Melatonin in headache disorders

A melatonina nas cefaleias

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ABSTRACT

Melatonin have diverse physiological functions, including the control of circadian rhythms, sleep regulation, enhancement of immunological functioning, free radical scavenging and antioxidant effects, inhibition of oncogenesis, mood regulation, vasoregulation, regulation of seasonal reproductive activity and analgesia. Melatonin also have several actions within the central nervous system and in the pathophysiology of headaches, which include an anti-inflammatory effect, toxic free radical scavenging, reduction of proinflammatory cytokine up-regulation, nitric oxide synthase activity and dopamine release inhibition, membrane stabilization, GABA and opioid analgesia potentiation, glutamate neurotoxicity protection, neurovascular regulation, serotonin modulation, and the similarity of chemical structure to that of indomethacin. A relation with seasonal and circadian pattern has been observed in cluster an hypnic headache. The literature of headache is convergent in pointing to low levels of melatonin in patients with migraine and cluster headache. Treatment of headache disorders with melatonin and other chronobiotic agents is promising. Some trials showed that melatonin was effective in cluster headache and migraine prevention but future studies are necessary for the better understanding of the role of melatonin in headache disorders treatment.

Keywords: Melatonin; Pineal gland; Migraine; Pathophysiology; Treatment

RESUMO

A melatonina tem diversas funções fisiológicas, incluindo o controle de ritmos circadianos, regulação do sono, melhoria do funcionamento imunológico, varredura de radicais livres e efeitos antioxidantes, inibição da oncogênese, regulação do humor, vasoregulação, regulamentação da atividade reprodutiva sazonal e analgesia. A melatonina também tem várias ações dentro do sistema nervoso central e na fisiopatologia das cefaleias, as quais incluem um efeito anti-inflamatório e de limpeza de radicais livres tóxicos, a redução de citocinas pró-inflamatórias, da inibição da atividade da óxido nítrico sintase e da produção de dopamina, a estabilização das membranas, potencialização da analgesia GABA e de opioides, proteção contra a neurotoxicidade do glutamato, regulação neurovascular, modulação da serotonina, além de possuir estrutura química similar à da indometacina. Uma relação com padrão sazonal e circadiano tem sido observada na cefaleia em salvas e hipnica. A literatura de dor de cabeça e melatonina é convergente em apontar a presença de baixos níveis deste hormônio em pacientes com enxaqueca e cefaleia em salvas. O tratamento das cefaleias com melatonina e outros agentes cronobióticos é promissor. Alguns estudos mostraram que a melatonina foi eficaz na cefaleia em salvas e na prevenção da enxaqueca, porém futuros estudos são necessários para comprovar seu beneficio no tratamento das cefaleias.

Palavras-chave: Melatonina; Glândula Pineal; Enxaqueca; Fisiopatologia; Tratamento

INTRODUÇÃO

Melatonin (5-methoxy-N-acetyltryptamine) was discovered by Aaron Lerner in 1958. Melatonin synthesis has been described in numerous peripheral organs, such as the retina,[1] bone marrow,[2] skin,[3] platelets,[4] lymphocytes,[5] testis,[6] and in the gastrointestinal tract.[7,8] In these tissues melatonin seems to plays either an autocrine or a paracrine role. Data on messenger RNA expression

of two key enzymes responsible for melatonin synthesis, arylalkyamine-N-acetyltransferase and hydoxyindole-O-methyltransferase, suggest that even more peripheral organs may be able to produce this hormone.[9]

Physiology of melatonin

The pineal gland is highly vascular and consists of two types of cells: neuroglial cell and pinealocytes, which predominate and produce indolamines (melatonin) and peptides (such as arginine vasotocin). In the biosynthesis of melatonin, tryptophan is converted by tryptophan hydroxylase to 5-hydroxytryptophan, which is decarboxylated to serotonin. Melatonin is produced after serotonin is catalyzed by two enzymes (arylalkylamine N-acetyltransferase and hydroxyindole-O-methyltransferase).[10,11] The production and secretion of melatonin are mediated largely by postganglionic retinal nerve fibers that pass through the retinohypothalamic tract to the suprachiasmatic nucleus, then to the superior cervical ganglion, and finally to the pineal gland. This neuronal system is activated by darkness and suppressed by light. The activation of alpha-1 and beta-1-adrenergic receptors in the pineal gland raises cyclic AMP and calcium concentrations and activates arylalkylamine N-acetyltransferase, initiating the synthesis and release of melatonin. The daily rhythm of melatonin secretion is also controlled by an endogenous, free-running pacemaker located in the suprachiasmatic nucleus. Melatonin is able to enter every cell of the body and readily crosses the blood-brain barrier and the placenta. Melatonin is enzymatically degraded in the liver by hydroxylation (to 6-hydroxymelatonin) and, after conjugation with sulfuric or glucuronic acid and is finally excreted in the urine as 6-sulphatoxymelatonin (aMT6s). Analysis of urine by the ELISA method is used as a measure of melatonin secretion, since it closely parallels with the profile of plasma nocturnal melatonin concentrations.[12] There is some evidence suggesting that a seasonal variation exists in the synthesis of melatonin in humans, the levels possibly being higher in winter than in summer.[13]

Melatonin is a potent antioxidant, which can exert its action in directly or indirectly. In addition to its direct free radical scavenging action, melatonin has been reported to increase the activity of some important antioxidant enzymes at molecular level, including superoxide dismutase and glutathione peroxidase.[14] Also melatonin decreases the activity of nitric oxide synthase, a pro-oxidative enzime.[15] In fact melatonin can also scavenge hydroxy radical, peroxil radical, peroxinitrite anion, and singlet oxigen protecting cell membrane, proteins in the cytosol and DNA in the nucleus.

Pharmacology

The half-life of melatonin in the serum is between 30 and 57 minutes.[16] Intravenously administered melatonin is rapidly distributed and eliminated.[17] In normal subjects, 80 mg of melatonin orally administered promote serum melatonin concentrations that were 350 to 10,000 times higher than the usual nighttime peak, 60 to 150 minutes later, and these values remained stable for 90 minutes.[18] Lower oral doses (1 to 5 mg), result in serum melatonin concentrations that are 10 to 100 times higher than the usual nighttime peak, within one hour after ingestion, followed by a decline to base-line values in four to eight hours. Very low oral doses (0.1 to 0.3 mg) given in the daytime result in peak serum concentrations that are within the normal nighttime range.[19]

Potential use of melatonin in analgesia: mechanisms of action

Melatonin has been shown to exert antinociceptive and antiallodynic actions in a variety of experimental models in animals.[20] Induction of pain involves the release of several pro-inflammatory mediators like cytokines and the activation of a number of neurotransmitter receptor sites present in both the spinal cord and brain. The mechanisms that melatonin may act in pain are control the release of pro-inflammatory mediators; inhibit the activation of receptors involved in pain perception present at spinal cord; inhibit receptor activation in brain regions involved in pain perception and promote sleep that can be extremely effective for controlling/inhibiting pain perception.

The available evidence demonstrates that melatonin seems to have a action in the opioid system and a modulatory effect on the circadian rhythm of nociception. Yousaf, in a review[21] of the use of melatonin in peri-operative setting, reports anxiolytic and analgesic properties. Melatonin premedication is effective in ameliorating perioperative anxiety in adults. Compared with midazolam, melatonin has similar anxiolytic efficacy but less psychomotor impairment and fewer side effects. The elderly population has been shown to be refractory to the hypnotic and anxiolytic effects of melatonin.[22] The clinical impact of melatonin on pain need to more studied and the evidence regarding its potential analgesic effects in the perioperative setting is inconsistent and limited. Melatonin premedication was associated with an analgesic

effect in the studies with pain as a primary outcome, whereas the lack of analgesic effect was observed in studies with pain as a secondary outcome.[23-25] It seems that high doses of melatonin are required to produce major analgesic effects.[20] The antinociceptive and antiallodynic properties of melatonin have a perspective in future studies in patients that suffer from pain due to inflammation, occurring during headache, cancer patients, neuropathic pain and fibromyalgia. It may be useful in patients with comorbidities like anxiety that is frequently associated with headache disorders.

Table 1- The pathophysiological and therapeutic role of melatonin

Disease	Melatonin Response	Melatonin Pathophysiology
Cluster headache	RCT shows efficacy	Decreased levels
Paroxysmal hemicrania	Potential	Unknown
Hypnic headche	Case report	Unknown
Hemicrania continua	Case report	Unknown
Episodic migraine	Open study shows good results	Decreased levels
Chronic migraine	Potential	Decreased levels and peak shift
Tension-type headache	Open-label trial shows good results	Unknown

RCT = Randomized, placebo- controlled clinical trial

MELATONIN AND HEADACHES

Melatonin indeed demonstrates several actions within the central nervous system (SNC), which may account for its putative analgesic role in headache.[26] (Table 1).

First, melatonin potentiates the inhibitory action of GABA on SNC and several GABAergic drugs have been used successfully in the prophylaxis of migraine, such as topiramate, divalproex and gabapentin.Thus, reduced concentrations of melatonin might lower the activation threshold of pain circuits normally inhibited by GABAergic transmission. Second, because melatonin modulates the entry of calcium into cells, a reduction in melatonin might alter the tone or vasoreactivity of cerebral blood vessels. Furthermore, melatonin receptors have been identified on cerebral arteries and melatonin has also been shown to modulate 5-HT2 receptors on cerebral arteries. Antagonism at this 5-HT receptor is exploited by drugs used to prevent migraine and CH. Additionally, a melatonin-driven modulation of 5HT2 receptors was suggested, similar to drugs used for migraine prophylaxis, such as flunarizine, methysergide and beta-blockers.[27] Melatonin modulates different serotonin receptors which is known to be important in the pathophysiology of migraine. Finally, melatonin inhibits the synthesis of prostaglandin E_2, which has been identified as one of many substances that can lead to sterile perivascular inflammation (neurogenic inflammation) that activates the trigeminovascular nociceptive afferents.

Potential therapeutic use of melatonin in headache disorders

Melatonin has been implicated in the treatment of different types of headaches (Table 2).

Table 2 - Mechanism of action of melatonin in the central nervous system

Mechanisms of action of melatonin in CNS
GABA and opioid analgesia potentiation
Calcium entry into the cells modulation and promotion of neurovascular regulation
Modulation of 5HT2 receptors on cerebral arteries
Serotonin modulation
Anti-inflammatory effect
Toxic free radical scavenging
Reduction of proinflammatory cytokine up-regulation
Nitric oxide synthase activity and dopamine release inhibition
Glutamate neurotoxicity protection
Membrane stabilization

MIGRAINE

The literature of headache and melatonin is convergent point to low levels of this hormone in patients with migraine,[28-29] menstrual migraine,[30-31] chronic migraine[32] and cluster headache.[33-38]

Claustrat et al.[28] were the first to demonstrate lower plasma melatonin levels in samples from migraine patients compared with controls. Migraine patients without depression had lower levels than controls, but migraineurs with superimposed depression exhibited the greatest melatonin deficiency. Murialdo et al.[31] also found nocturnal urinary melatonin to be significantly decreased throughout the ovarian cycle of migraine patients without aura compared with controls. Melatonin excretion was further decreased when patients suffered a migraine attack.

Brun et al.[30] studied urinary melatonin in women with migraine without aura attacks associated with menses and controls. Melatonin levels throughout the cycle were significantly lower in the migraine patients than in controls. In the control group, melatonin excretion increased significantly from the follicular to the luteal phase, whereas no difference was observed in the migraine group.

Peres et al.[32] studied plasma melatonin nocturnal profile in chronic migraine patients and controls. Lowered melatonin levels in patients with insomnia were observed compared with those without insomnia, and a phase delay in the melatonin peak in patients versus controls.

Masruha et al.[39] were the first to demonstrate reduction in melatonin levels during attacks in episodic and chronic migraine. The study assessed 6-sulphatoxymelatonin (aMT6s) levels in a large consecutive series of patients with migraine, comparing with controls. A total of 220 subjects were evaluated (146 had migraine and 74 were control subjects). aMT6s urinary samples were measured with quantitative ELISA technique. Among patients with migraine, 53% presented pain on the day of the urine samples collection. Their urinary aMT6s concentration was significantly lower than in the urine of patients without pain. There was no significant difference in the aMT6s concentration of patients with migraine without pain on the day of their urine samples collection. AMT6s levels were even lower in patients with chronic migraine and in the presence of a migraine attack. It was also observed that the higher is the frequency of migraine attacks, lower levels of aMT6s. These are also strongly correlated, inversely, with levels of depression, anxiety, fatigue, diagnosis of excessive daytime sleepiness and the number of points of fibromyalgia.[40]

CHRONIC MIGRAINE

The role of the hypothalamus in the pathophysiology of chronic migraine (CM) was first studied by Peres el al.[32] in a experiment to explore the hypothalamic-tuberoinfundibular system (prolactin, growth hormone), the hypothalamic hypophyseal-adrenal axis (cortisol), and pineal gland function (melatonin) in CM. A total of 338 blood samples (13/patient) from 17 patients with CM and nine (age and sex matched) healthy volunteers were taken. Melatonin, prolactin, growth hormone, and cortisol concentrations were determined every hour for 12 hours. The study showed an abnormal pattern of hypothalamic hormonal secretion in CM. Forty-seven per cent of patients with CM had a significant phase delay in the melatonin peak, and half had insomnia. Melatonin concentrations, peak secretion, and AUCs were significantly lower in patients with CM who had insomnia than in controls and patients with CM without insomnia. In conclusion, they found a decreased nocturnal prolactin peak, a increased cortisol concentrations, a delayed nocturnal melatonin peak in patients with CM, and lower melatonin concentrations in patients with CM with insomnia. It supports the report of Nagtegaal et al.[41] that showed a phase delay in the nocturnal melatonin peak in patients with delayed sleep phase syndrome and associated headaches. They had a great improvement of both symptoms after treatment with 5 mg melatonin.

Treatment of migraine

Claustrat et al.[29] reported six patients with status migranous which were treated with infusion of 20 mg of melatonin. Four patients have a headache relief in the morning after night melatonin infusion and the other two patients reported an improvement after the third night of infusion, and three patients reported a decrease in intensity during the migraine attacks.

Nagtegaal et al.[41] reported the case of a 54-year-old man who suffered from disabling migraine attacks without aura, twice a week. After starting melatonin treatment, only three migraine attacks were reported in 12 months.

In an open study carried out by Peres et al.[42] the use of 3 mg of melatonin was effective in the preventive treatment of migraine. Of the 34 patients who were evaluated, 78.1% showed clinical response, defined as a reduction greater than 50% of the frequency of attacks. The complete response, i.e. a reduction of 100% of seizures, was observed in 25% of patients. The frequency of headache, duration, intensity and analgesic consumption decreased significantly ($p < 0.001$) in the first month of treatment in relation to the baseline period.

Miano et al.[43] designed a 3-month open label trial of melatonin prophylaxis in children with primary headache. After a one month baseline period patients received preventive therapy with melatonin (3 mg) administered orally at bedtime for three months without receiving preventive drugs. A total of 22 children were enrolled and 13 subjects had migraine without aura, one male had migraine with aura. On assessment at the completion of the trial, 14 of the 21 subjects reported that the headache attacks had decreased by more than 50% with respect to baseline, and 4 reported having no headache attacks. In 7 of the 21 children the frequency of headache attacks remained unchanged from baseline (three with migraine without aura and four with chronic tension-type headache). None of the patients reported an increased number of attacks during the trial. One subject dropped out because of excessive daytime sleepiness.

Side effects have been reported in association with the ingestion of melatonin but are not serious. Physiologic

effects of the hormone (hypothermia, increased sleepiness, decreased alertness, and possibly reproductive effects), that are dose-dependent, have not yet been properly evaluated in individuals that use large doses of melatonin for prolonged periods of time.

TENSION-TYPE HEADACHE

In 1998, Nagtegaal et al.[41] reported three women (aged 14, 14, and 23) suffering from chronic tension-type headache (CTTH) in a total of 30 patients with delayed sleep phase syndrome which were treat with 5 mg melatonin. After treatment with melatonin their headache disappeared within two weeks.

In a trial of melatonin prophylaxis in children, Miano et al.[43] treated eight patients with CTTH in total of 22 children with primary headache. After a one month baseline period without receiving preventive drugs, all children received a 3-month course of melatonin (3 mg) administered orally, at bedtime. The study lasted four months: during the first month (baseline period) patients received no preventive therapy for recurrent headache and for the next three months received therapy with pure melatonin (3 mg) administered orally at bedtime. From the total of eight patients four are males. Headache attacks had decreased, by more than 50%, in four patients, and none reported a complete remission of headache.

CLUSTER HEADACHE

The circadian rhythmicity of CH has oriented the studies toward the hypothalamus. The suprachiasmatic nucleus (SCN) is the main control center of the biological clock, which receives retinal information on luminosity and projects it to the pineal gland where melatonin needs to be produced in a circadian rhythm to act satisfactorily.[44] During the symptomatic phase of CH, the melatonin production is reduced until its nocturnal peak disappears,[35] thus altering biological rhythms and decreasing its additional analgesic effect related to gabaergic reinforcement,[33] calcium modulation[26] and prostaglandin synthesis inhibition.[45]

In 1984, Chazot et al.[35] detected a decrease in nocturnal melatonin secretion and abolished melatonin rhythm in CH patients. Waldenlind et al.[37] also showed lowered nocturnal melatonin levels during cluster periods than remissions and found that women had higher melatonin levels than men throughout the year.[36] Smokers had lower levels than non-smoking cluster headache patients. Leone et al.[34] observed melatonin and cortisol peaks significantly correlated in controls but not in cluster headache patients, indicating a chronobiological disorder in these patients. Blau and Engel[46] observed that 75 of 200 CH patients have a increase in body temperature from exercise, and hot bath or elevated environmental temperature may trigger cluster headache attacks. This finding can be explained by a decrease in melatonin secretion caused by temperature increase.[47]

Melatonin has been implicated in the treatment of cluster headache. There is one study Class II RCT on melatonin for cluster prevention.[33] This is a double-blind, placebo-controlled, parallel-group trial. The RCT (20 people; 18 with episodic cluster headache; two with chronic cluster headache) compared oral melatonin 10 mg daily versus placebo for two weeks. In comparison to the run-in period, there was a reduction in daily headache frequency in the melatonin group ($p < 0.03$), but not the placebo group. Two patients with chronic cluster headache did not respond to melatonin therapy. Adverse events were not reported.

Peres and Rozen[48] described two chronic CH patients who responded to melatonin (9 mg at bedtime). Melatonin prevented nocturnal cluster attacks and also daytime attacks. Nagtegaal et al.[41] reported one patient with delayed sleep phase syndrome in association with episodic CH in whom both disorders improved after melatonin treatment. There are a few trials to evaluate melatonin in prevention of CH and it was considered Level C for the prevention of CH.[49]

INDOMETHACIN-RESPONSIVE HEADACHE SYNDROMES

Melatonin has a chemical structure similar to that of indomethacin and thi fact has led researchers to use melatonin in the treatment of indomethacin-responsive headache.

Primary stabbing headache

Rozen[50] reported three patients with primary stabbing headache (PSH) with a positive response to indomethacin that were administered melatonin to assess its effectiveness. The three patients were given different dosages of melatonin (3, 9 and 12 mg, respectively). All the patients became asymptomatic and remained so throughout a 2- to 4-month follow-up. Melatonin appears to be an effective alternative treatment for PSH. Melatonin has a clearly more favorable side-effect profile than indomethacin. Rozen recommended to start with a bedtime

dose of 3 mg and then to increase the dose by 3 mg every four nights until pain relief is obtained, setting 24 mg as the upper dose limit. However, in most cases, no treatment is necessary given that PSH has a natural course of spontaneous fluctuations, with only 14% of patients experiencing persistent symptoms.[51]

Hypnic headache

Hypnic headache (HH) or primary sleep-related headache is a rare primary headache disorder that mainly affects elderly people. It was first described by Raskin, in 1988,[52] and 174 cases have been reported in the literature so far.[27] The exact pathophysiological mechanisms of HH have not yet been elucidated. It has been postulated that HH may be the result of a chronobiological disorder, serotonin, and melatonin dysregulation or a disturbance of rapid eye movement (REM) sleep. In most of the patients with HH who had polysomnographic studies, attacks were associated with REM sleep,[53-57] however, non-REM related HHs have also been reported.

Many patients reported a good response to indomethacin, but some could not tolerate it. Caffeine and melatonin treatments did not yield robust evidence to recommend their use as single preventive agents. Nevertheless, their association with lithium or indomethacin seems to produce an additional therapeutic efficacy. Lithium indirectly increases the level of melatonin[58-60] and may thus affect the pathophysiology of HH.

Domitrz describes a case of HH, which were effectively treated with flunarizine and melatonin (3 mg) in a 45-year-old woman.[61]

Dodick[54] describe a 68-year-old woman presented with a 6-year history of nocturnal headaches that awaken her from sleep. Treatment with melatonin (3 mg) at bedtime was begun, and headache severity decreased from moderate to mild and duration decreased to 15 to 20 minutes. The dose was increased to 6 mg, which rendered her headache-free over a 4-month period.

Ghiotto et al.[62] report two cases of HH that improve after treatment with melatonin.

Melatonin seems to be effective in a daily dose 3-5 mg and in association with caffeine or another drug for prophylaxis of HH. Melatonin was effective in four of 174 cases, in a recent review; thus, more studies are necessary to evaluate your efficacy in HH.[27,63]

Hemicrania continua

In a few reports melatonin was shown to be effective for HC. Spears[64] reported a case of hemicrania continua in which attacks were successfully eliminated while taking melatonin (7 mg) at bedtime after the patient was no longer able to tolerate indomethacin due to gastrointestinal side effects. Rozen[65] also reported an improvement in the hemicrania continua after treatment with melatonin.

HEADACHES AND PINEAL CYSTS

Pineal cysts are benign lesions found in up to 2.6% of adults. Asymptomatic pineal cysts are usually an incidental neuroimaging finding.

Peres et al. described five cases of primary headaches associated with pineal cysts and suggested that pineal cysts could be related to headache disorders not because of compression but abnormal secretion of the pineal hormone melatonin.[66] Seifert et al. studied 51 pineal cysts patients compared with 51 controls. Pineal cyst patients had 2-fold more headaches than controls (51% vs 25%).The most common diagnosis in pineal cysts patients was migraine in 26%, including 14% with migraine with aura. One patient had hemicrania continua. The authors suggest pineal cysts may be related to headaches, particularly migraine. Interestingly, cyst diameter was not different in patients with headache as compared with those without headache. This finding supports the idea of Peres et al.[66] that melatonin dysfunction may be the main mechanism related to the headache. Melatonin has been linked extensively to headache disorders with experimental and clinical evidence.[33,39,42,67,68] Unfortunately, to date, no measures of melatonin secretion have been performed in pineal cysts patients. Small, asymptomatic pineal cysts require no therapy. If they become symptomatic from hydrocephalus, surgical options can be considered. The patient with a headache disorder and a pineal cyst may be treated preventively with melatonin starting with 3 mg at bedtime and increasing to 15 mg.[67]

MELATONIN, HEADACHE AND MEDICINAL PLANTS

Melatonin have been found in several plants of medicinal value in species like feverfew (*Tanacetum parthenium*), St John's wort (*Hypericum perforatum*) and huang-qin (*Scutellaria baicalensis*).[69-71] Feverfew has been used in migraine treatment but sufficient scientific evidence of efficacy has not been established to date.[72,73] *Angelicae Dahurica* combined with *Scutellaria baicalensis* has been widely used as herb-pairs in traditional Chinese medicine to treat migraine headache. The interplay between

melatonin and these other reportedly potent compounds may be a promising field of future research.

Melatonin agonists

Melatonin and melatoninergic agonists may also be important in migraine comorbidity.[67] Insomnia in headache patients is the most likely associated condition in migraine to respond to melatonin therapy. Ramelteon (Rozeren®), a selective melatonin 1 or 2 receptor agonist can also be used for treatment of insomnia in migraine patients and have a profile with few side effects comparing with hypnotics drugs.

Agomelatine is a novel antidepressant and a melatonin agonist, a MT1 and MT2 receptor-site. It has been approved for major depression in Brazil.

Although no controlled studies with large samples have been published, two randomized clinical trials controlled with placebo for migraine prevention are registered in clinicaltrials.org, one with melatonin and other with ramelteon.

In Brazil there is no approval of Brazilian Health Survillance Agency (ANVISA) for the use of melatonin as a vitamin, as is in the United States and most of developed countries, we totally agree with that. Brazilian law enables public advertisement when a compound is registered as a vitamin and this is not desirable for melatonin with the current health assistance access for the general population. In contrast, melatonin as a natural substance found in the human body cannot be applied for a patent, it is cheap, therefore no pharmaceutical company has financial interest in the application of melatonin as a medication. Important to notice that melatonin is not a banned drug, and not prohibited in Brazil, it is only not registered as a vitamin or a medication, as many other compounds, including vitamins and not yet approved medication for oncology treatments, the patient has the right to take it and receive the best treatment option, and the physician has the right to prescribe the best treatment option for his or her patient. We hope in the near future melatonin could be better delivered to patients with the regulatory issues resolved.

CONCLUSION

Melatonin plays a significant role in the patho-physiology of headaches. Melatonin can also be a good option in the treatment of primary headaches, not only those with nocturnal occurrence but also migraine and other headaches. In the presence of insomnia or circadian rhythm disturbance melatonin may also be helpful. However more randomized clinical trials should be done in order to give more evidence for melatonin prescription in our current practice (see take home messages).

Table 3. Take home messages

Melatonin should be considered in association with another drugs in the preventive treatment of headaches
Use melatonin in comorbidities with sleep disorders
Further studies are necessary for evaluating the effectiveness of melatonin in primary headache

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