DRUG DEVELOPMENT RESEARCH 68:329–334 (2007)

DDR

Clinical Perspective

Melatonin Therapy for Headache Disorders

Mario F.P. Peres,* Marcelo Rodrigues Masruha, and Alan M. Rapoport

Strategy, Management and Health Policy				
Enabling Technology, Genomics, Proteomics	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT Even though efficacy is often the most important consideration for patient preference in migraine prevention, currently available medications do not meet patient expectation. Efficacy is in the range of 50% reduction in migraine attacks in 50% of patients studied for the best medications. Therefore, new options for migraine treatment are needed. Melatonin has been considered a good candidate for migraine and other headaches prevention due to its favorable mechanisms of action and excellent tolerability profile. In this article, we review the putative role of the pineal gland and melatonin in migraine pathophysiology and treatment. Drug Dev Res 68:329–334, 2007. © 2007 Wiley-Liss, Inc.

Key words: melatonin; pineal gland; migraine therapy; headache treatment

INTRODUCTION

Effective migraine management begins with a good treatment plan. It is important to consider not only patient diagnoses, symptoms, and any coexistent or comorbid conditions, but also patient expectations, needs, and goals [Peres et al., 2007]. Migraine prophylaxis is divided into a nonpharmacologic and a medication-based approach. Education, trigger avoidance, lifestyle reformulation, and getting adequate sleep are the main nonpharmacologic strategies [Holroyd and Penzien, 1990]. Several medications are used in migraine prevention, including antidepressants, β-adrenergic blockers, anticonvulsants/neuromodulators, and calcium channel antagonists [Bigal and Lipton, 2006]. Other categories are sometimes used including serotonin type 2 blockers and angiotensin receptor blockers. Even though efficacy is often the most important consideration for patient preference in migraine prevention, medications currently available do not meet patient expectation. Efficacy is within the range of 50% reduction in migraine attacks in 50% of patients studied for the best medications. Therefore, new options for migraine treatment are needed.

The pineal hormone melatonin is a remarkable molecule, with a conserved time-keeping function across species [Arendt, 2006]. It is extensively used as a self-administered remedy for sleep disturbance in countries where it is freely available, and to some extent when it is available by prescription.

Melatonin has been considered a good candidate for migraine and other headaches prevention due to its favorable mechanisms of action and excellent tolerability profile. In this article, we review the putative role of the pineal gland and melatonin in migraine pathophysiology and treatment.

MELATONIN AND THE PINEAL GLAND

Melatonin (N-acetyl-5-methoxytryptamine) was characterized after its isolation from bovine pineal tissue by Lerner et al roughly 50 years ago [Arendt, 2007]. This indolamine is now known to be the major secretory product of the pineal gland in all mammals, including man.

*Correspondence to: Mario Fernando Prieto Peres, Al. Joaquim Eugenio de Lima, 881 cj 708, 01403-001 São Paulo SP, Brazil. E-mail: marioperes@yahoo.com

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ddr.20196

© 2007 Wiley-Liss, Inc.

WILEY InterScience® DISCOVER SOMETHING GREAT

Changes in behavior occurring on a 24-h basis to match the 24-h changes in the physical environment due to the rotation of the earth on its axis are a hallmark of life on the planet Earth. The nervous system of both lower and higher organisms has evolved over millions of years to meet the demands changes in the environment that occur in relation to the changes in the light–dark cycle, optimizing the survival and reproductive success of the organism [Turek and Gillette, 2004]. A synchronization system to adapt the internal to the external environment is one of the key elements of the central nervous system to maintain life. It has been clearly established that the 24-h nature of life was not simply a response to the 24-h changes in the physical environment imposed by celestial mechanics, but instead was due to an internal time-keeping system in the brain.

The pineal gland and melatonin are the main elements in the synchronization of internal biological events to the environment. Melatonin is absent during the day in men, and its nocturnal secretion is the main biological event signaling to the organism when it is night.

The pineal gland is a circumventricular organ located behind the third ventricle, below the splenium of the corpus callosum. Because of its pine-shaped structure, the organ was coined the "pineal" gland. The gland is usually 8 mm in diameter [Ackermann and Stehle, 2006]. It is composed of two kinds of the cells: pinealocytes and neuroglial cells. The pinealocytes are the principal location of melatonin synthesis. Melatonin is produced from tryptophan first by hydroxylation then decarboxylation resulting in the formation of serotonin, then *n*-acetylation, and finally methylation to form melatonin [Macchi and Bruce, 2004]. Because melatonin is so lipophilic, once it is produced it is quickly released into the blood stream and then readily crosses all physiologic barriers, including the placenta and blood–brain barrier [Barrenetxe et al., 2004].

The suprachiasmatic nucleus (SCN) of the hypothalamus regulates the synthesis of melatonin. The pathway from the hypothalamus to the pineal gland has been established. Visual input passes along fibers from the retinal ganglion cells to the SCN of the hypothalamus forming the retinohypothalamic tract. The fibers then pass through the paraventricular nuclei of the hypothalamus and through the brainstem to the intermediolateral cell column of the thoracic spinal cord. Connections are made with the preganglionic cell bodies of the sympathetic superior cervical ganglia. Noradrenergic fibers from the superior cervical ganglia project to the pineal gland and stimulate the production of *n*-acetyl transferase by increasing intracellular cAMP [Macchi and Bruce, 2004].

There is marked individual variation in the timing, duration, and amount of nocturnal melatonin produced. Photic stimulation and usual daytime light suppresses melatonin production; however, even in constant darkness, there is an endogenously driven rhythm of release of melatonin. Melatonin levels start to rise from detectability thresholds during the evening and are at maximum levels at night [Ackermann and Stehle, 2006].

Melatonin has substantial clinical implications and is associated with effects on sleep, mood, sexual maturation and reproduction, immune function, aging, cancer, and the antioxidative defense system [Reiter, 2003].

It has been linked not only to the pathophysiology of migraine and other headaches but also many neurological disorders.

MELATONIN IMPLICATION IN NEUROLOGICAL DISORDERS

Sleep is well known to play an important role as a restorative function. In human beings, it has a circadian rhythm, normally occurring at night, usually together with the nocturnal melatonin secretion [Rodenbeck et al., 1999]. This has led to the idea that melatonin is an internal sleep facilitator in humans, and therefore useful in the treatment of insomnia and the readjustment of circadian rhythms. There is evidence that administration of melatonin induces sleep when the drive to sleep is insufficient; inhibits the drive for wakefulness from the SCN; and induces phase shifts in the circadian clock such that the circadian phase of increased sleep propensity occurs at a new, desired time [Cajochen et al., 2003b].

Many neurological disorders occur with a marked rhythmicity, dependent on either the 24-h or the seasonal cycle, thus probably linked to the pineal function and melatonin secretion, including stroke [Beloosesky et al., 2002], multiple sclerosis [Hutter and Laing, 1996], facial paralysis [de Diego et al., 1999], and seasonal affective disorder [Checkley et al., 1993]. Chronobiological disorders can be external and related to life style and environment, as in shift workers, individuals crossing time zones in the jet lag syndrome, and in disadaptation to clock change for daylight savings time; or they can be endogenous or internal, including the delayed and advanced sleep phase syndromes, and the non-24-h sleep–wake disorder with free-running circadian rhythm. It has been proposed that the endogenous type may underlie several conditions including depression, chronic fatigue, fibromyalgia, and migraine [Gordijn et al., 1998].

The pineal gland is a photo-neuroendocrine organ, converting external luminous stimuli into a hormone secretion, being responsible for the synchronization between the internal homeosthasis and the

10982299, 2007, 6, Downloaded from https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/10.1002/ddr.20196 by Univ of Sao Paulo - Brazil, Wiley Online Library on [15/02/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

environment; therefore, an altered synchronization system may interfere with all neurological diseases. Sleep and circadian rhythms are often disrupted in people with neurological disorders [Turek et al., 2001]. The symptoms associated with neurological diseases may be due in part to disruption of the sleep–wake cycle. In addition, various neurological disorders may themselves disrupt the sleep–wake cycle, resulting in a positive feedback loop whereby disrupted sleep and waking exacerbate the neurological disorders, while the disease itself has a negative effect on the sleep–wake states [Cajochen et al., 2003a]. Symptoms associated with those disorders may fluctuate according to a specific rhythm (circannual, circamenal, circadian) and are often related to either sleep or wake periods. Epilepsy, dementia, movement disorders, multiple sclerosis, cerebrovascular disorders, neuromuscular disorders, and brain tumors have all been linked to an altered chronobiology, melatonin dysfunction, or benefit from melatonin treatment [Peres, 2004].

RELEVANCY OF MELATONIN MECHANISMS OF ACTION IN HEADACHE DISORDERS

The role of melatonin in headache pathophysiology is via several mechanisms. Melatonin has anti-inflammatory effects. Melatonin prevents the translocation of NF-κB to the nucleus and its binding to DNA, thereby reducing the upregulation of a variety of pro-inflammatory cytokines, interleukins, and tumor necrosis factor-α (TNF-α) [Cuzzocrea and Reiter, 2002]. Melatonin inhibits the production of adhesion molecules that promote the sticking of leukocytes to endothelial cells, attenuating transendothelial cell migration and edema. Animal and cell culture models of several inflammatory disorders have benefited from the application of melatonin. The mechanisms underlying the neuroprotective properties of melatonin are likely to involve activation of specific melatonin receptors. This can lead to modulation of transcription factors and consequent altered gene expression, resulting in enhancement of antioxidant enzymes and downregulation of basal levels of inflammation [Carrillo-Vico et al., 2006].

By its ability to scavenge toxic free radicals directly [Aydogan et al., 2006], it can reduce macromolecular damage in all organs. Melatonin inhibits the activity of nitric oxide synthase [Reiter et al., 2000], as well as acting in membrane stabilization [Arendt, 2005b].

Inhibition of dopamine release by melatonin has been demonstrated in specific areas of the mammalian CNS (e.g., hypothalamus, hippocampus, medulla pons, and retina) [Zisapel, 2001]. A growing body of biological, pharmacological and genetic data supports a role for dopamine in the pathophysiology of migraine [Fanciullacci et al., 2000].

Melatonin has been implicated in both GABA and glutamate neurotransmission [Malhotra et al., 2004] as in headache pathophysiology, and it is thought that the hypnotic activity of melatonin is mediated by the GABAergic system [Arendt and Skene, 2005]. Melatonin antagonistic effects on glutamate release and neurotoxicity in cerebral cortex has also been reported [Arendt, 2005a].

A melatonin–immuno-opioid network has been proposed as it has been found that melatonin induces activated T lymphocytes to release opioid peptides with immunoenhancing and antistress properties. Cytokines named melatonin-induced opioids (MIOs) have been found to act at an opioid-binding site. Because melatonin may behave as a mixed opioid receptor agonist/antagonist, it is possible to potentiate the opioid analgesic efficacy [Potenza et al., 1999]. Melatonin is also involved in cerebrovascular regulation; it potentiates the vasoconstrictive effect of norepinephrine and the modulation of 5-HT neurotransmission (spontaneous efflux and evoked release) [Dubocovich et al., 2003].

MELATONIN LEVELS IN HEADACHE DISORDERS

Melatonin and migraines are linked in several ways. Clinical symptoms of migraine may fluctuate, and a circadian pattern may be reported by some patients. Both episodic (55%) and chronic (62.5%) migraineurs report waking up in the morning or being awakened during the night by headaches [Galego et al., 2002]. A distribution of migraine attacks according to the estrous cycle is common and true menstrual migraine occurs in 14% of migraineurs and menstrually associated migraine occurs in 55% of cases [Silberstein, 2000]. A circannual variation is a hallmark in cyclic migraine [Friedman, 1982].

In a study of chronobiological features in chronic and episodic migraine patients, 46.5% reported headaches after changing their sleep schedule. A significant shift was present in 54% of patients, ranging from −2.5 to +5 h. Most patients (69%) delayed the sleep phase (went to bed too late), as opposed to those (31%) who advanced it [Peres, 2005a,b].

Melatonin levels in plasma and urine are lower in migraine patients [Claustrat et al., 1989; Brun et al., 1995] and nocturnal urinary melatonin decreased throughout the ovarian cycle in patients suffering from migraine without aura compared with controls [Murialdo et al., 1994]. During the luteal phase (when melatonin levels should normally increase), migraine patients showed a less pronounced change compared with controls and melatonin excretion was further decreased when patients suffered a migraine attack.

10982299, 2007, 6, Downloaded from https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/10.1002/ddr.20196 by Univ of Sao Paulo - Brazil, Wiley Online Library on [15/02/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

The plasma melatonin nocturnal profile was studied in chronic migraine patients and controls. Lower melatonin levels were observed in patients with insomnia compared to those without insomnia; there was a phase delay in the melatonin peak in patients as compared with controls, suggesting a chronobiological dysfunction in chronic migraineurs [Peres et al., 2001a].

Melatonin has been suspected to be involved in cluster headache genesis, primarily because melatonin is a sensitive marker of endogenous rhythms, which are disrupted in cluster headache [Peres et al., 2000]. Studies show a decrease in nocturnal melatonin secretion and an abolished melatonin rhythm in cluster headache patients both during and outside bouts [Chazot et al., 1984; Waldenlind et al., 1987, 1994; Leone et al., 1995].

MELATONIN THERAPY IN HEADACHE DISORDERS

Melatonin is an orphan drug; therefore, limited studies are available in headache treatment. Claustrat et al. [1997] studied melatonin infusion in six patients with status migrainosis. Four patients reported headache relief the morning after melatonin 20 mg infusion began, and the remaining two patients did so after the third night of infusion. In addition, three patients described that there was a decrease in the pulsatility of pain during the migraine attacks.

In a study investigating the effects of melatonin in 30 patients with delayed sleep phase syndrome (DSPS) and their related headache disorders, attacks dramatically decreased after the initiation of melatonin treatment [Nagtegaal et al., 1998].

An open-label trial has been performed using melatonin 3 mg for migraine prevention [Peres et al., 2004]. A total of 34 patients (27 women and 5 men) were included, and a significant headache relief was found in 64.7% of the patients. Headache response was observed in the first month of treatment and a complete response (no headaches in the previous month of treatment) was found in 25% of the patients. Headache frequency, duration, intensity and analgesic consumption decreased when baseline was compared with the last month of treatment ($P < 0.001$). The medication was very well tolerated, with only two patients dropping out the study.

Melatonin has been tested in trigemino-autonomic cephalgias including cluster headaches, hemicrania continua, paroxysmal hemicranias, and other headaches such as hypnic headache and idiopathic stabbing headache.

In a double-blind, placebo-controlled trial [Leone et al., 1996], there was a significant decrease in cluster headache attacks in the melatonin-treated group compared with placebo. A total of 20 patients (2 primary chronic and 18 episodic) received a single evening dose of melatonin 10 mg po ($n = 10$) or placebo ($n = 10$) for 14 days. Of the 10 treated patients, five had a decline in attack frequency 3–5 days after treatment and experienced no further attacks until melatonin treatment was discontinued. No side effects were observed in either group. A total of two patients with chronic cluster headache did not respond to melatonin therapy, but Peres and Rozen [2001] described two chronic cluster headache patients who responded to melatonin 9 mg at bedtime. Melatonin prevented both nocturnal and daytime cluster attacks. Pringsheim et al. [2002] studied melatonin as an adjunctive treatment for cluster headaches and showed no significant benefit. Their methodology (1 month of placebo, too many chronic clusters, and small sample size) and the melatonin dose may explain the discrepancies in the results.

In hypnic headache scarce reports have shown an improvement with melatonin treatment and a good response was detected in three patients; however, no controlled trial has been conducted [Evers and Goadsby, 2003]. The structural similarity of melatonin to indomethacin could be one of the possible mechanisms of action that is involved in indomethacin-responsive headaches [Peres et al., 2001b]. Rozen [2006] reported hemicrania continua patients who responded to melatonin, and described three idiopathic stabbing headache patients treated with melatonin who displayed an excellent clinical response and side effect profile [Rozen, 2003].

Melatonin is a potential candidate for the treatment of migraine and other headaches [Rozen, 2003]. Several melatonin analogues and other chronobiotic agents may be useful for headache treatment. A new sleeping medication (ramelteon) is available in certain countries stimulating both melatonin-type 1 and 2 receptors in the hypothalamus. It will be interesting to know how it will affect various headache disorders. Further studies are necessary for better understanding the role of melatonin in the pathophysiology and treatment of headache disorders.

REFERENCES

Ackermann K, Stehle JH. 2006. Melatonin synthesis in the human pineal gland: advantages, implications, and difficulties. Chronobiol Int 23:369–379.

Arendt J. 2005. Melatonin: characteristics, concerns, and prospects. J Biol Rhythms 20:291–303.

Arendt J. 2006. Melatonin and human rhythms. Chronobiol Int 23:21–37.

Arendt J. 2007. Aaron Lerner, who discovered melatonin. J Pineal Res 43:106–107.

10982299, 2007, 6, Downloaded from https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/10.1002/ddr.20196 by Univ of Sao Paulo - Brazil, Wiley Online Library on [15/02/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Arendt J, Skene DJ. 2005. Melatonin as a chronobiotic. Sleep Med Rev 9:25–39.

Aydogan S, Yerer MB, Goktas A. 2006. Melatonin and nitric oxide. J Endocrinol Invest 29:281–287.

Barrenetxe J, Delagrange P, Martinez JA. 2004. Physiological and metabolic functions of melatonin. J Physiol Biochem 60: 61–72.

Beloosesky Y, Grinblat J, Laudon M, Grosman B, Streifler JY, Zisapel N. 2002. Melatonin rhythms in stroke patients. Neurosci Lett 319:103–106.

Bigal ME, Lipton RB. 2006. The preventive treatment of migraine. Neurologist 12:204–213.

Brun J, Claustrat B, Saddier P, Chazot G. 1995. Nocturnal melatonin excretion is decreased in patients with migraine without aura attacks associated with menses. Cephalalgia 15:136–139.

Cajochen C, Krauchi K, Wirz-Justice A. 2003a. Role of melatonin in the regulation of human circadian rhythms and sleep. J Neuroendocrinol 15:432–437.

Cajochen C, Krauchi K, Wirz-Justice A. 2003b. Role of melatonin in the regulation of human circadian rhythms and sleep. J Neuroendocrinol 15:432–437.

Carrillo-Vico A, Reiter RJ, Lardone PJ, Herrera JL, Fernandez-Montesinos R, Guerrero JM, Pozo D. 2006. The modulatory role of melatonin on immune responsiveness. Curr Opin Invest Drugs 7:423–431.

Chazot G, Claustrat B, Brun J, Jordan D, Sassolas G, Schott B. 1984. A chronobiological study of melatonin, cortisol growth hormone and prolactin secretion in cluster headache. Cephalalgia 4:13–220.

Checkley SA, Murphy DG, Abbas M, Marks M, Winton F, Palazidou E, Murphy DM, Franey C, Arendt J. 1993. Melatonin rhythms in seasonal affective disorder. Br J Psychiatry 163: 332–337.

Claustrat B, Loisy C, Brun J, Beorchia S, Arnaud JL, Chazot G. 1989. Nocturnal plasma melatonin levels in migraine: a preliminary report. Headache 29:242–245.

Claustrat B, Brun J, Geoffriau M, Zaidan R, Mallo C, Chazot G. 1997. Nocturnal plasma melatonin profile and melatonin kinetics during infusion in status migrainosus. Cephalalgia 17:511–517.

Cuzzocrea S, Reiter RJ. 2002. Pharmacological actions of melatonin in acute and chronic inflammation. Curr Top Med Chem 2:153–165.

de Diego JI, Prim MP, Madero R, Gavilan J. 1999. Seasonal patterns of idiopathic facial paralysis: a 16-year study. Otolaryngol Head Neck Surg 120:269–271.

Dubocovich ML, Rivera-Bermudez MA, Gerdin MJ, Masana MI. 2003. Molecular pharmacology, regulation and function of mammalian melatonin receptors. Front Biosci 8:D1093–D1108.

Evers S, Goadsby PJ. 2003. Hypnic headache: clinical features, pathophysiology, and treatment. Neurology 60:905–909.

Fanciullacci M, Alessandri M, Del RA. 2000. Dopamine involvement in the migraine attack. Funct Neurol 15(Suppl 3):171–181.

Friedman AP. 1982. Overview of migraine. Adv Neurol 33:1–17.

Galego JC, Cipullo JP, Cordeiro JA, Tognola WA. 2002. Clinical features of episodic migraine and transformed migraine: a comparative study. Arq Neuropsiquiatr 60:912–916.

Gordijn MC, Beersma DG, Korte HJ, van den Hoofdakker RH. 1998. Testing the hypothesis of a circadian phase disturbance underlying depressive mood in nonseasonal depression. J Biol Rhythms 13:132–147.

Holroyd KA, Penzien DB. 1990. Pharmacological versus non-pharmacological prophylaxis of recurrent migraine headache: a meta-analytic review of clinical trials. Pain 2:1–13.

Hutter CD, Laing P. 1996. Multiple sclerosis: sunlight, diet, immunology and aetiology. Med Hypotheses 46:67–74.

Leone M, Lucini V, D'Amico D, Moschiano F, Maltempo C, Fraschini F, Bussone G. 1995. Twenty-four-hour melatonin and cortisol plasma levels in relation to timing of cluster headache. Cephalalgia 15:224–229.

Leone M, D'Amico D, Moschiano F, Fraschini F, Bussone G. 1996. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. Cephalalgia 16:494–496.

Macchi MM, Bruce JN. 2004. Human pineal physiology and functional significance of melatonin. Front Neuroendocrinol 25:177–195.

Malhotra S, Sawhney G, Pandhi P. 2004. The therapeutic potential of melatonin: a review of the science. Med Gen Med 6:46.

Murialdo G, Fonzi S, Costelli P, Solinas GP, Parodi C, Marabini S, Fanciullacci M, Polleri A. 1994. Urinary melatonin excretion throughout the ovarian cycle in menstrually related migraine. Cephalalgia 14:205–209.

Nagtegaal JE, Smits MG, Swart AC, Kerkhof GA, van der Meer YG. 1998. Melatonin-responsive headache in delayed sleep phase syndrome: preliminary observations. Headache 38:303–307.

Peres M. 2005a. Melatonin in neurological disorders. Einstein 2:217–219.

Peres MF. 2005b. Melatonin, the pineal gland and their implications for headache disorders. Cephalalgia 25:403–411.

Peres MF, Rozen TD. 2001. Melatonin in the preventive treatment of chronic cluster headache. Cephalalgia 21:993–995.

Peres MF, Seabra ML, Zukerman E, Tufik S. 2000. Cluster headache and melatonin. Lancet 355:147.

Peres MF, Sanchez del RM, Seabra ML, Tufik S, Abucham J, Cipolla-Neto J, Silberstein SD, Zukerman E. 2001a. Hypothalamic involvement in chronic migraine. J Neurol Neurosurg Psychiatry 71:747–751.

Peres MF, Stiles MA, Oshinsky M, Rozen TD. 2001b. Remitting form of hemicrania continua with seasonal pattern. Headache 41:592–594.

Peres MF, Zukerman E, da Cunha TF, Moreira FR, Cipolla-Neto J. 2004. Melatonin, 3 mg, is effective for migraine prevention. Neurology 63:757.

Peres MF, Silberstein S, Moreira F, Corchs F, Vieira DS, Abraham N, Gebeline-Myers C. 2007. Patients' preference for migraine preventive therapy. Headache 47:540–545.

Potenza MN, Gold SJ, Roby-Shemkowitz A, Lerner MR, Nestler EJ. 1999. Effects of regulators of G protein-signaling proteins on the functional response of the mu-opioid receptor in a melanophore-based assay. J Pharmacol Exp Ther 291:482–491.

Pringsheim T, Magnoux E, Dobson CF, Hamel E, Aube M. 2002. Melatonin as adjunctive therapy in the prophylaxis of cluster headache: a pilot study. Headache 42:787–792.

Reiter RJ. 2003. Melatonin: clinical relevance. Best Pract Res Clin Endocrinol Metab 17:273–285.

10982299, 2007, 6, Downloaded from https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/10.1002/ddr.20196 by Univ of Sao Paulo - Brazil, Wiley Online Library on [15/02/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Reiter RJ, Calvo JR, Karbownik M, Qi W, Tan DX. 2000. Melatonin and its relation to the immune system and inflammation. Ann NY Acad Sci 917:376–386.

Rodenbeck A, Huether G, Ruther E, Hajak G. 1999. Nocturnal melatonin secretion and its modification by treatment in patients with sleep disorders. Adv Exp Med Biol 467:89–93.

Rozen TD. 2003. Melatonin as treatment for idiopathic stabbing headache. Neurology 61:865–866.

Rozen TD. 2006. Melatonin responsive hemicrania continua. Headache 46:1203–1204.

Silberstein SD. 2000. Sex hormones and headache. Rev Neurol (Paris) 156(Suppl 4):4S30–4S41.

Turek FW, Dugovic C, Zee PC. 2001. Current understanding of the circadian clock and the clinical implications for neurological disorders. Arch Neurol 58:1781–1787.

Turek FW, Gillette MU. 2004. Melatonin, sleep, and circadian rhythms: rationale for development of specific melatonin agonists. Sleep Med 5:523–532.

Waldenlind E, Gustafsson SA, Ekbom K, Wetterberg L. 1987. Circadian secretion of cortisol and melatonin in cluster headache during active cluster periods and remission. J Neurol Neurosurg Psychiatry 50:207–213.

Waldenlind E, Ekbom K, Wetterberg L, Fanciullacci M, Marabini S, Sicuteri F, Polleri A, Murialdo G, Filippi U. 1994. Lowered circannual urinary melatonin concentrations in episodic cluster headache. Cephalalgia 14:199–204.

Zisapel N. 2001. Melatonin–dopamine interactions: from basic neurochemistry to a clinical setting. Cell Mol Neurobiol 21:605–616.

10982299, 2007, 6, Downloaded from https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/10.1002/ddr.20196 by Univ of Sao Paulo - Brazil, Wiley Online Library on [15/02/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License