REVIEW ARTICLE

Melatonin: Role in the Prophylaxis of Migraine

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Abstract

Melatonin and migraine have been linked in most ways, from mechanisms to treatment. Migraine is one of the common neurological diseases and it is characterized by throbbing unilateral headache attacks. Migraine is an issue for both individuals and society. Migraine can lead to reduced work productivity and a flawed family and social life. It has been suggested that melatonin plays a key therapeutic role in treating migraines and several other types of headaches. Early and exact diagnosis is essential in enhancing treatment and in preventing progression. This review aimed to evaluate the available evidence related to the efficacy and safety of melatonin in the prophylaxis and prevention of migraine. Research in regard the administration of melatonin found it safe in migraine patients, with few or no side effects. This review concluded that Melatonin can be considered a safe integrative prophylactic treatment for children, adults and menstrual-related migraines, thus improving outcomes related to patient's quality of life and patient-centered care. However, further studies and evaluation is required to confirm its effects.This review aimed to evaluate the available evidence related to the efficacy and safety of melatonin in migraine prophylaxis. Melatonin and migraine have been linked in a majority of ways, from mechanisms to treatment. Melatonin is an endogenous hormone and is secreted by the pineal gland. It plays an important role in regulating circadian rhythm and the sleep-wake cycle. It has been proposed for migraine prevention due to its anti-inflammatory effects against calcitonin gene-related peptides and other pro-inflammatory mediators in vitro, and its pro-regulatory effect on the circadian rhythm. Also, low melatonin levels have been reported in serum and urine due to hypothalamic dysfunction in patients with migraine. Hence, in this article, we review those papers describing the results of the administration of melatonin in humans for therapeutic purposes in treating migraines.This narrative literature review was based on studies on Melatonin's effectiveness, safety and tolerability for the prophylactic and preventive treatment of migraine in children and adolescents and menstruating women. The literature search was conducted using the Google Scholar and PubMed database and included articles published up to December 2021, utilizing the keywords: "melatonin", "migraine", "melatonin and migraine", and "prophylaxis of migraine". Observational studies, randomized controlled trials (RCTs), case reports and systematic reviews were included. The articles focusing on the latest medication for preventing migraines were also reviewed.

Keywords: Melatonin, Migraine, Prophlyaxis, Menstrual Related Migraines, Agomelatine.

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INTRODUCTION

MIGRAINE

Migraine is the most common of all neurological diseases. Migraines are described as throbbing unilateral headache attacks, which are also associated with phonophobia, photophobia, nausea, and vomiting, and are usually exacerbated by physical activity.[1, 2]

Migraine affects at least 1 in 10 people globally, and its prevalence is on the rise. According to the World Health Organization (WHO), migraines rank as the second most disabling neurological condition and the third most prevalent medical condition in the world.[3-5]

Migraines may be unilateral, may change sides, and often involve the head's posterior cervical and trapezius regions.[3, 4, 6] However, migraines can also be bilateral, in which case they may be confused with tension-type headaches.[7] The headaches are often associated with other symptoms, such as sensitivity to light and sound, dizziness, tinnitus, gastrointestinal disturbances, cognitive impairment, and cutaneous allodynia - or the onset of pain in response to non-painful stimuli being applied to the skin.[3, 4, 8]

The frequency, intensity, and symptoms vary from patient to patient and even from attack to attack in a single patient.[9]

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Migraines can occur anytime, but they often occur soon after waking or early in the morning. The median time for a migraine headache to reach its peak pain intensity is 1 hour, though the median duration is 24 hours. [2]

Symptoms Related to Migraine

Migraines are characterized by premonitory and postdromal symptoms. Acute migraines are often preceded by premonitory symptoms that usually last for hours or days.[10] The most common symptoms include fatigue, neck stiffness, and trouble concentrating. Other symptoms that may be experienced are psychological symptoms, such as anxiety

or depression, as well as lacrimation, photophobia, diarrhea, increased urination, food cravings, and nausea.[11]

Once the migraines headache resolves, 80% of migraines sufferers undergo a postdromal phase that can potentially last for days.[12-15] Symptoms during this phase include fatigue, photophobia, nausea, irritability, and problems with concentration.[2, 4]

Risk Factors for Migraines

Genetics

Migraines run in families. For those with a parent who suffers from migraines, there is a 40% chance of developing migraines too. If both parents have migraine, then the risk increases to 75%. Research related to genetics is turning out to be useful in providing more information on the specific genes that may be involved in migraines. [3]

Age

It has been reported that those between the ages of 25 and 55 are most likely to suffer from migraines and that 18- to 44-year-olds have the highest migraines.[4, 17] However, it seems clear that prevalence reaches a peak in people in their 40s.[5]

Sex and Race

The lifetime prevalence of migraines is estimated at 33% for women, and 13% for men, though before puberty, migraines occur slightly more frequently in boys than in girls.[4, 18] Data from 2015 suggest that migraines occur most in American Indian and Alaska Native populations, with a prevalence of more than 18% in these groups. Asians were found to suffer less from migraines not only from these groups but also from whites, blacks, and hispanics. The prevalence of migraines amongst Asians was found to be approximately 11%.

Other Factors

Migraines prevalence is over 21% in those who are unemployed and nearly 20% in those with an annual family income of less than $35,000.28 These associations do not, however, provide any information on if these conditions may cause migraines or vice versa.[3]

Diagnostic Criteria

The International Headache Society [18, 19] classifies migraine according to whether the patient experiences an aura.

Migraine without aura

Migraine without aura (previously called common migraine) is a headache that, if untreated or unsuccessfully treated, lasts 4 to 72 hours and is at least two of the following:

- Unilateral
- Pulsating
- Moderate to severe in intensity
- Aggravated by usual physical activity.

In addition, the symptoms must not be attributable to another disorder, and at least one of the following must be present during the headache:

- Nausea or vomiting, or both
- Photophobia or phonophobia, or both.[18, 19]

Migraine with aura

Migraine with aura was previously called classic migraine. An aura is a combination of focal neurologic

Symptoms preceding or accompanying the migraine attack. The symptoms may affect vision (flickering lights, blurring or loss of vision), sensation ("pins and needles," numbness), and speech (dysphasia). Visual symptoms are the most common. Auras typically develop gradually, lasting 5 minutes to 1 hour, and then completely disappearing.[9, 18, 19]

Pathophysiology of Migraine

Migraine is a common primary headache with a high disability and complex, hereditary neurovascular conditions arising based on the functional and structural abnormality of the brain.[21, 22] The exact neurovascular pathogenesis of migraine remains unclear. It was reported that migraine headache depends on altered excitability or dysfunction of the brain state by activating the trigeminovascular pathway.[21, 23] Several neuropeptides, such as calcitonin gene-related peptides, nitric oxide, serotonin, and glutamate, are involved in the pathogenesis of migraine. [21, 22, 26]

It is believed that various triggering factors activate the trigeminal nerve and trigeminovascular system, leading to the release of several neurotransmitters (calcitonin gene-related peptide, substance P) that affect vasomotor tone, causing neurogenic inflammation of intracranial and extracranial cerebral vessels.[20] Before or during the onset of aura, the brain's arteries first undergo vasoconstriction with decreased blood flow, followed by hyperemia and headache.[18] Common triggers of migraine headache include alcohol, anxiety, change in sleep pattern, depression, flashing lights, visual stimulation foods and beverages containing- nitrites, aspartate, glutamate, tyramine, high altitude medications—nitroglycerine, hydralazine, histamine, estrogen, reserpine, steroid withdrawal, menstruation, ovulation, organic solvents, perfumes, physical exertion, sexual activity, skipping meals, smoke, stress and weather changes.[9]

Treatment for Migraines

Management includes non-pharmacological, behavioral and physical measures and pharmacotherapy.[27]

The pharmacologic types of treatment include abortive (acute) and preventive (prophylactic) therapy. These two types differ significantly in their mechanisms as abortive treatment is used to attenuate symptoms of the attacks whereas preventive therapy is used to reduce headache frequency, severity, or duration.[1, 28] Till now nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, ergot alkaloids, and triptans are the drugs being used for an acute attack of migraine.[27]

Prophylactic treatment is indicated if acute treatment alone is insufficient, the patient experiences more than two to three attacks per month, contraindication of acute therapy, use of abortive medicine more than twice a month, presence of migraine with prolonged aura, hemiplegic migraine, migrainous infarction. [29, 30] A variety of diverse pharmacological classes of drugs are used to prevent attack. Medications with proven effectiveness for prevention include β-blockers, calcium channel blockers, antiepileptic drugs and antidepressants. But these all available drugs have certain limitations. [27, 31]

In recent years, complementary and integrative medicines (CIMs) have been increasingly used for health maintenance and treating diseases like migraines.[32, 33] The integrative medicines used for preventing migraines include riboflavin, coenzyme Q10, magnesium, melatonin, polyunsaturated fatty acids (PUFAs), feverfew, butterbur, vitamin D, and ginkgolide.[34, 35] Integrative medications are becoming a regular choice for migraine prevention as they do not produce severe side effects, and underlying research data propose their efficacy in preventing migraine. Additional studies are warranted to confirm the role of CIMs in treating patients with migraines.[32]

MELATONIN

Melatonin is also known as the 'sleep hormone'.[36] Melatonin (N-acetyl-5-methoxytryptamine) is an indole compound mainly produced in the pineal gland from tryptophan amino acid and secreted into the blood cerebrospinal fluid and its main role is modulation of the circadian rhythm of sleep.[39, 40]

Melatonin was discovered by Aaron Lerner in 1960.[41, 42] Melatonin is synthesized during the night in the pineal gland from tryptophan, taken up from the circulation and transformed into serotonin. The serotonin is then converted into melatonin by a two-step process involving two enzymes, serotonin-N-acetyltransferase (NAT), the limiting enzyme in the synthesis of melatonin, and hydroxy indole-*O*-methyltransferase (HIOMT).[41, 43, 44] Melatonin is produced according to an endogenous circadian rhythm (circa dies = around a day) under the influence of the master circadian clock located in the supra-chiasmatic nucleus (SCN). For most people, the periodicity of the circadian clock is closed to 24 hours and the clock is reset every morning by exposure to daylight. [41, 45] Melatonin secretion is inhibited by light and is produced only during darkness (melatonin is a darkness hormone).[41] During the night, 80% of melatonin is produced which results in serum concentrations varying between 80–120 pg/mL. The serum concentrations are low during the daytime (10-20 pg/mL).[36, 38]

Melatonin is well established to have anti-oxidant, anti-inflammatory and immune-modulatory effects. Melatonin is also known to have anti-depressant, anti-anxiety, anti-nociceptive and anti-neophobic effects.[36, 38]

NEED FOR THE PROPHYLACTIC TREATMENT OF MIGRAINE

Migraine is a common disabling primary headache disorder of high prevalence and high socio-economic and personal impacts.[10] Migraine is an issue for both individuals and society and causes reduced productivity at work and impaired family and social life.[47, 48] Early and accurate diagnosis is fundamental in optimizing treatment and in preventing progression.[47-49]

- Prophylactic therapy is essential in order to reduce recurrences and relapses and may be measured in terms of
- The reduction in the frequency of acute attacks,
- The impact of acute treatment on headache recurrence within the next 24 hours,
- Reduction in overall functional impairment.

According to recent guidelines candidates eligible for prophylaxis for migraine should have the following features:

- Migraine attacks exceeding more than two per month or migraines unmanageable by acute therapy,
- strong side effects of acute therapy,
- contraindication, failure of acute medication,
- use of acute medication more than twice per week,[47, 50, 51] and risk of overusing acute medication.[47, 5]

The goal of prophylactic treatment is to reduce the frequency and intensity of attacks and improve the quality of life.[47, 52-54, 57] The prophylactic therapy may cause problems in relation to adverse effects (e.g., fatigue, dizziness, reduced concentration, loss of appetite, weight gain, hair loss, changes in libido, and drowsiness), tolerability, cost, dosing frequency, the patient's compliance, and failure to complete treatment.[49, 59]

Exploratory efficacy outcome measures should include the number of migraine attacks per four weeks, number of headache days, pain intensity, headache index, and global response.[47, 58]

MELATONIN ROLE IN THE PROPHYLAXIS OF MIGRAINE

There is growing evidence that headaches are connected to melatonin secretion.[62] The level of melatonin might be decreased in migraine headaches and it may play an important role in migraine pathogenesis.[39, 40] Also, the quality and quantity of sleep decreases in patients with migraines.[47, 60, 61]

Melatonin is known to exert an anti-migraine effect in a variety of ways. Melatonin's antioxidant effect protects the brain from damage occurred due to toxic molecules. It helps maintain brain structural and functional integrity by acting as membrane-stabilizer. It can prevent the migraine attacks its controlling neural pathways and neurotransmitters, for example, inhibiting dopamine release, limiting nitric oxide synthesis, and antagonizing excitotoxicity. Also, Melatonin can regulate the brain's blood flow by suppressing Calcitonin

gene-related peptide (CGRP) release.[1, 63, 64] It is found that Melatonin also exhibits analgesic action via the release of endorphins. Thus, Melatonin's anxiolytic and antidepressant properties can also help with migraine patient's' pain feelings.[36, 63]

Melatonin is similar to indomethacin, a non-steroidal anti-inflammatory drug (NSAID) belonging to indoles for various headaches.[65, 67] It has been shown that melatonin 3 mg is effective for migraine prevention, but further work is needed to determine whether there is a dose response.[64, 65] Melatonin receptors (MT1 and MT2) are present in the suprachiasmatic nucleus of the hypothalamus, so direct action of exogenous melatonin at the hypothalamus is possible.[65, 66]

It has been suggested melatonin may play a key therapeutic role in the treatment of migraines and several other types of headaches, specifically those related to delayed sleep phase syndrome. Current research supports the hypothesis that migraines result from pineal circadian irregularity in cases in which the administration of melatonin can normalize this circadian cycle; i.e., melatonin may play a role in resynchronizing biological rhythms to lifestyle and after that relieve migraines and other forms of headaches. In addition, research testing the administration of melatonin found it safe in migraine sufferers, with few or no side effects.[61]

FINDINGS

Melatonin is a multi-functional hormone that is yet to be studied. Exogenous melatonin is increasingly becoming an integral part of the treatment program for various sleep disorders.[68]

Melatonin, as a promising treatment for migraines,[69] has been investigated in different studies including adults, pediatrics and menstruating women. Various comparative studies of melatonin with other prophylactic drugs used in the prevention of migraines like amitriptyline, topiramate, propranolol, and sodium valproate have also been done.

To assess the potential effectiveness of melatonin for primary headache prevention, a study was conducted by Bougea *et al.* [62] on 49 patients (37 with migraine and 12 with chronic tension-type headache, TTH). They were prescribed oral melatonin, 4 mg, and 30 minutes before bedtime for six months. A statistically significant reduction in headache frequency was found between baseline and final follow-up after six months of treatment. [62]

Amitriptyline has proved to be efficient for migraine prevention, but its use has been limited due to its side effects. Several studies have been conducted to compare the efficacy of melatonin with amitriptyline in headache disorders. In one study carried out by Gonclaves AL et al. [64] in 178 patients to compare melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention, it was found that Melatonin was superior to Amitriptyline with a greater than 50% reduction in migraine frequency. Melatonin was better tolerated than amitriptyline. Also, weight loss was found in the melatonin group, a slight weight gain in placebo and significantly for amitriptyline users. [64]

Besides amitriptyline, few other antidepressants are efficacious for migraine prophylaxis. Among antidepressants, agomelatine has a unique neurochemical mechanism. Some studies have been done on using melatonin as an antimigraine agent. It is an agonist for both melatonin receptor 1 and melatonin receptor 2 and a selective antagonist of the 5-hydroxytryptamine (serotonin) 2C receptors. Given its specific mechanism of action and similarity with melatonin, agomelatine may be a promising new treatment option for migraine prophylaxis. The potential therapeutic action of agomelatine could be due to its synergistic action on both melatonergic and 5-HT2C receptors. [70]

Topiramate was first approved in 1996 as an antiepileptic drug and was later approved in 2004 for migraine prophylaxis in adults.[1, 71] Not many studies have been conducted to compare the effectiveness of Melatonin with Topiramate. In a study conducted by Alkhaffaf *et al.* [1] to compare the effectiveness and tolerability of these drugs as monotherapy in migraine prophylaxis and to support the use of Melatonin as preventive therapy. 200 patients diagnosed with migraine were enrolled. This study showed that Melatonin is effective as Topiramate for episodic migraine prophylaxis. Moreover, it is more tolerated and has fewer adverse events than Topiramate. [1]

To investigate the therapeutic effect of melatonin versus sodium valproate in the prophylaxis of chronic migraine, a study was conducted by Monfared E *et al.* [72] The trial included patients with chronic migraine who were divided into three equal-sized groups and baseline therapy with nortriptyline (10–25 mg) and propranolol (20–40 mg) was used. Patients in groups A, B, and C were adjunctively treated daily with 3 mg melatonin, 200 mg sodium valproate, and a placebo for 2 months and followed up. The study concluded that adjuvant melatonin treatment was superior to the placebo and had the same clinical efficacy as sodium valproate, but with higher tolerability. Melatonin may prove to be an efficient substitute for sodium valproate, as a chronic migraine prophylaxis.[72]

FDA has approved Propranolol for migraine prophylaxis where studies have found that chronic therapy with propranolol reduces the frequency and severity of migraine in 60 to 80 per cent of patients.[46, 73, 74] A study conducted by Ali *et al.*, [75, 77] to compare the effectiveness of melatonin for migraine prevention with propranolol concluded that melatonin has similar efficacy to propranolol in migraine prevention with comparable safety for Aspartate Aminotransferases(AST), Alanine Aminotransferases(ALT) [75, 77] and serum creatinine[76] levels. Melatonin might be recommended as an option for common migraine prevention for patients not well tolerated with Propranolol. [46]

There are limited data about the role of melatonin in migraine and menstrual-related headaches.[69]

When menstrual related migraines are considered, more than 90% of migraine attacks occur between the two days

Table 1: Various studies involving the use of Melatonin on Migraine and associated discomforts

STUDY	*DESIGN*	*TITLE*	*SAMPLE SIZE*	*CONCLUSION*
Bougea A et al. [62]	Pilot study	To assess the potential effectiveness of melatonin for primary headache prevention.	Forty-nine patients (37 with migraine and 12 with chronic tension-type headache, TTH) were prescribed oral melatonin, 4 mg, and 30 minutes before bedtime for six months.	This pilot study showed promising results, in terms of headache frequency reduction and daily quality of life improvement, in both groups.
Ansari et al. [87]	Prospective, observational study	To determine the anti-inflammatory effects of melatonin on the CGRP expression, inducible nitric oxide synthase (iNOS) activity, NO, and IL-1β release.	This study was performed on 12 pure menstrual migraine patients and 12 age-and sex-matched healthy subjects	Melatonin treatment significantly decreases mRNA expression of CGRP release, NO production, and iNOS (inducible nitric oxide synthase) activity in the patient groups.
Gonçalves AL et al. [64]	Randomized, double-blind, placebo-controlled study	Comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention	196 participants were randomized to placebo, amitriptyline 25 mg or melatonin 3 mg, and were Followed for 3 months.	Melatonin 3 mg is better than placebo for migraine prevention, and more tolerable than amitriptyline and as effective as amitriptyline 25 mg.
Alkhaffaf et al. [1]	Prospective, comparative study	To compare the effectiveness and tolerability of Topiramate and Melatonin in a migraine prophylaxis	160 patients, (76 in the topiramate group (50mg) and 84 in the melatonin group (3mg). Followed up for 3 months 160 patients, (76 in the topiramate group and 84 in melatonin group). 160 patients, (76 in topiramate group and 84 in melatonin group).160 patients, (76 in topiramate group and 84 in the melatonin group).	This study showed that Melatonin is effective as Topiramate for episodic migraine prophylaxis. Moreover, it is more tolerated and has fewer adverse events than Topiramate.
Fallah et al. [32]	Prospective, comparative study	To compare the effectiveness and tolerability of melatonin and amitriptyline in pediatric migraine prevention.	Forty-one girls and 39 boys were randomly allocated to receive 1 mg/kg amitriptyline or 0.3 mg/kg melatonin for three consecutive months.	Both drugs were effective in the reduction of monthly frequency, severity, duration and disability of migraine. Daily sleepiness was seen in 7.5% of the melatonin group as a side effect and adverse events were seen in 22.5% of the amitriptyline group including daily sleepiness, constipation and fatigue. Melatonin was found to be safer than amitriptyline
Fallah R et al. [90]	Experimental study	The present research aimed to investigate the safety and efficacy of melatonin in pediatric migraine prophylaxis.	32 girls and 28 boys were treated with a single dose of 0.3 mg/kg melatonin for three months.	Monthly frequency, severity and duration of headache reduced. Melatonin might be considered an effective and without life-threatening side effects drug in the prophylaxis of migraine in children.
Kozak et al. [94]	Case-control study	To assess levels of serum melatonin in migraine patients	55 (47 females and 8 males) were compared to 57 gender and age-matched control subjects (40 females and 17 males).	In comparison with controls, melatonin levels were significantly lower among migraine patients.
Ali et al. [46]	Prospective, comparative, interventional study	To compare the effectiveness of melatonin for migraine prevention in comparison with FDA-approved propranolol.	41 common migraineurs patients were enrolled in this study and divided into two groups. Group 1 included 21 patients treated with melatonin 5mg tablet daily, whereas group2 included 20 patients treated with Propranolol 40 mg tablet twice daily.	Melatonin has similar efficacy to the FDA-approved drug propranolol in the common migraine prevention within comparable safety for AST, ALT and serum creatinine. Melatonin might be recommended as an option of choice for common migraine prevention for patients that are not well tolerated propranolol.

***Abbasian P et al.*[91]**	Prospective, comparative study	To investigate the effect of propranolol with melatonin on improving migraine intensity in patients without sleeps disorders.	49 patients with migraine were randomly divided into two groups (27 boys and 22 girls). The first group (control group) was treated with propranolol tablets daily and the second group (case group) was treated with propranolol and melatonin tablets daily and followed up for 3 months.	Propranolol alone can be considered an effective drug for the treatment of various migraine headaches in children, but the results showed that melatonin consumption, especially with a duration of use of more than one month if combined with propranolol, can be both more effective in reducing patient's headaches and improving treatment satisfaction.
***Monfared E et al.*[72]**	Randomized, double-blind, placebo-controlled clinical	This study aimed to investigate the therapeutic effect of melatonin versus sodium valproate in chronic migraine prophylaxis.	Patients with chronic migraine were divided into three equal-sized groups, and baseline therapy with nortriptyline (10–25mg) and propranolol (20–40mg) was used. Patients in groups A, B, and C were adjunctively treated daily with 3mg melatonin, 200mg sodium valproate, and a placebo, respectively for 2 months	The adjuvant treatment with melatonin was superior to the placebo and had the same clinical efficacy as sodium valproate, but with higher tolerability. Melatonin may prove to be an efficient substitute for sodium valproate, as a chronic migraine prophylaxis.
***Mohammadyahya E at al.*[69]**	Open-label randomized clinical trial	To investigate the effect of melatonin on menstrual-related migraine and compare melatonin treatment efficacy with naproxen, which is currently used as preventive therapy in this specific type of migraine Headaches.	The study evaluated 56 patients, 26 in the melatonin (3 mg, half an hour before sleep) arm and 30 in the naproxen (250mg, every 12 hours) arm. The patients were assessed at the end of the first and third menstrual bleeding phases.	We showed the beneficial role of melatonin in reducing the attack frequency and severity in migraine patients with menstrual-related headaches. Preventive therapy with melatonin also showed a significant reduction in sedative drug use during attacks and improved the patients' sleep quality compared to naproxen.

before menses and the first few days of menses. Thus, the distinction between "menstrual" and "menstrual related" migraine is important.[80] Migraine attacks distribution changes with the hormonal changes during the menstrual cycle. A study showed that a reduction in sex hormone levels in females, especially during the end days of the luteal phase and menstruation, is associated with an increased attack rate in 55% - 70% of migraine patients.[78, 79]

The presence of specific receptors for progesterone has been reported in the bovine pineal gland.[81] In addition, it has been shown that the circadian secretion of melatonin is modulated via native progesterone levels[82] and increased by progesterone administration [83] in healthy women. Thus, it could be inferred that melatonin secretion is influenced by gonadal steroids. However, this relationship has not been commonly confirmed in reported studies.

Murialdo *et al.* [84] reported a significant decrease in nocturnal urinary melatonin during the ovarian cycle in common-type migraine patients compared to healthy controls. These studies showed a significantly lower melatonin urinary excretion in migraines' subjects than in the control group in all phases of the menstrual cycle. The melatonin levels in both groups were higher during the luteal phase than during the follicular and menstrual phase. However, there were no significant changes in the melatonin level when the data were analyzed between different ovarian cycle phases.[84] Melatonin level further decreases in a migraine attack. Brun *et al.*[85] also emphasized that decreased urinary melatonin was associated with menses in female patients.

Considering the potential role of melatonin in the circadian system and its relationship with gonadal steroid blood level changes in patients, a study was conducted on patients with menstrual-related migraines to investigate the therapeutic efficacy of melatonin. 56 patients (26 in the melatonin arm and 30 in the naproxen arm) were evaluated and randomly assigned to either naproxen (250 mg every 12 hours) or melatonin (3 mg, half an hour before sleep) treatment groups. Attack days and headache severity improved in both groups compared to baseline. A significant difference was found between the melatonin and naproxen treatment groups in their use of sedative and analgesic medications. Also, melatonin significantly changed the snoring rate and post-sleep tiredness compared to baseline, whereas no improvement was observed in the naproxen treatment group concerning sleep quality. [69]

Although naproxen is the treatment of choice for menstrual related migraine, it has been shown that non-steroidal anti-inflammatory drugs (NSAIDs), which reduce pain by inhibiting of prostaglandin synthesis, may also reduce

melatonin synthesis.[86] Therefore, it can be concluded that melatonin could be considered a potential treatment for menstrual-related migraines, with effectiveness comparable to that of naproxen in reducing attacks.[69]

In another study conducted to determine the anti-inflammatory effects of melatonin on the CGRP expression, inducible nitric oxide synthase (iNOS) activity, NO, and IL-1β release in 12 menstrual migraine patients it was reported that melatonin treatment significantly decreases mRNA expression of CGRP release, NO production, and iNOS activity in the patient groups. Putting together, it appears that melatonin reduces inflammation by decreasing the activity of CGRP and iNOS in migraine patients; however, further studies are needed in this context. The neuropeptide calcitonin gene-related peptide (CGRP) is a potent vasoactive and a marker of trigeminal inflammation. It has been considered an important mediator in a variety of migraines such as pure menstrual migraine. CGRP can regulate the synthesis and release of other inflammatory factors including nitric oxide (NO) and interleukin-1beta (IL-1β) from trigeminal ganglion glial cells. Exogenous melatonin protects the tissues from inflammatory damage. [87]

Migraine headaches are common, occurring in 3–5% of young children and up to 18% of adolescents.[32, 88] Up to one-third of migraineur, children have criteria for drug prophylaxis. Migraine prevention therapy should be prescribed if headaches occur more than 3-4 times per month to reduce its frequency to 1-2 attacks or less per month.[39, 89] There is a limited—but growing—number of available studies on the effectiveness of melatonin for migraine prophylaxis, most of which are seemingly valid.[32]

Preventive therapy for migraine must be started with frequent or disabling headaches in children.

In a study, 32 girls and 28 boys with a mean age of 10.31 ± 2.39 years were treated with a single dose of 0.3 mg/kg melatonin for three months. The monthly frequency, severity, and duration of migraines are significantly reduced in the pediatric population. Although some side effects were reported, including sleepiness, vomiting, mild hypotension and constipation, it was concluded that melatonin can be considered an effective and without life-threatening side effects drug in the prophylaxis of migraine in children.[90] In another study conducted by Fallah R *et al.*, [32] the effectiveness and tolerability of amitriptyline and melatonin for pediatric migraine prophylaxis in 5-15 yr old children were compared. The results showed that both drugs were effective and melatonin was safer than amitriptyline. Melatonin was also better tolerated and no severe clinical side effects were seen. The adverse events were more frequent in the amitriptyline group. [32]

To study and compare the effect of propranolol with melatonin on improving migraine intensity, Abbasian P *et al.*[91] conducted a study on 49 children aged 5 to 15 years old were investigated. According to the results of this study, although propranolol alone can be considered an effective drug for the treatment of various migraine headaches in children, melatonin consumption, especially with duration of use of more than one month, if combined with propranolol, can be both more effective in reducing patient's migraine severity and duration and improving treatment satisfaction. [91]

Concluding the results from the above-mentioned studies, exogenous melatonin has proven to be useful in the pathophysiology of migraines. It can be speculated that melatonin has a role in the relationship between sleep disturbances and migraines. Initiating and maintaining sleep and altering the circadian rhythm phases are some of the primary effects of endogenous melatonin secretion, thus making exogenous melatonin a major treatment option in many cases of sleep disturbances in normal people and the ones affected with neurological or neuropsychiatric disorders.

The pineal gland produces the hormone melatonin and is largely influenced by environmental stimuli.[92] Specifically, pineal gland irregularity may be the physical origin of migraine headaches, with subsequent physiologic0al changes being secondary.[47, 93] Migraines often have environmental triggers with research showing lower levels of circulating melatonin found in migraineurs.[92] In a study conducted by Kozak *et al.*[94] on 55 migraine patients (47 females and 8 males) and their age-matched control subjects (40 females and 17 males), it was found that melatonin levels were significantly lower among migraine patients. Also, Migraine patients who had nausea during the migraine attacks and reported bouts relevant to certain food consumption, such as cheese or chocolate, had significantly lower melatonin levels.[94]

Reduced melatonin levels during the night prior to a migraine attack were observed in some pediatric patients, and supplementation with melatonin may be particularly beneficial in these patients.[32] The administration of melatonin may normalize the circadian cycle, and it may play a role in re-synchronizing biological rhythms to lifestyle and in relieving migraines and other forms of headaches.[47, 93]

The quality and quantity of sleep are decreased in patients with migraine.[47] Headache and sleep are related interdependently, lack of sleep and excessive sleep can cause migraines and melatonin irregular production, which has some links to sleep disorders, linked to a headache.[8, 95] Interruption of night sleep due to headache might cause sleeplessness and daytime drowsiness and the effectiveness of melatonin in control of migraine headache might be related to normalization and adjustment of sleep circadian rhythm.[39, 96] Melatonin has a sedative effect.[46, 97] It is thought to potentiate the effects of gamma-aminobutyric acid (GABA) via direct interaction with GABA receptors.[98, 99] research indicates that melatonin exerts a sleep-promoting action by accelerating sleep initiation, improving sleep maintenance, and marginally altering sleep architecture [100] and since a high percentage of the common migraineurs patient have sleep disturbance as a trigger factor. In contrast, the frequency and occurrence of migraine attacks in any individual depend

strongly on their CNS response to migraine-specific triggers, [97] of which one of them is sleep disturbance. This can explain the activity of melatonin in decreasing the frequency of migraine attacks. [46]

Ongoing research on the use of melatonin agonist drugs in migraine therapy is promising, although only a few clinical trials have been conducted in patients with migraine. Effective treatment has been achieved with melatonin agonists: ramelteon (used efficiently to treat insomnia and circadian sleep disorders)[101] and agomelatine (used efficiently to treat depression).[102] Agomelatine (in doses of 25 mg/day for six months) decreased both the frequency and duration of migraine attacks and thus reduced the intensity of pain. It also significantly reduced the severity of depression and normalized sleep disturbances.[65, 103]

CONCLUSION

In conclusion, this review's results are promising because they showed that melatonin is effective and without life-threatening adverse events in migraine prophylaxis. Many drugs like Amitriptyline, Sodium valproate, Topiramate and Propranolol have been approved for migraine prophylaxis and prevention but due to their unfavorable side effects melatonin was found to be superior and better tolerated. The accumulated shreds of evidence showed the positive effects of Melatonin in several migraine pathologies and suggest that Melatonin could be used as a remedy to treat migraine and other headache disorders. Also, Melatonin proved to be beneficial in strengthening the efficacy of available medications to treat migraines. Melatonin is an inexpensive, easily procured, and natural hormone with a minimal side effect profile compared to current pharmacologic migraine treatments. This systemic review suggests that melatonin could be a suitable and beneficial alternative for migraine prophylaxis with doses corresponding to 3 mg in adults and 0.3 mg/kg/day in children and therapy duration of about three months or more. Therefore, Melatonin can be considered a safe integrative prophylactic treatment for children, adults and menstrual-related migraines, thus improving outcomes related to the patient's quality of life and patient-centered care. However, further studies and evaluation are required to confirm its effects.

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