possible association between the two pathological conditions exists (100). A study by Gebhardt et al. showed that women who had been diagnosed with an eating disorder during their lifetime were twice as likely to also report having a history of migraines, as women from the same cohort without an eating disorder (88). Mustelin et al. hypothesized that this relationship was via the comorbidity that both migraine and eating disorders had with major depression disorder (MDD) (101). Thus, eating disorders may enhance the likelihood of developing a migraine, in a specific subgroups of subjects, possibly through the influence of other factors, such as anxiety or depression (88).

Cardiovascular Diseases

Currently, migraine is considered to be a risk factor for cardiovascular disease (104). This connection is stronger in patients who experience aura than in those without aura (104). Generally, migraines and cardiovascular diseases involve changes in blood flow, meaning that the comorbidity between cardiovascular diseases and migraines may be due to insufficient blood flow to the brain and heart as a result of a genetic predisposition, hormonal imbalance, endothelial dysfunction, coagulation abnormalities, or arterial dissection (104, 105). Polygenic risk analysis of genome-wide association studies, which focused on candidate genes, revealed the predisposing role of genetics in the development of both cardiovascular diseases and migraine (106). Gene expression enrichment analyses have also confirmed there to be a shared biological basis between migraine and coronary artery disease (34, 104, 106–108).

Movement Disorders

Clinical and experimental research on the interactions between migraine and the extrapyramidal system, which is a part of the motor system network causing involuntary actions, confirmed a higher prevalence of migraines in patients with basal ganglia disorders (112). The basal ganglia has an important role in the pathophysiology of some chronic pain disorders, including migraines (112).

Neurological Disorders

The available evidence confirms the co-occurrence of several neurological disorders with migraine (89). This fact highlights the role that the same biological pathways have in the pathogenesis of these disorders. However, similarities in the symptoms of neurological disorders and migraines can also lead to misdiagnosis.

As a result, it seems likely that raising awareness about these comorbidities among health care providers can help to enable better management of these patients. There is also evidence that migraines have a relationship with both epilepsy and multiple sclerosis (117, 118)

Epilepsy

Migraine and epilepsy are distinct neurological disorders, with one of the hallmark of both being their paroxysmal nature (119). Moreover, there are several overlaps in the triggering factors, clinical symptoms, and pathogenic mechanisms (119). Some systemic symptoms, such as nausea, vomiting, visual and other sensory disturbances, such as olfactory dysfunction are common in both migraines and epilepsy (117, 119, 120). Neurogenic and neurovascular findings have found that migraine attacks, like epileptic seizures, can originate from electrical disturbances in the brain (117, 121). Evidence also shows that neuronal over activity in migraine leads to cortical spreading, depression and aura, and that excess neuronal activity leads to the recruitment of larger populations of neurons firing in a rhythmic manner that eventually leads to epileptic seizures (117, 121).

Psychological Risk Factors and Comorbidities

The relationship between migraine and certain psychological factors, such as the tendency toward perfectionism, neuroticism, repressed aggression, and a melancholic mood have been reported for over a century (141). On a theoretical level, triggers raise intriguing questions about the nature of migraines (142). Clinically, triggers seem to be additive, with a migraine resulting when a particular threshold is breached (142). In the laboratory, isolated triggers tend to have less effect than exposure to several triggers in succession (142). This implies that triggers are converging using a common pathway, but the mechanism by which, for instance, psychological, social, occupational, genetic, and nutritional factors interact needs further investigation (142).

Stress

Increasing stress levels contribute to a higher prevalence of migraine (143). In fact, stress may be the most important factor in triggering migraine attacks 97)). However, it should be noted that the word stress means different things to different people and can also be described using various synonymous words. About 70 years ago, Dr. John Graham hypothesized that “migraine is an inherited disorder occurring in people who have both an undue tendency to seek stress and also have a deficiency in their physiological adaptation to stress.” This hypothesis has been shown to be correct by a systematic review which was conducted in 2014 (87).

Anxiety Disorders

Anxiety disorders include generalized anxiety disorder, phobia, panic disorder, and social anxiety (147). Several studies have shown that individuals with migraine are at an increased risk for affective and anxiety disorders (34, 141, 148–151). Among these psychiatric disorders, anxiety is a common comorbidity in migraine patients (91, 152–154).

Panic Disorder

PD is an anxiety disorder in which the patient suffers from panic attacks, which are sudden feelings of terror when there is no real danger (155). Individuals with migraines are between 1.2 and 10 times more likely

to suffer from PD than those without migraine (88, 147, 159), with the highest ORs being for migraine with aura (147). However, these findings contrast slightly with research which has shown phobic and panic disorders to be more common among patients suffering from migraines without aura (160). All cross-sectional studies on the prevalence of psychiatric disorder in migraine patients, compared with individuals' without migraine, have found migraine sufferers have an increased risk of anxiety disorders, particularly PD and phobias (141). According to the literature, PD normally appears earlier in patients with migraine, compared to people without migraines (88). However, like many other anxiety disorders, the relationship between PD and migraine is likely to be bidirectional (141), with the relationship being primarily from migraine to PD, although a weaker significant relationship has also been observed in the opposite direction (88). Migraine increased the risk for the first onset of PD, and PD increased the risk for the first onset of migraine (147). Also, during the follow-up period, the risk of panic disorder and phobia onset were greater for patients with migraine, than for those without (141). The data suggests that the temporal relationship is in the migraine-to-panic disorder direction, rather than the reverse, and also the comorbidity with panic disorder is not specific to migraine, but also includes other headache types (161).

Bipolar Disorder

BD is a chronic disease characterized by repeated manic (or hypomanic) and depressive episodes alternating over a long period of time (155). BD is one of the disorders that has a comorbidity with migraine (11, 34, 141, 170). Patients with BD show an increased prevalence of migraine, which has been reported in up to 55.3% of patients (88) and most often migraine precedes the onset of BD (171). There is research that suggests the prevalence of migraine is higher in subjects with both manic and depressive episodes, than it is among those only with depressive episodes (88). Compared to major depression, the relationship between migraine and bipolar spectrum disorders is about three times higher, with a stronger relationship for migraine with aura than for migraine without aura (147). The comorbidity of migraine and depression made individuals more susceptible to BD, so migraine in depressed patients might be a bipolar spectrum trait (147, 172). The mechanism of comorbidity between BD and migraine may be explained by heritability, alterations in the sodium/calcium channels, pro-inflammatory cytokines, and neurotransmitters (e.g., serotonin, dopamine, and glutamate) (88).

is not strong (174).

Attention Deficit Hyperactivity Disorder

There is very little research on the relationship between migraine and ADHD (85, 183). However, a cross-sectional study reported an increased prevalence of migraine in patients with persistent ADHD, compared with the general population (183). It has been shown that comorbid depression and anxiety were more prevalent in migraine patients with persistent ADHD, in comparison to those without migraines (85). Furthermore, a systematic review and meta-analysis found that there was a significant association between migraine and ADHD (184).

Suicide

Migraine has also been shown to lead to an increased risk of suicidal behaviors, in both the clinical and general population, and among chronic migraineurs with and without aura (185, 186). The research with low bias ratings overwhelmingly supports a strong relationship between migraine and suicidal behaviors (34, 185). The role of depression in this relationship is unquestionable, with a clear bidirectional relationship between depression or anxiety disorders and migraines, which can increase the risk of suicide (34, 88). There is also evidence to show migraines are associated with suicide attempts in migraine patients with aura, even after adjusting for major depression (141, 147). In population studies, migraine sufferers are between 2.2 and 4.0 times more likely to suffer from MDD, than non-migraineurs, and they are also at higher risk for suicide attempts, regardless of depression status (157). A meta-analysis showed a modest positive association between migraine and suicidal ideation (187). However, the complex interaction of factors underlying the relationships between migraine, suicide risk, and mood disorders deserves more scientific attention and research with strong methodological rigor (141).

Herbal medicine for prevention and treatment of migraine

While this research will focus on herbal prevention and treatment of migraine, it is important to note that other natural therapies can be crucial for these purposes as well. It is most important to identify and eliminate triggers of migraines, if possible, and thereby potentially cure the patient's problem without the need for any drug or herbal treatments. It is fairly common that migraine patients are triggered by various foods or food components such as vasoactive amines, tannins, salicylates, food additives, monosodium glutamate, caffeine, aspartame, nitrites, and alcohol. (194-196). It is imperative, therefore, to start most patients on an elimination-challenge diet as soon as possible to identify these food triggers as clearly as possible. It is particularly important to note that use of blood antibody tests for food reactivity is not recommended in this setting, as there are many non-immunologic reactions to food that these tests cannot detect, and will thus deliver false-negative results far too often. One of the most rigorous randomized trials found only a dubious, short-lived benefit from serum antibody guided elimination at best(197). Other triggers that may need to be addressed include regulating the menstrual cycle, managing stress, sleeping on a regular cycle and for enough time, and eating regularly (as fasting is frequently reported as a trigger). While patients work with their practitioner to identify and eliminate triggers, however, herbal medicines may provide symptomatic relief and help calm

reactions by neurovascular processes that trigger migraine, thus potentially contributing to prevention of attacks.

Zingiberaceae Herbs and Migraine

One of the most clinically effective herbs for preventing and treating migraine is Zingiber officinale (ginger) rhizome, from the Zingiberaceae family(198), It is native to southern and southeastern Asia. It has a long history of use for rheumatic pain, headache, indigestion, and motion sickness, all of which have been confirmed to varying degrees in modern clinical trials(199). Here, the efficacy, safety, and mechanisms of action of ginger in migraine will be reviewed in more depth. The most recent double-blind clinical trial of ginger for migraine randomized 100 Iranian patients to take either ginger powder 250 mg or sumatriptan 50 mg at the onset of migraine for one month(200). There was no difference between the groups in terms of the percentage that achieved 90% headache pain relief within two hours of taking their assigned treatment (64% for ginger, and 70% for sumatriptan) or in terms of satisfaction with treatment (88% for ginger and 86% for sumatriptan in terms of having high or superior satisfaction). The therapeutic equivalence between the two treatments was particularly notable, given the low dose of ginger used. Those who took sumatriptan were significantly more likely to report adverse effects than those who took ginger, with upset stomach being the only adverse effect reported for ginger. Other trials using a combination of ginger and feverfew are discussed later, but together this all supports the use of this extremely common, inexpensive, and safe treatment as a first-line treatment for acute migraine headache. Numerous constituents in ginger have been shown to have actions that would explain its beneficial effect in migraine. Zerumbone, a sesquiterpene lactone found in ginger as well as other members of the Zingiberaceae family, has been shown to be an agonist of 5-HT1A/B(201). This reduces neuropathic pain in mice. Aromatic phenylpropanoid derivatives such as [6]- gingerol and various shogaols mainly appear to inhibit 5-HT3, which is clearly part of their antinauseal action and which may help offset digestive symptoms that commonly co-occur with migraine headache(202). Crude ginger extracts have been experimentally shown to inhibit CGRP and calcium channels, both of which are crucial to migraine path physiology (203-204).

The usual recommended dose of ginger is 1,000 mg of crude powder in capsule, 1–2 mL of tincture, or 2–3 mL of glycerite, or one cup of tea (made from 2–3 g of rhizome) at the onset of a migraine. A second dose

should be taken after two hours if there are still symptoms. Doses should be reduced with subsequent use if heartburn or gastric irritation occur with the stated doses. The sooner treatment is initiated, the better it works generally. Patients who feel cold, who have migraine aura, and who have nausea are most likely to respond favorably to ginger. Other substitutes used at very similar doses in the Zingiberaceae family include Alpinia galanga (greater galangal), A. officarinum (lesser galangal), Curcuma zedoaria (white turmeric), and Kaempferia galanga (sand ginger) rhizomes or Aframomum melegueta (grains of paradise) or Elettaria cardamomum (cardmomum) fruit. Other Zingiberaceae family plants show promise for migraine patients as well, most prominently Curcuma longa (turmeric) rhizome. Among other potentially beneficial mechanisms, particularly inflammation modulation, studies in humans with other conditions consistently show that oral curcuminoids reduce CGRP levels (205-206). One randomized trial of 74 Iranian migraine patients found that a combination of a formulation of curcumin using nanotechnology with fish oil significantly reduced frequency of migraine attacks compared to either treatment by itself (207). Further research is needed to confirm this, but it presents a potentially very useful and safe way to prevent migraine recurrence. A usual dose of crude turmeric is 3–5 g b.i.d. with food, or of curcumin, 1 g b.i.d.–t.i.d. with food.

Feverfew

Tanacetum parthenium (feverfew) is perhaps the best known herb today for migraine prophylaxis and treatment. This umble member of the Asteraceae family is native to central Eurasia but is now widely cultivated in North America as well. Clinical trials regarding using the leaf to prevent migraines started to appear in the 1980s (208). Previously, it was little known in the general Western herbal world, but may have had uses as an antirheumatic and, as the common name suggests, a febrifuge in traditional medicine. In a meta-analysis of five clinical trials, feverfew was not effective for preventing migraines (209). There are many explanations for this, including variability between the extracts tested, but it could be that it is simply not that effective. There is also extensive evidence that different parts of feverfew (leaf, flower, or both) from different regions have quite variable chemistry, which may have also contributed to differences in efficacy between trials and in different clinical preparations (210-211). One additional randomized, doubleblind trial (published after the meta-analysis noted above) of a supercritical carbon dioxide extract of feverfew in 170 German migraine patients found it was more effective than placebo at preventing migraine attacks with no increased adverse effects (212). Clinically, the author has also only very rarely seen feverfew help patients prevent migraines, and so it is not recommended for use unless other treatments fail. Combinations of feverfew and other natural products have also been studied, with mixed results. An open trial of 12 French migraine patients used a combination of 300 mg of feverfew and Salix alba (white willow) bark twice daily and found it significantly reduced frequency and severity of migraine headaches compared to baseline (213). A combination of feverfew 100 mg, riboflavin 400 mg, and magnesium 300 mg was no better than riboflavin 25 mg at reducing migraine frequency in a double-blind, randomized trial in 49 American migraine patients(214). Both products allowed 42–44% of patients to achieve a 50% reduction in migraine frequency. This fits with prior research showing that high-dose riboflavin

by itself is effective at preventing migraine recurrence, though not all trials have reached the same conclusion (215-216). Given the incredible safety of riboflavin and its extremely low cost, it is still worth considering adding this to protocols for migraine prevention. Many lines of experimental evidence suggest a range of antimigraine actions for feverfew. The transient receptor potential A1 (TRPA1) or ankyrin 1 receptor is integrally involved in stimulating CGRP release from neurons in response to a wide range of migraine-initiating stimuli, and the sesquiterpene lactone known as parthenolide from feverfew has been shown to block this receptor experimentally (217). Feverfew extracts, related in part to their parthenolide content, have also been shown to inhibit serotonin release from platelets, a known problem in many migraine sufferers (218). Crude feverfew powder (and, less potently, feverfew extracts or isolated parthenolide) block neuronal serotonin release, and the crude powder inhibited 5-HT2A/2B receptors in rats, degrading parthenolide content in extracts by > 10%, with heat exposure dramatically abrogated such activity(219).

Butterbur

Petasites spp. are native in a ring around the Northern Hemisphere and are in the Asteraceae family. Though sometimes called coltsfoot, this common name is better applied to Tussilago farfara, a similar-appearing Asteraceae family plant but with completely different actions. This name confusion is also important because Petasites contains far more dangerous unsaturated pyrrolizidine alkaloids (uPA) than Tussilago, and some cases of supposed Tussilago-induced hepatotoxicity were actually due to Petasites (220). This also means that only butterbur that has been processed to remove the uPAshould be used long term. Use of such extracts has been shown to be safe (221). Combination of butterbur with Glycyrrhiza glabra (licorice) may also reduce risk from any lingering uPA, as this herb's constituent glycyrrhizin has repeatedly been shown to offset the toxicity of uPAs in rodents (222-23). A meta-analysis of two randomized clinical trials of a uPAfree butterbur extract at a dose of 50 mg b.i.d.–t.i.d found they reduced frequency of migraine compared to placebo (224). However, the data from the trials could not be combined due to heterogeneity. A total of 293 subjects were involved in the trials, which lasted 12–16 weeks. Since this meta-analysis was published, a preliminary, randomized, double-blind trial in 58 German children with migraines was published that compared the same butterbur extract, music therapy, and placebo (225). Only music therapy reduced migraine attack frequency compared to placebo eight weeks after the end of the 12-week treatment period, but both butterbur and music

therapy reduced migraine frequency compared to placebo six months after the end of treatment. Clearly, more research is needed, but this provides some preliminary support for using butterbur extracts to prevent migraine.

Ergot: From Herb to Drug

Claviceps purpurea (ergot of rye, though it also infests wheat, triticale, and barley) and other species of this genus of fungus are a fascinating study of an ancient herbal medicine and also a major cause of disease. Eventually, it gave rise to a whole class of extremely useful, multifunctional medicines, including the natural alkaloids ergotamine and ergometrine (ergonovine) and the synthetic derivatives methylergometrine (methylergonovine), dihydroergotamine, ergoloid mesylates, methysergide, cabergoline, pergolide, and bromocriptine. Ergot of rye was recognized in ancient times (in writing, at least as early as 600 BCE) as a contaminant of grains (226). Failure to understand the toxicity of eating too much ergot led to periodical epidemics of what was almost certainly ergotism, based on symptomatic descriptions that are very close to this disease. This includes epidemic outbreaks throughout the Middle Ages of gangrene, nausea, vomiting, and burning pain in the limbs, or convulsions and hallucinations, which often led to death. (227). Such problems were exacerbated by famines and wars when poor people were forced to eat low-quality rye without removing the ergot. The role of ergot in causing epidemic ergotism was not recognized until 1630, though epidemics still occurred after this time (228). Ergot was also recognized since ancient times as a method of inducing abortion early in pregnancy, stopping postpartum hemorrhage, and inducing labor (229). Unfortunately, dosing of crude ergot was a tricky business: use too little and it wouldn't work; use too much and it could cause severe toxicity or kill. It was also a problem as ergot lost its potency after just two to three months. In 1822, David Hosack (1769–1835), a ScottishAmerican physician and botanist, published an influential paper describing a precipitous rise in stillborn children in New York that he linked to the widespread use of ergot (230). However, its use continued to rise, and it was entered into many national pharmacopoeias in the 19th century. The first descriptions of using ergot to treat migraine also appeared in the 1800s, perhaps starting with Edward Woakes (1837–1912), a British physician, in 1868, and more clearly by Albert Eulenburg (1840–1917), a German neurologist, in 1883 (231). Ergotamine was isolated in 1818 by Arthur Stoll (1887–1971), a Swiss biochemist, and came into wide use as an acute migraine treatment in 1926. It is now known that ergotamine is a 5-HT1 agonist very similar to triptans, though being less specific to 5-HT1B/1D receptors (which are found predominantly in the central nervous system and meningeal blood vessels compared to other receptors in the family), and is more likely than triptans to cause nausea, vomiting, and peripheral vasoconstriction, potentially leading even to intermittent claudication or gangrene. Furthermore, oral ergotamine is very poorly absorbed,

though this is improved by its combination with caffeine. Therefore, it is mainly used as a either a suppository, tablet, or sublingual tablet in a dose of 1– 2 mg combined with 100 mg of caffeine, which is taken at the first sign of aura or migraine pain.

Menthol

Menthol is a naturally occurring compound found in mint plants such as peppermint and spearmint. It promotes a cooling sensation when applied to the skin and mucosal skin and works on nerve fibers and smooth muscle fibers. Menthol has several side effects that can positively affect migraine pathology. It has analgesic effects by making the kappa opioid receptor; acts on TRPM8 receptors to produce a cooling sensation and inhibits energy-sensitive sodium channels (inhibiting sensory reduction); as a spasmolytic agent, it may contribute to the tendency of precranial tissue and by correcting myofascial input, reduce cognitive impairment such as migraine intolerance; can prevent the transmission of nociceptive sensations from pain-producing vessels, through the branches of the trigeminal nerve, to higher brain centers; and with its anti-inflammatory effects, by suppressing prostaglandin E2, leukotriene B4, and interleukin-1β, it may act as a pain reliever.

Coriander

Coriander (C. sativum), a member of the family Apiaceae (Umbelliferae), Fruit (seeds) forms an important component of curry powder and is traditionally used to treat intestinal disorders such as loss of appetite, dyspepsia, bloating, diarrhea, pain, and vomiting. Fruits (seeds and pericarp) are the most widely used coriander plant and the most important nutrients are essential oils and oils Coriander and its constituents as a promising treatment for migraines as shown in animal studies that coriander has analgesic and anti-inflammatory activity and can delay both neurogenic pain and inflammation. Lanalol Corriander is considered safe and well tolerated, based on animal toxicology studies. However, it can lower blood glucose levels and have hypotensive effects so caution is needed in qualified individuals .

Ginger

Ginger (Zingiber officinale Rosc.), belonging to a tropical and sub-tropical family – Zingiberaceae, originating in South-East Asia and introduced to many parts of the globe, has been cultivated for thousands of years as a spice and for medicinal purposes . Ginger have been proposed to justify the analgesic action of ginger, including the inhibition of arachidonic acid metabolism via the cyclooxygenase (COX) pathways, similar to the non-steroidal anti-inflammatory drugs. Ginger also acts to block lipoxygenase (LOX), another enzyme associated with the arachidonic acid pathway . The concomitant inhibition of COX and LOX may increase anti-inflammatory action and reduce its side effects. Furthermore, shogaols seem to modulate neuroinflammatory response through the down-regulation of inflammatory markers on microglial cells, while gingerols may act as agonists of the capsaicin-activated vanilloid receptors. To date, only a few uncontrolled studies and one case report have shown the analgesic effect of ginger in migraine

Conclusion

Numerous herbs, herbal constituents, and herbal formulas have been shown to have varying degrees of benefit for preventing or treating migraine. For patients with relatively mild migraines, ginger (most clinically effective), cannabis, intranasal cayenne (best evidence), or Spanish lavender volatile oil could all be considered for initial treatment, particularly by patients who prefer to avoid pharmaceuticals. While triggers are being identified and eliminated if possible, a large number of herbs could be tried for prevention, but butterbur, Spanish lavender volatile oil, turmeric and fish oil, citron, or Rectify Heaven Formula could all be tried for mild migraines. Feverfew (with or without willow), ginkgo, and bushy mat grass are less well supported for prevention. All these same treatments could be used in patients with more severe migraines, but they are probably best used in combination with pharmaceutical agents. Patients who have not responded, or who have responded poorly, to multiple medications are another group who could find real benefit in these very different treatment options. Often it requires trying one or more natural products along with trigger elimination to achieve good clinical results. The safety and low cost of the natural products recommended here are other strong reasons to consider their clinical use.

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