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Review Article

An Overview of Clinical Studies of Melatonin as an Effective Migraine Preventive Drug

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Abstract

Migraine is a global chronic disorder. According to World Health Organization (WHO) estimation, the worldwide prevalence of current migraine to be 10% and the lifetime prevalence to be 14%. Several classes of drugs such beta blocker, antiseizure drugs, amitriptyline and nortriptyline, serotonin-norepinephrine reuptake inhibitors, calcitonin gene-related peptide (CGRP) antibodies, NSAIDS, antihypertensive drugs, botulinum toxin type A are used to prevent migraine. While these drugs are effective to prevent headache the adverse effects sometimes become intolerable for many patients. Therefore, there is a need for a preventative therapy with less or no adverse effect profile. Melatonin, which is a pleiotropic hormone synthesized and secreted mainly by the pineal gland in vertebrates, can be a good option as it significantly minimizes the adverse effect. Melatonin is an endogenous regulator of circadian and seasonal rhythms. Melatonin is involved in many physiological and pathophysiological processes demonstrating antioxidant, antineoplastic, anti-inflammatory and immunomodulatory properties. Accumulating evidence has revealed that melatonin plays an important role in pain modulation through multiple mechanisms. Melatonin is also available in multiple dosage forms and can be administered through various routes of administration, including oral, sublingual, trans-buccal, topical and intramuscular. It can be used by pediatric patients, geriatric patients with sleep disorder eliminating all the adverse effects caused by other drugs. In this review article we discuss the results of the clinical studies that demonstrated melatonin as an effective and more tolerable preventive agent for migraine with fewer side effects.

Keywords: *Melatonin; Migraine Prevention; Endogenous Hormone; Headache; Chronic Migraine*

Introduction

Migraine is a common headache disorder that places a significant burden on those afflicted, as well as on society [1]. Each year in the United States, it is estimated that 17.1% of women and 5.6% of men will have at least one migraine headache. Society is also impacted by the loss of productivity associated with migraines. The American Migraine Prevalence and Prevention study found that 28.1% of patients surveyed reported a reduction of work or school productivity by at least 50% for at least one day in the 3 months prior to the survey [2]. The disease burden to patients is also notable with the study revealing that 47.7% of these patients did no household work for at least one day in the same period and 29.1% had missed a family or social activity. Of the patients surveyed, 53.7% reported having severe impairment, or requiring bed rest, during a severe headache [2].

Patients with migraine headaches that are frequent, severe, or refractory to acute treatment should receive preventive therapy [2-4]. Depending on the severity of headache, migraine's drugs are categorized in to first line or second line therapy. First line drugs are used to prevent mild migraine headache and mostly administered via oral route. The common drugs included in this category are propranolol, timolol, amitriptyline, divalproex, sodium valproate and topiramate as first-line agents for migraine prevention. Some other drugs such as candesartan, lisinopril, atenolol, metoprolol, nadolol, fluoxetine, magnesium, vitaminB_2 (riboflavin), coenzyme Q10 and hormone therapy are also used as in migraine prevention as an alternative option [5].

Second-line drugs are used when the first line of drugs is not sufficient to prevent migraine. These drugs are administered for acute condition and via intravenous, intramuscular, or subcutaneous route. Agents that could be used as second-line therapy for migraine prophylaxis in adults (listed by evidence of effectiveness) include gabapentin (Neurontin), naproxen (Naprosyn) or naproxen sodium (Anaprox), timed-release dihydroergotamine mesylate (DHE-45), candesartan (Atacand), lisinopril (Zestril), atenolol (Tenormin), metoprolol (Toprol XL), nadolol (Corgard), fluoxetine (Prozac), verapamil (Calan), magnesium, vitamin B2 (riboflavin), coenzyme Q10, hormone therapy (estradiol topical gel [Estrogel]), feverfew and botulinum toxin type A (Botox) injections [6].

The use of these preventive drugs is associated with numerous adverse effects and contraindications [7]. It is estimated that 38% of migraine patients should be receiving preventive therapy [2-4]. Despite these significant burdens on individuals and on society, only an estimated 3 - 13% of migraine patients are taking preventive therapy, while it is possible that the adverse effects of the prophylactic treatments available may have too significant an impact on quality of life for patients to justify using them. The prophylactic medications with established efficacy are antiepileptic drugs, including divalproex sodium, sodium valproate and topiramate; beta-blockers, including metoprolol, propranolol and timolol; and the triptan frovatriptan. The medications that are classified as being probably effective include other drugs from the aforementioned drug classes, with the addition of antidepressants, including amitriptyline and venlafaxine. These medications are also not without significant adverse effects. Antiepileptic drugs have been associated with increased risk of teratogenicity, pancreatitis and hepatic failure. In particular, studies of topiramate showed that 15% of patients reported adverse effect, with the most common being drowsiness, gastrointestinal intolerance and paresthesias. The adverse effects, reported in a study of propranolol, included fatigue, sleepiness, dry mouth, weight gain and sleep disturbances. All three of the studies that evaluated the tricyclic antidepressant amitriptyline for migraine prevention, discussed in the guideline update published by the American Academy of Neurology in 2012, had dropout rates of greater than 20% [4]. While the adverse effects of these medications may not be tolerable to many patients, preventative therapy is still a highly important facet of treatment. However, there are new biologics for preventing migraine with relatively few side effects. Recently FDA has approved three CGRP antagonists erenumab, fremanezumab and galcanezumab for the preventive treatment of migraine in adults. These are injectable agents that cause minimum adverse effects. The most common adverse events (in > 10% of the study population) for all three CGRP antagonists were injection-site reactions and pain such as hypersensitivity reactions, including redness, swelling, pain, or irritation at the injection site [8]. Symptomatic therapy may be less effective following increased central sensitization from a migraine attack, which highlights the importance of preventing the occurrence of migraine attacks [7]. This suggests a need for a preventative therapy with a more tolerable side effect profile and a more favorable risk to benefit ratio.

Melatonin is an endogenous neurohormone synthesized in the pineal gland in the brain. It is synthesized from the amino acid tryptophan and acts as a chronobiotic, meaning that it is used to maintain circadian rhythms. Endogenous synthesis is controlled by exposure to dark and light environments throughout the day, with darkness promoting synthesis and light preventing synthesis. Melatonin is metabolized in the liver primarily via cytochrome P450 1A2 with some metabolism by CYP1A1, CYP1B1, CYP2C9 and CYP2C19. A small amount is excreted unchanged in the urine in patients with normal renal function [9]. As a dietary supplement in the United States, oral melatonin is being promoted for the use of migraine prevention [10,11]. The melatonin in these dietary supplements is typically synthesized in a lab [11]. It may also be obtained from the pineal glands of animals; however, this practice is less common and is discouraged due to risk of

disease or contamination. Melatonin is available in multiple dosage forms and given through various routes of administration, including oral, sublingual, trans-buccal, topical and intramuscular [12].

Pharmacology of melatonin

There are several physiological effects of melatonin in the body that include detoxification of free radicals and antioxidant actions, bone formation and protection, reproduction and cardiovascular, immune or body mass regulation, protection and therapeutic effects on brain, psychiatric disorders, cardiovascular diseases and oncostatic effects [13].

The mechanism of action of melatonin involves different molecular pathways. Of these pathways, the most common is the activation of two types of membrane specific melatonin receptors: high affinity MT1 receptors and low affinity MT2 receptors [14,15]. The activation of MT1 receptors, which are G protein-coupled receptors, leads to an inhibition of the adenylate cyclase in target cells. The activation of MT2 receptors leads to phospho-inositides hydrolysis [16]. By binding to melatonin receptors 1 and 2, the downstream signaling cascades have various effects in the body. MT1 receptors are expressed in many regions of the central nervous system (CNS) such as suprachiasmatic nucleus of the hypothalamus (SNC), hippocampus, substantia nigra, cerebellum, central dopaminergic pathways, ventral tegmental area and nucleus accumbens. Also, MT1 is expressed in other areas such as retina, ovary, testis, mammary gland, coronary circulation and aorta, gallbladder, liver, kidney, skin and the immune system [17]. MT1 receptor activation inhibits the adenylyl cyclase which then triggers a rippling effect of non-activation by starting with decreasing formation of cyclic adenosine monophosphate (cAMP). This process is then ensued by progressing to less protein kinase A (PKA) activity, which in turn hinders the phosphorylation of cAMP responsive element-binding protein (CREB binding protein) into P-CREB. Furthermore, MT1 receptors activate phospholipase C (PLC), affect ion channels and regulate ion flux inside the cell. On the other hand, MT2 receptors are expressed mainly in the CNS and also in the lung, cardiac, coronary and aortic tissue, myometrium and granulosa cells, immune cells, duodenum and adipocytes areas. The binding of melatonin to MT2 receptors inhibits adenylyl cyclase which decreases the formation of cAMP [17]. It also hinders guanylyl cyclase and therefore the forming of cyclic guanosine monophosphate (cGMP). Binding to MT2 receptors probably affects PLC which increases protein kinase C (PKC) activity. Activation of the receptor can lead to ion flux inside the cell.

Melatonin is an endogenous hormone best known for its importance to the normal physiology of the sleep cycle. There is not a well-established mechanism for the effects of melatonin in the prevention of migraines; however, there are multiple proposed mechanisms for the observed benefits of melatonin seen in migraine patients. One proposed explanation for these effects is that melatonin is implicated in the pathophysiology of migraines and, since plasma melatonin levels have been found to be reduced in migraine patients, replacement of melatonin could help to correct the deficiency and prevent migraine attacks [18,19]. This is supported by studies showing a significant reduction in plasma and urinary melatonin levels in migraine patients during migraine attacks and by a study showing an altered melatonin profile in patients with status migranosis [18-22]. Another possible mechanism is that the restorative effect of melatonin on sleep prevents migraine attacks caused by a disruption in the sleep patterns of patients. This is supported by the evidence that there is an association between the sleep schedules of patients and migraines [23,24]. Patterns of plasma melatonin levels were also found to be altered in patients with migraines associated with their menstrual cycles, implicating melatonin in menstrual related migraines as well [20,25,26]. Other studies have suggested hypothalamic involvement in chronic migraine after finding abnormal patterns in nocturnal melatonin levels [25,26]. Another proposed mechanism is the anti-nociceptive effect of melatonin seen in studies performed in rats and mice. Trigeminal c-fos expression, a marker of neuronal activity in a region of the brain implicated in neurovascular headache, was found to be reduced in pinealectomized rats receiving melatonin [27]. Another animal study showed that melatonin had a significant antinociceptive effect in mice after nociception was induced by glutamate, as well as by capsaicin [28]. Melatonin has also been found to scavenge free radicals and exert an anti-inflammatory effect [19,29]. A possible explanation for this anti-inflammatory effect is the structural similarity between melatonin and the NSAID indomethacin [30]. Another proposed anti-inflammatory mechanism is that the inhibition of prosta-

glandin E synthesis may prevent inflammation within the trigeminovascular system [29]. While there are many speculations concerning the potential mechanism of melatonin when used for migraine prophylaxis, there is no established mechanism for these effects.

Clinical studies

In this article we reviewed eight human clinical trials that studied the use of melatonin for migraine prophylaxis. Studies were identified by performing a literature search in PubMed and OVID/Medline databases using the f search terms melatonin and migraine prevention.

The first clinical trial evaluating the efficacy of melatonin for migraine prevention was an open-label, intention-to-treat trial by Peres., *et al* [31]. The study consisted of a 1-month period for establishing baseline measures, followed by a 3-month treatment period. Melatonin 3 mg was given to 34 patients, for migraine prophylaxis, 30 minutes prior to bedtime. Two patients did not complete the study. The primary endpoint was the percentage of patients who experienced a reduction, of greater than 50%, in frequency of headaches after the 3-month treatment period. Other endpoints included duration and intensity of headaches, as well as analgesic usage. The frequency of reported headaches was significantly reduced at the end of the 3-month treatment period ($p < 0.001$). There was also a significant reduction in headache intensity, duration and triptan and analgesic usage ($p < 0.001$). The authors concluded that melatonin was effective at reducing headache frequency over the treatment period and that placebo-controlled studies were warranted. Major limitations of this study included its lack of a placebo control group, blinding, or randomization. Another major limitation is its small sample size of 34 patients.

Nagtegaal., *et al*. [32] conducted a randomized, double-blind, placebo-controlled, cross-over study, evaluating the use of melatonin in 30 patients with delayed sleep phase syndrome and published their preliminary observations seen in the patients experiencing headaches. Each patient was questioned about the presence of headaches and diagnoses were based on the IHS diagnostic criteria. Plasma levels of endogenous melatonin were measured every 24 hours, with the patients in dim light. Each patient received either placebo or melatonin 5 mg for the first 2 weeks, then the opposite intervention for the following 2 weeks. After this 4-week period, each patient was given at least 3 months of melatonin treatment. A 24-hour melatonin curve was also performed before and after melatonin treatment. One of the five participants, who experienced headaches, reported having migraines. This patient was a 54-year-old male presenting with migraines without aura. Over the previous 5 years, he experienced an increase in migraine attack frequency to 2 attacks each week. Prior to the trial, the patient used paracetamol (acetaminophen) and sumatriptan. The authors reported that, on the second day of treatment with melatonin, his sleep schedule improved and his migraines no longer occurred. After the second day of the placebo period, the patient's difficulty sleeping and migraines recurred with 3 migraine attacks occurring over the length of the placebo period. During the 3-month melatonin treatment period that followed, the patient's sleep pattern returned to the improved state it was in during the first treatment period. The 24-hour melatonin curve was performed 6 weeks into the study and showed a shift of the curve to 2 hours earlier. The authors concluded that melatonin could be effective for patients with delayed sleep phase syndrome, who experience headaches and that the mechanism of melatonin may be related to its effect on headache pathophysiology. Major limitations include the sample size of only one patient with migraines and the lack of statistical testing of the results.

Miano., *et al*. [33] published an open-label trial to evaluate the effectiveness of melatonin in the prevention of primary headaches in 22 pediatric patients. The patients shared many similar characteristics as they were all recruited in the same area and shared the same socioeconomic status and race. Of these patients, 13 of them had recurrent migraine without aura and 1 patient had recurrent migraine with aura. The study consisted of 1-month baseline period and a 3-month treatment period, during which time, all patients received melatonin 3 mg at bedtime. A structured daily headache diary was used to record information about headache duration and intensity. Patients were evaluated at follow-up visits, which occurred after months 1, 2 and 3. A reduction in headache frequency by greater than 50% was the primary endpoint in this study. Of the total 14 patients who reported migraine, 10 of the patients without aura reported a reduction in headache frequency by greater than 50%. Three of these patients and the patient who experienced migraines with aura, reported hav-

ing no attacks at all, however 3 of the patients without aura reported no change in headache frequency from baseline. After the 3-month treatment period, the number of children reporting severe headache attacks reduced from 17 to 6. In the group of children studied, there was a statistically significant reduction in both headache frequency ($p < 0.001$) and attack duration ($p < 0.001$). The authors concluded that, although the results should be confirmed with placebo-controlled trials, melatonin could be a safe alternative for primary headache prophylaxis in children. Major limitations of this study include the lack of randomization, placebo control or blinding, as well as the small sample size and the lack of diversity of the study participants.

Alstadhaug., *et al*. [34] evaluated the use of melatonin for migraine prophylaxis, as well as for improving sleep quality, in a randomized, double-blind, placebo-controlled, crossover study. The study was conducted in two different centers in northern Norway. Of the total 48 patients included, 46 completed the study and were included in the analysis. The patients were randomized to receive either prolonged-release melatonin 2 mg, given 1 hour before bedtime, or placebo for an 8-week period. This was followed by a 6-week washout period, then a treatment period with the opposite intervention for another 8-week period. Patient diaries were used to collect information concerning the characteristics of migraine attacks, sleep and the potential attack treatment effect. Other information collected included information concerning pain and pain intensity from migraine attacks, the beginning and end of auras, attack treatment and treatment effectiveness and associated symptoms. Migraine attack frequency was measured starting with the baseline measure taken during the 1-month run-in period before the start of the trial and then continuing over the course of the trial. Data was collected after the first 8-week period, the washout period and at the end of the trial at 22 weeks. The primary outcome was reduction in mean migraine attack frequency over the melatonin treatment period compared to the reduction seen over the placebo period. Those achieving a reduction in attack frequency of greater than 50% were considered responders. No significant difference was found between melatonin and placebo in the primary outcome ($p = 0.75$). A 33% reduction from baseline was seen with melatonin and a 30% reduction was seen with placebo. There was also no significant difference seen in the number of responders to each intervention. Twenty-one of the patients (44%) responded to melatonin and 19 patients (40%) responded to placebo. During treatment 7 patients worsened while taking melatonin and 6 patients worsened while taking placebo. The authors concluded that their results failed to confirm the findings of the open label trial by Peres., *et al*. [2] and that, despite the small sample size, the results were clearly negative. Major limitations of this study include its small sample size, as well as its low dose and different dosage form of melatonin used, when compared to the 3 mg of immediate release melatonin used in the open label study by Peres., *et al* [2].

Bougea., *et al*. [35] evaluated the efficacy of melatonin for primary headache prophylaxis in an open-label, per-protocol trial based in an outpatient clinic, which included 49 patients. Thirty-seven of these patients had migraines. Only 41 patients completed the study and were included in the analysis. During the 6-month treatment period, each of these patients received oral melatonin, 4 mg, 30 minutes prior to bedtime. Patients also continued their current systemic prophylactic and rescue medications for headache attacks. Follow-up visits occurred after 2 and 6 months of treatment. Blood levels of melatonin were also measured in dim light, at the same time of day, during a headache attack and during a period the patient was free of pain. At baseline, patients completed the Headache Impact Test (HIT-6), the Epworth Sleepiness Scale (ESS) and the Hamilton Depression Rating Scale (HAMD) to evaluate differences between the two primary headaches. Patients were given diaries to record the duration and frequency of headache attacks. After 8 weeks of treatment, patients met for a patient interview at the follow-up visit where data was collected from the diaries and adverse drug reactions were reported. The final visit occurred after 6 months of treatment. At this visit, headache diaries were returned to the investigators and the patients completed the HIT-6 once again. After the 6-month treatment period, headache attack frequency was significantly reduced from baseline in patients suffering from migraines ($p < 0.001$). The HIT-6 score was also significantly reduced from baseline in migraine patients ($p < 0.001$). The authors concluded that, when given orally, melatonin 4 mg has a positive role in lowering the frequency of headache attacks. They also concluded that, because of the significant reduction in HIT-6 score, there was an improvement in the quality of life in these patients. Major limitations of this study include the lack of a placebo control group, randomization, or blinding. The small sample size was another limitation. A major strength was that separate statistical analyses were performed on the group of patients with migraines, providing clearer

data on the response seen in these patients. Another strength was that patients were permitted to remain on their current prophylactic and rescue medications, giving readers a better idea of how melatonin could fit into therapy as an adjunctive treatment.

Fallah., *et al*. [36] evaluated the safety and efficacy of melatonin for migraine prophylaxis in an open-label, non-randomized, uncontrolled quasi-experimental study of 60 pediatric patients (age 5 - 15). All participants also had an indication for prophylactic therapy and had one or more headache attacks per week or a Pediatric Migraine Disability Score (PedMIDAS) greater than 20. These patients received 0.3 mg/kg (maximum 6 mg) of melatonin each day at bedtime over a 3-month treatment period. Duration, frequency per month, disabling effect and intensity of migraine attacks, as well as the adverse effects of melatonin, were measured. The disabling effects of migraines were analyzed using PedMIDAS. After the treatment period, 15 children (25%) had a PedMIDAS of less than 10 and a good response (more than 50% reduction in monthly headache frequency) was seen in 70% of children. Pediatric Migraine Disability Assessment scores were reduced from 31.72 ± 8.82 to 17.78 ± 10.64 ($p = 0.0001$). Monthly attack frequency reduced from 15.63 ± 7.64 to 7.07 ± 4.42 ($p = 0.0001$). Headache duration reduced from 2.26 ± 1.34 to 1.11 ± 0.55 hours ($p = 0.001$). Severity scores were reduced from 6.20 ± 1.67 to 3.55 ± 2.11 ($p = 0.001$). Number of analgesic usages was reduced from 10.41 ± 1.8 to 4.33 ± 1.76 ($p = 0.001$). The authors concluded that melatonin could be used as an effective treatment option for migraine prophylaxis in pediatric patients without life-threatening adverse effects. Limitations of this study include the lack of placebo and the study design. The study did, however, meet a power of 80% to detect a 25% difference in efficacy between the two groups and allowed nonsteroidal anti-inflammatory analgesics (acetaminophen or ibuprofen) to be taken throughout the study for symptomatic relief of moderate to severe headache attacks.

Gonçalves., *et al*. [37] conducted a multicenter, randomized, double-blind, placebo-controlled study comparing melatonin to amitriptyline and placebo for migraine prevention. 178 patients were included in the study. After randomization, 60 patients received melatonin 3 mg, 59 patients received amitriptyline 25 mg and 59 patients received placebo. The treatment period continued for 12 weeks following the 4-week baseline period. Patients used a diary to document the occurrence of headaches, symptoms, utilization of analgesics and migraine duration and mean intensity. Data were collected from diaries, by neurologists with training in headaches, at the end of the baseline period and after each month of the 3-month treatment period. The primary efficacy outcome was the number of migraine headache days per month. The secondary efficacy outcomes included percentage of patients with reductions in migraine headache days by greater than 50%, duration of migraine headache attack, number of analgesics each patient used and reduction in mean intensity of migraines. In the last month of the treatment period, patients in both the melatonin 3 mg group and the amitriptyline 25 mg group had a significant reduction in number of migraine headache days per month when compared to placebo ($p < 0.05$). Both the melatonin group and the amitriptyline group were superior to placebo in reducing duration of migraine headache attacks, number of analgesics each patient used and mean intensity of migraines ($p < 0.05$). However, melatonin was superior to both placebo ($p < 0.01$) and amitriptyline ($p < 0.05$) in percentage of patients with reductions in migraine headache days by greater than 50%. While there was no significant difference in number of adverse events between the melatonin and placebo groups (p = not significant), the study found a significantly higher number of adverse events reported in the amitriptyline group ($p < 0.03$). A reduction in patient weight was noted in the melatonin group; however, an increase in patient weight was noted in the amitriptyline and placebo groups. Patient weight in the melatonin group was significantly lower when compared to that of the amitriptyline group ($p < 0.01$) and the placebo group ($p < 0.05$). The authors concluded that melatonin was effective for migraine prevention, as demonstrated by its superiority to placebo in all outcomes and more tolerable than amitriptyline, based on the lower number of reported adverse events in the melatonin group when compared to amitriptyline. A major limitation of this study was that the dose of amitriptyline used was lower than the doses commonly studied in migraine prophylaxis [31,32]. Other limitations of this study were the subjective nature of migraine intensity as an endpoint, as well as the questionable clinical significance of the 0.14 kg weight reduction seen in the melatonin group. The use of neurologists to review patient diaries and the larger sample size, relative to the other trials, were strengths of this study.

Gelfand., *et al*. [38,39] conducted a single-center, randomized, double-blind, placebo-controlled study comparing 3mg of melatonin to placebo daily for migraine prevention. 31 adolescent patients (age 12 - 17) were included in the home-based study and completed a 28-day baseline period in which an electronic headache diary was kept. 26 patients met randomization criteria by having 80% or greater diary compliance and 2 - 24 migraine days/month. They were randomized 1:1 to melatonin 3 mg or placebo for 12 weeks following the baseline period. All baseline characteristics, including mean migraine days per month, were similar except for a higher mean PedMIDAS in the melatonin group (P=0.04). Outcome data was only available for 23 patients, because three participants withdrew from the study (two from the placebo group and one from the melatonin group). The primary efficacy outcome was the mean migraine days in the final four weeks of treatment. In the final four weeks of treatment, the primary efficacy outcome was 1.3 days lower in the melatonin group vs. the placebo group but was not statistically significant (P = 0.83). When the analysis was adjusted for baseline PedMIDAS, the primary efficacy outcome was 2.3 days lower in the melatonin group but was still not statistically significant (P = 0.25). It was determined that there would need to be 75 participants per arm to detect a difference of 2.3 migraine days per month. The authors concluded that migraine days in the last 4 weeks of treatment were lower in the melatonin group compared to the placebo group, but this difference could be due to chance since it was not statistically significant. There were no serious adverse events and sleep outcomes did not differ between groups. A major limitation of this study was that it was not fully powered due to the small sample size and there was not a statistically significant difference between groups in the primary efficacy outcome. Strengths of this study were the location and patient population. This was the first trial in the United States that has tested the use of melatonin for migraine prophylaxis and the adolescent population had not previously been included in randomized controlled studies with a placebo group.

In summary, all eight clinical studies show that melatonin can be effective in reducing headache for adult, pediatric and patients with delayed sleep syndrome. It was also shown that melatonin can improve the patient's quality of life by reducing the headache in headache impact test (HIT-6 level). For pediatric patients, melatonin could be used as an effective treatment option for migraine prophylaxis without life-threatening adverse effects. In the following table (Table 1) the findings, limitations and strength of all eight studies have been summarized.

Lead Researcher [Reference]	Type of study	Number of patients and their age group	Research findings	Major Limitations of the study	Strengths of the study
Peres., *et al*. [31]	Open-label, intention-to-treat trial	34 Adult patients	Melatonin was effective at reducing headache frequency over the treatment period and that placebo-controlled studies were warranted.	Major limitations of this study included its lack of a placebo control group, blinding, or randomization. Another major limitation is its small sample size of 34 patients.	
Nagtegaal., *et al*. [32]	Randomized, double-blind, placebo-controlled, cross-over study	30 Adult patients	Melatonin could be effective for patients with delayed sleep phase syndrome, who experience headaches and melatonin may be related to its effect on headache pathophysiology.	Major limitations include the sample size of only one patient with migraines and the lack of statistical testing of the results.	

Miano., *et al*. [33]	open-label trial	22 Pediatric patients	Melatonin could be a safe alternative for primary headache prophylaxis in children.	Major limitations of this study include the lack of randomization, placebo control or blinding, as well as the small sample size and the lack of diversity of the study participants.	
Alstadhaug., *et al*. [34]	randomized, double-blind, placebo-controlled, crossover study.	48 Adult patients	The results failed to confirm the findings of the open label trial by Peres., *et al*. [2] and that, despite the small sample size, the results were negative.	Major limitations of this study include its small sample size, as well as its low dose and different dosage form of melatonin used, when compared to the 3 mg of immediate release melatonin used in the open label study by Peres., *et al*. [2].	
Bougea., *et al*. [35]	open-label, per-protocol trial based in an outpatient clinic,	41 Adult patients	Melatonin significantly reduces the HIT-6 score, which cause an improvement in the quality of life in these patients.	Major limitations of this study include the lack of a placebo control group, randomization, or blinding. The small sample size was another limitation.	A major strength was that separate statistical analyses were performed on the group of patients with migraines, another strength was that patients were permitted to remain on their current prophylactic and rescue medications.
Fallah., *et al*. [36]	open-label, non-randomized, uncontrolled quasi-experimental study	60 Pediatric patients	Melatonin could be used as an effective treatment option for migraine prophylaxis in pediatric patients without life-threatening adverse effects.	Limitations of this study include the lack of placebo and the study design.	meet a power of 80% to detect a 25% difference in efficacy between the two groups and allowed nonsteroidal anti-inflammatory analgesics (acetaminophen or ibuprofen) to be taken throughout the study for symptomatic relief of moderate to severe headache attacks.

Gonçalves., *et al*. [37]	multicenter, randomized, double-blind, placebo-controlled study	178 Adult patients	Melatonin was effective for migraine prevention and more tolerable than amitriptyline, based on the lower number of reported adverse events in the melatonin group when compared to amitriptyline.	A major limitation of this study was that the dose of amitriptyline used was lower than the doses commonly studied in migraine prophylaxis**.** Other limitation was questionable clinical significance of the 0.14 kg weight reduction seen in the melatonin group.	The use of neurologists to review patient diaries and the larger sample size, relative to the other trials, were strengths of this study.
Gelfand., *et al*. [38,39]	A single-center, randomized, double-blind, placebo-controlled study	31 Adolescent patients	Migraine was lower in last 4 weeks of treatment compared to the placebo group. There were no serious adverse events and sleep outcomes did not differ between groups.	A major limitation of this study was that it was not fully powered due to the small sample size and there was not a statistically significant difference between groups in the primary efficacy outcome.	This was the first trial in the United States that has tested the use of melatonin for migraine prophylaxis and the adolescent population had not previously been included in randomized controlled studies with a placebo group.

Table 1: *Research finding, limitations and strength of the clinical studies on melatonin as migraine preventive drug.*

Dosage forms

Melatonin has been studied for migraine prophylaxis in oral dosages of 2 - 5 mg daily in adults as well as 3 mg daily and 0.3 mg/kg daily (maximum 6 mg) in pediatric patients. Nagtegaal., *et al*. [32] evaluated one adult patient with migraines whose sleep pattern and migraine attacks improved during treatment with 5 mg daily of melatonin. Bougea., *et al*. [35] evaluated the use of 4mg daily 30 minutes prior to bedtime in 37 adult patients with migraines. The headache attack frequency and HIT-6 score were significantly decreased from baseline, but the results were not compared to placebo. In the Peres., *et al*. [31] trial, 3 mg daily prior to bedtime was sufficient to show a significant decrease in headache frequency, intensity and duration as well as triptan and analgesic use in 32 adult patients, but the results were not compared to placebo. A lower dosage of 2 mg of prolonged release melatonin (a different dosage form) given one hour before bedtime was studied in 46 adult patients in the randomized, double-blind, crossover Alstadhaug., *et al*. [40] trial. However, there was no significant difference between the melatonin and placebo groups in the reduction in mean migraine attack frequency over an 8-week period. Goncalves., *et al*. [37] consisted of 178 adult patients and compared 3 mg daily of melatonin to 25 mg daily of amitriptyline or placebo. Melatonin and amitriptyline had a significant reduction in number of migraine headache days per month when compared to placebo and were superior to placebo in reducing the duration of migraine headache attacks, number of analgesics each patient used and mean intensity of migraines. However, melatonin was superior to both placebo and amitriptyline in percentage of patients with reductions in migraine headache days by greater than 50%.

Two trials conducted in pediatric patients showed good results, but they were not placebo-controlled. Miano., *et al*. [33] evaluated the efficacy of 3 mg daily at bedtime in pediatric patients with migraines and found that 10 out of the 14 patients with migraines reported a reduction in headache frequency by more than 50%. Fallah., *et al*. [36] evaluated the efficacy of 0.3 mg/kg/day (maximum 6 mg) in 60 pediatric patients and found a significant decrease in pediatric migraine disability assessment scores (PedMIDAS) and monthly attack frequency, duration and severity. There was also a significant decrease in the number of analgesic usages during the follow up period. Gelfand., *et al*. [38,39] more recently compared 3 mg daily of melatonin to placebo in adolescent patients and found that the mean migraine days per month were lower in the melatonin group in the last four weeks of treatment but was not statistically significant. In conclusion, 3 - 5 mg of daily oral melatonin looks promising for migraine prophylaxis in adults and dosages of 3 mg and 0.3 mg/kg/day have been studied safely in the pediatric population. However, no trials have titrated melatonin doses based on patient responses or adverse effects and it is still unknown if higher doses will have a greater effect.

Adverse effects

There have been no long-term studies of melatonin use in humans. However, melatonin is normally tolerated well in humans without grade 3 or 4 (severe or life-threatening) toxicities. The highest dose for severe migraine does not causes any severe toxicity. The dose ranges from mild, moderate to severe condition of migraine headache. In several clinical trials the following doses were found to be non-toxic [41-45]. The doses for acute migraines are Sumatriptan 6 mg subcutaneous injection, Prochlorperazine 10 mg intravenous (IV) or intramuscular (IM), Metoclopramide 10 mg IV, Chlorpromazine 0.1 mg/kg (or 12.5 mg) single dose as a slow IV infusion (maximum rate 1 mg/minute); maximum cumulative dose 25 mg, Dihydroergotamine (1 mg IV) combined with metoclopramide (10 mg IV), Ketorolac 30 mg IV or 60 mg IM (15 mg IV or 30 mg IM for patients ≥ 65 years, < 50 kg, or renal impairment). These dose range of different drugs didn't cause any adverse effect [41-45].

Although there are no apparent serious side effects of oral melatonin, there appear to be some common adverse effects. According to drug databases, the most commonly reported adverse effects of melatonin are headache, dizziness, nausea, drowsiness, sedation, somnolence, fatigue and hypothermia. Severe toxicities have not been reported and acute overdose is not expected to cause any significant clinical toxicities. Other possible adverse effects include: excessive daytime somnolence, enuresis, insomnia, nightmares, transient depression, mild tremor, mild anxiety, abdominal cramps, agitation/irritability, confusion, vertigo, disorientation and hypotension [11,12,46].

Out of the 46 patients that took melatonin for eight weeks in the Alstadhaug., *et al*. [40] trial, eight participants (17%) reported adverse effects. During the melatonin treatment period, two patients reported fatigue and dizziness and 1 patient reported nervousness and nightmares. During the placebo treatment period, five patients reported different adverse effects such as night sweats, higher dream activity, dry mouth and fatigue. No comments were made about the significance of the observed adverse effects. In the Gonçalves., *et al*. [37] trial, 77 adverse effects were reported by 60 participants, but the majority were mild to moderate. There was no significant difference in the number of adverse events between the melatonin and the placebo groups (p value not significant), but there was a significantly lower number of adverse events in the melatonin group than in the amitriptyline group ($p < 0.03$). Common adverse effects in the melatonin group were daytime sleepiness, epigastralgia, dry mouth, constipation and pruritus. No blood pressure changes or hypoglycemic symptoms were reported. Weight loss was found in the melatonin group, a slight weight gain in the placebo group and a significant weight gain in the amitriptyline group. In this trial it was concluded that melatonin was as tolerable as placebo and more tolerable than amitriptyline.

Only one out of 22 pediatric patients in the Miano., *et al*. [33] trial experienced excessive daytime sleepiness. Out of 60 pediatric patients in the Fallah., *et al*. [36] trial, about 23% experienced clinical adverse effects including sleepiness (11.7%), vomiting (6.7%), mild hypotension (3.3%) and constipation (1.7%). Drug use was stopped in three of these patients due to excessive daytime sleepiness, but all other side effects disappeared within three weeks. Gelfand., *et al*. [38,39] reported no serious adverse events, however, two adolescent participants in the melatonin group had daytime tiredness, but only one discontinued the study drug. There were also two reports of

unscheduled medical visits for migraines, one report of low iron on blood work and one episode of vomiting in the melatonin group. The placebo group experienced none of these adverse effects and no comments were made on the significance of the adverse effects experienced by participants in the melatonin group. The migraine preventive drugs with their common dosage forms and adverse effects are shown in table 2.

Agent	Therapeutic class	Drugs	Dosage forms	Common adverse effects
Beta blocker	Antimigraine	Propranolol, timolol, metoprolol	Tablets, Liquid	Cold hands or feet, fatigue, weight gain, depression, shortness of breath, trouble sleeping [47].
Antiseizure	Sodium channel blocker	Valproate and topiramate	Tablets	Feelings of tiredness, stomach upset, dizziness or blurred vision [48]
Triptans	Antimigraine drugs	Frovatriptan and naratriptan	Tablets	Abdominal or stomach pain Anxiety Blurred vision Changes in patterns and rhythms of speech Chest pain or tightness [47].
Tricyclic antidepressant	Antidepressant	Amitriptyline and nortriptyline	Tablets, Capsules	Drowsiness, blurred vision, constipation, dry mouth, urine retention [47].
Serotonin-norepinephrine reuptake inhibitors	Antidepressant	Venlafaxine and duloxetine	Tablets, Capsules	Agitation, anxiousness, or shakiness Nausea and vomiting, stomachache and indigestion, loss of appetite Diarrhea, constipation dizziness Difficulty sleeping, fatigue, headache Low libido [47]
Calcitonin gene-related peptide (CGRP) antibodies	Anti-migraine	Erenumab, fremanezumab, galcanezumab and eptinezumab	Liquid	Injection site pain (5-6%), Constipation (1-3%), Cramps, muscle spasms (<3%), Post marketing reports. Immune system disorders: rash, angioedema, anaphylaxis, hypersensitivity. Gastrointestinal disorders: Oral mucosal ulceration, constipation with serious complications Vascular disorders: Hypertension [47].
NSAIDS	Anti-inflammatory	Naproxen, ibuprofen	Tablets, Capsules, Oral Suspensions	Abdominal pain, Acid or sour, stomach Belching, bloating, Cloudy urine, decrease in amount of urine Decrease in urine output or decrease in urine-concentrating ability Diarrhea [47], Difficulty having a bowel movement (stool) Excess air or gas in stomach or intestines, full feeling, heartburn, indigestion, Itching skin [47]

Antihypertensive	Thiazide-type diuretics. Calcium channel blockers. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)	Lisinopril, candesartan and verapamil	Tablets	First-dose reactions due to antihypertensive drugs are frequently dose related and may result from an abrupt lowering of blood pressure, causing postural hypotension, dizziness, syncope, headaches, lethargy, or other symptoms [49].
Botulinum toxin type A	Neurotoxin	Onabotulinumtoxina	Injectable Liquid	Puffy eyelids, Dry eyes Dropping eyebrows, Dry mouth, Headache, Tiredness, Increased sweating in areas other than underarms and Bruising, bleeding, pain, redness, or swelling at the injection site [50].

Table 2: *List of preventive anti-migraine drugs, dosage forms and common adverse effects.*

Precautions and contraindications

No black box warnings are associated with melatonin. However, until melatonin is studied more thoroughly and sufficient safety evidence is provided, this drug should be avoided in patients with autoimmune diseases, transplant recipients and in patients who are pregnant, planning to become pregnant, or breast-feeding [11,12]. Melatonin is a lipophilic hormone that has been found to easily cross the placenta and is excreted into breast milk. There are no located reports in the literature of exposure to exogenous melatonin in pregnant or breast-feeding humans [11]. One animal study showed significantly later vaginal opening and lower luteinizing hormone blood levels of female offspring when pregnant rats were given 2.5 mg/kg/day (much higher than normal human doses) of melatonin throughout gestation and compared with control groups [51]. Another animal study showed that when pregnant rats were given a dose of 200 mg/kg/day from gestational days 6 - 19, no toxicities were observed in both the mother and fetus [52]. Melatonin has been shown to inhibit ovarian function and cause significantly decreased levels of luteinizing hormones, estradiol and progesterone when used in higher doses of 75 mg/day or 300 mg/day in humans, but it is unknown if lower doses have the same effect [53].

Per the manufacturer, melatonin should be used cautiously in patients with severe allergies, hepatic impairment and renal impairment due to impurities that have been found in melatonin supplements that may cause allergic reactions and the pharmacokinetics of the drug [9,46]. Melatonin should also be used with caution in patients less than 21 years old due to the high levels of endogenously produced melatonin in younger patients and the possibility of additional exogenous melatonin in this population negatively affecting gonadal development [54,55]. Melatonin should be used cautiously in patients with bleeding disorders, depression, seizure disorders and diabetes. Melatonin has been shown to worsen bleeding and dysphoria in some patients [56,57]. There are some studies which suggest that melatonin may increase the incidence of seizures, impair glucose utilization, or increase insulin resistance in some patients [58-60]. Lastly,

cognitive and behavioral changes have been seen with melatonin analogs such as ramelteon [61]. Due to these findings, certain patient populations have been excluded from trials. The Nagtegaal., *et al*. [32] trial excluded patients with liver diseases, renal failure, severe neurological or psychiatric disorders and patients who were pregnant or planning to become pregnant. Patients met exclusion criteria in Alstadhaug., *et al*. [40] if they were pregnant, breast-feeding, or had any psychiatric conditions. Patients with psychiatric disorders were also excluded from the Miano., *et al*. [33], Bougea., *et al*. [35] and Gonçalves., *et al*. [37] trials. Fallah., *et al*. [36] excluded pediatric patients with renal disease, hepatic disease, or diabetes mellitus.

Drug Interactions

There are no documented major interactions between melatonin and other medications. However, there are a few established moderate severity interactions documented with good evidence. There are case reports of minor bleeding and decreased prothrombin activity in patients taking melatonin and warfarin together [11]. In a randomized, placebo-controlled, single-blind study of 46 young healthy men, just one oral dose of melatonin was associated with a lower plasma level of coagulant factors one hour after administration [57]. Melatonin may increase the effects of warfarin and should be used cautiously when used concomitantly with warfarin. Monitoring of INR, prothrombin time and signs and symptoms of excessive bleeding is warranted [11]. There is excellent evidence to support an interaction between melatonin and nifedipine for which blood pressure should be monitored [12]. A double-blind, randomized, placebo-controlled, crossover study of 50 mild-moderate essential hypertensive patients age 38 - 65 controlled by nifedipine showed that chronic evening ingestion of melatonin causes increased blood pressure and heart rate [62]. One animal study has also suggested that melatonin may reduce the effectiveness of other antihypertensive drugs such as methoxamine and clonidine by impairing alpha-1 and alpha-2 adrenergic responses [63]. Another interaction supported with good evidence is the interaction between melatonin and fluvoxamine. A total of 12 patients in two small studies showed an increase in melatonin levels with a 23-fold increase in the area under the concentration-time curve (AUC) after fluvoxamine administration [46,64,65]. Fluvoxamine may inhibit enzymes that metabolize melatonin, cytochrome P450 1A2 and 2C19, resulting in a significant increase in the bioavailability of oral melatonin and central nervous system depression. Patients taking fluvoxamine and melatonin concomitantly should be monitored for signs and symptoms of CNS depression such as lethargy, confusion, fatigue, headache, pruritus and vasodilation. Other drugs that may theoretically interact with melatonin but have not been well studied include: benzodiazepines, flumazenil, anticonvulsants, antidiabetic drugs, contraceptives, methamphetamine, immunosuppressant drugs, caffeine, St. John's Wort and echinacea [6,9,34].

Discussion

As described above, migraine headaches continue to have an individual and societal impact [1]. While the exact relationship between melatonin and migraine headaches is not clearly understood and the etiology is likely multifactorial, it is plausible to consider a potential role for supplementation of melatonin to correct deficiencies in the hormone or simply improve sleep to prevent or reduce the frequency of migraine headaches [12,16]. The clinical trials completed to date suffer from the same weaknesses that many natural supplement trials experience: finding no difference between groups or poor external validity of positive findings secondary to small sample size and/or weak trial design [24-26,28-33]. While these limitations are expected due to the limited funding for research in this area, it does make it difficult to know which type of migraine headache patient may benefit from intervention with melatonin. This may lead to a lack of consideration of melatonin and underuse of a potentially beneficial supplement. Conversely, synthetically derived melatonin supplements appear to be safe and well tolerated in most patients using recommended doses [6,9,10,34]. Those who do experience adverse effects typically experience mild, reversible effects or effects that subside with continued use. There are suggestions of the potential for more significant toxicities, but again, limited human exposure through clinical trials leaves clinicians to anecdotal descriptions of isolated events or conjecture based on proposed mechanisms or animal data. Unfortunately, the currently available data with melatonin leaves clinicians in the all too familiar position of wondering who is the correct patient and simply hoping for improvement. More data are needed to guide the selection of patient, dose and duration of therapy. Additionally, data describing the safety of melatonin use in combination with other preventative therapies for migraine as well as abortifacient therapies are needed.

Conclusion

Limited clinical evidence suggests that melatonin supplementation may be beneficial in preventing or reducing the frequency of migraine headaches. Melatonin supplements appear to be safe and well tolerated in most patients using recommended doses. More clinical studies are needed to guide the selection of patient, dose and duration of intervention and to evaluate the safety of melatonin use in combination with other migraine preventive therapies.

Bibliography

1. Bigal ME., *et al*. "The epidemiology and impact of migraine". *Current Neurology and Neuroscience Reports* 4.2 (2004): 98-104.
2. Lipton RB., *et al*. "Migraine prevalence, disease burden, and the need for preventive therapy". *Neurology* 68.5 (2007): 343-349.
3. Buse DC., *et al*. "Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers". *Journal of Neurology, Neurosurgery, and Psychiatry* 81.4 (2010): 428-432.
4. Silberstein SD., *et al*. "Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society". *Neurology* 78.17 (2012): 1337-1345.
5. Modi S and Lowder DM. Medications for Migraine Prophylaxis Brody School of Medicine at East Carolina University, Greenville, North Carolina.
6. Kazi F., *et al*. Second-line interventions for migraine in the emergency department: A narrative review Headache Current (2021).
7. Galletti F., *et al*. "Pathophysiological basis of migraine prophylaxis". *Progress in Neurobiology* 89.2 (2009): 176-192.
8. Glaser A. CGRP for migraine: what it is, why it matters, and how to get it (2019).
9. Melatonin Monograph. In: Clinical Pharmacology. Tampa, FL: Gold Standard, Inc. Online Database.
10. Melatonin. Monograph. *Alternative Medicine Review* 10 (2005): 326-336.
11. Melatonin. In: Natural Medicines. Somerville, MA: Therapeutic Research Center. Online database.
12. Melatonin (Natural Products Database). In: Lexicomp Online. Hudson, OH: Lexi-Comp.
13. Tordjman S., *et al*. "Melatonin: Pharmacology, Functions and Therapeutic Benefits". *Current Neuropharmacology* 15.3 (2017): 434-443.
14. Dubocovich ML. "Melatonin receptors: are there multiple subtypes?" *Trends in Pharmacological Sciences* 16.2 (1995): 50-56.
15. Ebisawa T., *et al*. "Expression cloning of a high-affinity melatonin receptor from Xenopus dermal melanophores". *Proceedings of the National Academy of Sciences of the United States of America* 91.13 (1994): 6133-6137.
16. Cardinali DP., *et al*. "Melatonin site and mechanism of action: single or multiple?" *Journal of Pineal Research* 23.1 (1997): 32-39.
17. Hattori A., *et al*. "Identification of melatonin in plants and its effects on plasma melatonin levels and binding to melatonin receptors in vertebrates". *Biochemistry and Molecular Biology International* 35.3 (1995): 627-634.

18. Claustrat B., *et al*. "Nocturnal plasma melatonin levels in migraine: a preliminary report". *Headache* 29.4 (1989): 242-245.

19. Peres MFP. "Melatonin, the pineal gland and their implications for headache disorders". *The International Classification of Headache* 25.6 (2005): 403-411.

20. Masruha MR., *et al*. "Urinary 6-sulphatoxymelatonin levels are depressed in chronic migraine and several comorbidities". *Headache* 50.3 (2010): 413-419.

21. Masruha MR., *et al*. "Low urinary 6-sulphatoxymelatonin concentrations in acute migraine". *The Journal of Headache and Pain* 9.4 (2008): 221-224.

22. Claustrat B., *et al*. "Nocturnal plasma melatonin profile and melatonin kinetics during infusion in status migrainosus". *Cephalalgia: an International Journal of Headache* 17.4 (1997): 511-517.

23. Peres MFP., *et al*. "Potential therapeutic use of melatonin in migraine and other headache disorders". *Expert Opinion on Investigational Drugs* 15.4 (2006): 367-375.

24. Peres M., *et al*. "Chronobiological features in episodic and chronic migraine". *Cephalalgia* 23.7 (2003): 9600.

25. Peres MF., *et al*. "Hypothalamic involvement in chronic migraine". *Journal of Neurology, Neurosurgery, and Psychiatry* 71.6 (2001): 747-751.

26. Bruera O., *et al*. "Plasma melatonin pattern in chronic and episodic headaches: evaluation during sleep and waking". *Functional Neurology* 23.2 (2008): 77-81.

27. Tanuri FC., *et al*. "Melatonin treatment decreases c-fos expression in a headache model induced by capsaicin". *Journal of Pineal Research* 10.2 (2009): 105-110.

28. Mantovani M., *et al*. "Mechanisms involved in the antinociception caused by melatonin in mice". *Journal of Pineal Research* 41.4 (2006): 382-389.

29. Vogler B., *et al*. "Role of melatonin in the pathophysiology of migraine: implications for treatment". *CNS Drugs* 20.5 (2006): 343-350.

30. Gagnier JJ. "The therapeutic potential of melatonin in migraines and other headache types". *Alternative Medicine Review: a Journal of Clinical Therapeutic* 6.4 (2001): 383-389.

31. Peres MFP., *et al*. "Melatonin, 3 mg, is effective for migraine prevention". *Neurology* 63.4 (200 4): 757.

32. Nagtegaal JE., *et al*. "Melatonin-responsive headache in delayed sleep phase syndrome: preliminary observations". *Headache* 38.4 (1998): 303-307.

33. Miano S., *et al*. "Melatonin to prevent migraine or tension-type headache in children". *Neurological Society and of the Italian Society of Clinical Neurophysiology* 29.4 (2008): 285-287.

34. Alstadhaug KB., *et al*. "Prophylaxis of migraine with melatonin: a randomized controlled trial". *Neurology* 75.17 (2010): 1527-1532.

35. Anastasia Bougea., et al. "Melatonin 4 mg as prophylactic therapy for primary headaches: a pilot study". *Functional Neurology* 31.1 (2016): 33-37.

36. Fallah R., *et al*. "Safety and efficacy of melatonin in pediatric migraine prophylaxis". *Current Drug Safety* 10.2 (2015): 132-135.

37. Gonçalves AL., *et al*. "Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention". *Journal of Neurology, Neurosurgery, and Psychiatry* 87.10 (2016): 1127-1132.

38. Amy A Gelfand., *et al*. "Home-Based Trials in Adolescent Migraine: A Randomized Clinical Trial". *JAMA Neurology* 74.6 (2017): 744-745.

39. Gelfand A. "Melatonin for Adolescent Migraine Prevention Study (The MAP Study)". *Clinical Trials* (2021).

40. Alstadhaug KB., *et al*. "Prophylaxis of migraine with melatonin: a randomized controlled trial". *Neurology* 75.17 (2010): 1527-1532.

41. Kelley NE and Tepper DE. "Rescue therapy for acute migraine, part 2: neuroleptics, antihistamines, and others". *Headache* 52 (2012): 292.

42. Rizzoli PB. "Acute and preventive treatment of migraine". *Continuum* 18 (2012): 764.

43. Friedman BW., *et al*. "Randomized trial of IV valproate vs metoclopramide vs ketorolac for acute migraine". *Neurology* 82 (2014): 976.

44. Orr SL., *et al*. "Canadian Headache Society systematic review and recommendations on the treatment of migraine pain in emergency settings". *Cephalalgia* 35 (2015): 271.

45. Marmura MJ., *et al*. "The acute treatment of migraine in adults: the American headache society evidence assessment of migraine pharmacotherapies". *Headache* 55 (2015): 3.

46. Melatonin Monograph. In: MicroMedex 2.0. Ann Arbor, MI: Truven Health Analytics. Online Database (2022).

47. https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/beta-blockers/art-20044522

48. General side effects and challenges associated with anti-epilepsy medication: A review of related literature, African Journal of Primary Health Care and Family Medicine (2020).

49. Adverse Drug Effects, Compliance, and Initial Doses of Antihypertensive Drugs Recommended by the Joint National Committee vs the Physicians' Desk Reference) (2001).

50. Onabotulinumtoxin A: Generic, Uses, Side Effects, Dosages, Interactions, Warnings (rxlist.com).

51. Colmenero MD., *et al*. "Melatonin administration during pregnancy retards sexual maturation of female offspring in the rat". *Journal of Pineal Research* 11.1 (1991): 23-27.

52. Jahnke G., *et al*. "Maternal and developmental toxicity evaluation of melatonin administered orally to pregnant Sprague-Dawley rats". *Basic and Clinical Pharmacology and Toxicology* 50.2 (1999): 271-279.

53. Voordouw BC., *et al*. "Melatonin and melatonin-progestin combinations alter pituitary-ovarian function in women and can inhibit ovulation". *The Journal of Clinical Endocrinology and Metabolism* 74.1 (1992): 108-117.

54. Cavallo A and Ritschel WA. "Pharmacokinetics of melatonin in human sexual maturation". *The Journal of Clinical Endocrinology and Metabolism* 81.5 (1996): 1882-1886.

55. Commentz JC., *et al*. "Melatonin and 6-hydroxymelatonin sulfate excretion is inversely correlated with gonadal development in children". *Hormone Research in Paediatrics* 47.3 (1997): 97-101.

56. Carman JS., *et al*. "Negative effects of melatonin on depression". *The American Journal of Psychiatry* 133.10 (1976): 1181-1186.

57. Wirtz PH., *et al*. "Oral melatonin reduces blood coagulation activity: a placebo-controlled study in healthy young men". *Journal of Pineal Research* 44.2 (2008): 127-133.

58. Cagnacci A., *et al*. "Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women". *Clinical Endocrinology* 54.3 (2001): 339-346.

59. Sandyk R., *et al*. "Melatonin as a proconvulsive hormone in humans". *International Journal of Neuroscience* 63.1-2 (1992): 125-135.

60. Sheldon SH. "Pro-convulsant effects of oral melatonin in neurologically disabled children". *Lancet* 351.9111 (1998): 1254.

61. 021782s011lbl.pdf (2022).

62. Lusardi P., *et al*. "Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study". *British Journal of Clinical Pharmacology* 49.5 (2000): 423-427.

63. Weekley LB. "Melatonin-induced relaxation of rat aorta: interaction with adrenergic agonists". *Journal of Pineal Research* 11.1 (1991): 28-34.

64. Härtter S., *et al*. "Increased bioavailability of oral melatonin after fluvoxamine coadministration". *Clinical Pharmacology and Therapeutics* 67.1 (2000): 1-6.

65. Von Bahr C., *et al*. "Fluvoxamine but not citalopram increases serum melatonin in healthy subjects-- an indication that cytochrome P450 CYP1A2 and CYP2C19 hydroxylate melatonin". *European Journal of Clinical Pharmacology* 56.2 (2000): 123-127.

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