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Potential therapeutic use of melatonin in migraine and other headache disorders

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There is increasing evidence that headache disorders are connected with melatonin secretion and pineal function. Some headaches have a clearcut seasonal and circadian pattern, such as cluster and hypnic headaches. Melatonin levels have been found to be decreased in both migraine and cluster headaches. Melatonin mechanisms are related to headache pathophysiology in many ways, including its anti-inflammatory effect, toxic free radical scavenging, reduction of pro-inflammatory cytokine upregulation, nitric oxide synthase activity and dopamine release inhibition, membrane stabilisation, GABA and opioid analgesia potentitation, glutamate neurotoxicity protection, neurovascular regulation, 5-HT modulation and the similarity in chemical structure to indometacin. The treatment of headache disorders with melatonin and other chronobiotic agents, such as melatonin agonists (ramelteon and agomelatin), is promising and there is a great potential for their use in headache treatment.

Keywords: circadian rhythm, melatonin, migraine, headache, headache disorders

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1. Introduction

Headache is a symptom of a range of systemic and neurological diseases. Headache disorders encompass a group of conditions that are usually characterised by recurrent episodes of head pain and associated symptoms. Although headache is a universal human experience, headache disorders have only gained increasing recognition in the past few decades. They vary in incidence, prevalence, duration and frequency (**Table 1**) [1].

After the first International Headache Classification was published in 1988 [2], headache disorders were more clearly classified and operationally defined. A second edition was recently published [3] with further advances in classification.

Headache disorders are divided into primary and secondary. Primary headache disorders are diagnosed when the pain is not due to another systemic or brain disorder; for example, metabolic or inflammatory conditions, infection, trauma, cerebrovascular diseases or CNS neoplasms. When headaches occur in these disorders, they are classified as secondary headaches [4]. Primary headaches include migraines, tension-type and cluster headaches, and paroxysmal hemicranias alongside others in which clinical, but not laboratory, aspects distinguish themselves. Primary headaches are also grouped according to particular hallmark features, including the trigemino-autonomic cephalgias (TACs), in patients who have unilateral pain with autonomic symptoms or indometacin-responsive headaches, as well as the very challenging group of chronic daily headaches (CDHs), defined as a headache frequency of > 15 days/month for > 3 months, with headaches lasting > 4 h [5].

Table 1. Main characteristics of different headache syndromes and the present knowledge on the pathophysiological and therapeutic roles of melatonin.

Disease	Frequency	Duration	Female:male ratio	Autonomic features	Melatonin response	Melatonin pathophysiology
Cluster headache	1 every other day to 8 attacks/day	15 – 180 min	1: 3 – 8	Prominent	RCT shows efficacy	Decreased levels
Paroxysmal hemicrania	1 – 40/day	2 – 30 min	2:1	Prominent	Potential	Unknown
Hypnic headache	3 – 7 days/week	60 – 90 min	1:2	Prominent	Case reports	Unknown
Hemicrania continua	Daily	Continuous	2; 5:1	Mild	Case report	Unknown
Episodic migraine	~ 1 – 14/month	4 – 72 h	3:1	None	Open study shows good results	Decreased levels
Chronic migraine	> 15 days/month	> 4 h	4:1	None	Potential	Decreased levels and peak shift

RCT: Randomised, placebo-controlled, clinical trial.

Migraine is a common disorder and probably the most studied headache condition in terms of the epidemiology, mechanisms and treatment aspects. In the US, > 17% of women and 6% of men had at least one migraine attack in the last year [6]. Although the term migraine derives from the Greek word 'hemicrania' (which means 50% of the head), it is not always a strictly unilateral headache; it can be bilateral and is characterised by various combinations of neurological, gastrointestinal and autonomic symptoms.

Migraine subtypes are: without aura; with aura; basilar migraine; familial hemiplegic migraine; status migrainous; and chronic migraine (previously known as transformed migraine, the most important of the CDHs) [3].

The aura is composed of focal neurological symptoms that usually precede the headache, generally lasting < 60 min. Visual symptoms are the most common, such as zigzag or scintilating figures (fortification spectrum), scotomata and distortions in shape and size. Motor, sensory or brainstem disturbances can also occur [8].

The headache phase is typically characterised by unilateral pain, throbbing (moderate to marked in severity) and aggravated by physical activity. The pain of migraine is invariably accompanied by other features; nausea occurs in ~ 90% of the patients and vomiting occurs in about a third of migraineurs. Many patients experience sensory hyperexcitability manifested by photo-, phono- and osmophobia, and seek a dark, quiet room. Other systemic symptoms (including anorexia, blurry vision, diarrhoea, abdominal cramps, polyuria, pallor of the face, stiffness and tenderness of the neck, and sweating) may be noted during the headache phase. Impairment of concentration is common; memory impairment is less frequent. Depression, fatigue, anxiety, nervousness and irritability are also common [7]. Lightheadedness, rather than true vertigo, and a feeling of faintness may also occur [9].

Migraine comorbidity is a very important issue as migraines are comorbid with several disorders, including stroke and epilepsy [10]. Chronic migraine is particularly more related to psychiatric comorbidity (anxiety and depression) [11], sleep disorders [12], fibromyalgia [13] and fatigue [14].

A number of mechanisms and theories have been proposed to explain the causes of migraine. The strong familial association and genetic mutations (found in familial hemiplegic migraine) [15], and early onset of this disorder suggest that there is an important genetic component.

The pain distribution suggests an involvement of the trigeminal nerve, as trigeminal activation results in the release of neuropeptides, thus producing neurogenic inflammation with increased vascular permeability and dilation of blood vessels. This is the trigeminal vascular model proposed by Moskowitz [16].

Muscle contraction and tenderness are other important symptoms for migraine patients. The cervical region is often affected. The cervico–trigeminal complex is a broader concept that helps to explain migraine pathophysiology [17]. Neurotransmitters including 5-HT, dopamine, noradrenaline, adrenaline, glutamate, nitric oxide, GABA and substances such as magnesium have also been considered in migraine pathophysiology [18]. The concept of central sensitisation has recently been recognised as an important mechanism in migraine. Cortical hyperexcitability is one of the main mechanisms that is involved in migraine pathophysiology; it may be the initial phenomena in this process and is modulated by several neurotransmitters.

Melatonin has been proposed to be an important element in migraine-causal mechanisms [19]. Its role in headache disorders may also have implications in treatment options. A potential therapeutic use of melatonin has been considered in several headache disorders, including cluster headaches (the

first to be studied), migraines and indometacin-responsive headache syndromes.

2. Melatonin and the pineal gland

Life on the planet Earth is under 24-h rhythmicity (the day–night cycle), due to the rotation of the Earth on its axis. It is also under the circannual rhythm, due to the movement generating a different day:night ratio according to the place's latitude and seasons of the year [20]. The nervous system evolved over the milenia to meet the demands of environmental conditions (including the light–dark cycle) to ensure survival and reproduction of living organisms. It has been demonstrated in the past decades that the circadian biological rhythm is not only the response to the 24-h day–night environment but is due to a system in the brain [21]. A synchronisation system to adapt the internal to the external environment is one of the key elements of the CNS that maintains life.

The French philosopher Rene Descartes, three centuries ago, described the pineal gland as 'the seat of the soul' but it was not until the late 1950s that melatonin, the principal substance secreted by the pineal gland, was identified [22] and it was no longer accepted as a vestigial organ.

The main elements for synchronisation between internal biological events and the environment are the pineal gland and its main secretary product, melatonin. In humans, melatonin is absent during the day and its nocturnal secretion is the main biological event that signals what is night to the organism.

The pineal gland lies in the centre of the brain, behind the third ventricle. Because of its pine shape format, the organ was coined the 'pineal' gland. The gland is usually 8 mm in diameter and weighs 1 g [23]. It consists of two types of cells: pinealocytes, which predominate and produce both indoleamines (melatonin) and peptides (such as arginine vasotocin); and neuroglial cells [24]. The pineal gland is highly vascular. Melatonin is a derivative of the essential amino acid tryptophan and the pinealocyte is the principal location for melatonin biosynthesis. After its uptake into cells, tryptophan is first hydroxylated and then decarboxylated, resulting in the formation of 5-HT [25], which is then N-acetylated to N-acetyl-5-HT. This is subsequently O-methylated to form melatonin [25], which is present in the earliest life forms and found in all organisms including bacteria, algae, fungi, plants, insects and vertebrates (including man). In all species, melatonin synthesis exhibits a circadian rhythm [26].

Once melatonin has been synthesised in the pineal gland, it is quickly released, generating a blood–melatonin rhythm reminiscent of that seen in the gland. As an amphiphilic molecule, melatonin is capable of entering every cell in the organism; in addition, it readily crosses all morpho-physiological barriers, including the placenta and blood–brain barrier [27]. Melatonin is enzymatically degraded in the liver to 6-hydroxymelatonin [28] and excreted in the urine as 6-sulfatoxymelatonin, which is widely used as a measure of melatonin secretion because it correlates with the nocturnal profile of plasma melatonin secretion [29].

Melatonin was first identified in bovine pineal tissue [30] and has been subsequently portrayed exclusively as a hormone. Recently, accumulated evidence has challenged this concept. Several characteristics of melatonin distinguish it from a classic hormone, such as its direct, non-receptor-mediated free radical scavenging activity [31]. As melatonin is also ingested in vegetables, fruits, rice, wheat and herbal medicines, melatonin can also be classified as a vitamin from a nutritional point of view. It seems likely that melatonin initially evolved as an antioxidant, becoming a vitamin in the food chain; and it has acquired autocoid, paracoid and hormonal properties in multicellular organisms in which it is produced [32].

A family of cell membrane receptors for melatonin has recently been cloned [33]. The distribution of the receptors seems to be broad, species specific and G-protein coupled. Principally, there are three high-affinity melatonin receptors (MEL1a, -1b and -1c), of which the first two are found in men. The gene for the MEL1a receptor is localised to human chromosome 4q35.1 [34] and is present in the kidney and intestine. The MEL1b receptor is mapped to human chromosome 11q21 – 22 [35].

At present, indications for the therapeutic applications of melatonin include sleep disorders, circadian rhythm disorders, insomnia in blind people, insomnia in elderly patients, ageing, Alzheimer's disease and as an adjuvant in cancer therapy [36].

3. Melatonin and chronobiology

Chronobiological disorders occurring in humans can be divided into two types: the environmental (external) variety caused by life style and the environment (as in shift workers), individuals crossing time zones in jet lag syndrome and in maladaptation to daylight savings; and the endogenous (internal) type, which includes 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 many conditions, including depression, chronic fatigue, fibromyalgia and migraine [37].

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 nocturnal melatonin secretion [38]. 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 melatonin administration is able to: induce sleep when the drive to sleep is insufficient; inhibit the drive for wakefulness from the suprachiasmatic nucleus; and induce phase shifts in the circadian clock, such that the circadian phase of increased sleep propensity occurs at a new, desired time [39].

Many neurological disorders occur with a marked rhythmicity, including stroke, multiple sclerosis, facial

paralysis and seasonal affective disorder, are dependent on the 24-h or seasonal cycle and are probably linked to pineal function and melatonin secretion [40].

The pineal gland is a fotoneuroendocrine organ, converting external luminous stimuli into the secretion of a hormone, being responsible for synchronisation between internal homeostasis and the environment; therefore, an altered synchronisation system may interfere with all neurological diseases (sleep and circadian rhythms are often disrupted in people with neurological disorders) [43]. The symptoms associated with neurological diseases may be partly due to the disruption of the sleep–wake cycle. In addition, various neurological disorders may themselves disrupt the sleep–wake cycle, resulting in a positive feedback loop; disrupted sleep and wake exacerbate the neurological disorders, but the disease itself has a negative effect on the sleep-wake states [41].

Symptoms associated to such disorders may fluctuate according to a specific rhythm (circannual, circamenal or circadian) and are often related to either sleep or wake periods. Epilepsy, dementia, movement disorders, multiple sclerosis, cerebrovascular disorders, neuromuscular disorders, brain tumours and primary headaches have all been linked to an altered chronobiology, melatonin dysfunction or benefit from melatonin treatment [21]. Migraines, cluster headaches, indometacin-responsive headaches and hypnic headaches have also been shown to be related to melatonin levels.

4. Melatonin and headache pathophysiology

Melatonin may play a role in headache pathophysiology via several mechanisms. Melatonin has been shown to possess anti-inflammatory effects among others. By virtue of its ability to directly scavenge toxic free radicals [25], it can reduce macromolecular damage in all organs. The free radicals and reactive oxygen and nitrogen species that are known to be scavenged by melatonin include: the highly toxic hydroxyl radical ($^{\cdot}OH$); peroxynitrite anion (ONO_2^-); and hypochlorous acid (HOCl) among others. Melatonin also 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 TNF-α [42]. Melatonin inhibits the production of adhesion molecules that promote the sticking of leukocytes to endothelial cells, attenuating transendothelial cell migration and oedema [47].

Melatonin inhibits the activity of nitric oxide synthase [44], as well as acting in membrane stabilisation [45].

Inhibition of dopamine release by melatonin has been demonstrated in specific areas of the mammalian CNS (such as the hypothalamus, hippocampus, medulla pons and retina) [46]. A growing body of biological, pharmacological and genetic data supports a role for dopamine in the pathophysiology of migraine [47].

Melatonin has been related to both GABA and glutamate neurotransmission and headache pathophysiology [48], and it is thought that the hypnotic activity of melatonin is mediated by the GABA-ergic system [49]. Melatonin rapidly and reversibly potentates the $GABA_A$ receptor-mediated response [50]. Neuroprotection by melatonin from glutamate-induced excitotoxicity occurs during the development of the brain [51] and its antagonistic effects on glutamate release and neurotoxicity in the cerebral cortex has also been reported [52].

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 [53]. Melatonin is also involved in cerebrovascular regulation, whereby it potentates the vasoconstrictive effect of noradrenaline in the renal artery, but it generally decreases vascular reactivity [54] and the modulation of 5-HT neurotransmission (spontaneous efflux and evoked release) [55].

5. Melatonin and migraine

Melatonin and migraines are linked in several ways. Clinical symptoms of migraine may fluctuate; some patients report their headaches predominantly or specifically during a certain period of the day. Both episodic (55%) and chronic (62.5%) migraineurs report waking up in the morning or being woken up during the night by headaches [56]. In addition, headaches occurring in the morning period have been attributed to sleep disorders [57] and a distribution of migraine attacks according to the estrous cycle is apparent (true menstrual migraine occurs in 14% of migraineurs [58] and menstrually associated migraine can occur in ≤ 55% of cases) [59]. A circannual variation can be observed during a cyclic or cluster migraine [60,61].

Peres *et al.* [62] studied the chronobiological features in 200 chronic or episodic migraine patients, 93 (46.5%) of whom reported headaches after changing their sleep schedule. A significant shift was present in 54% of the patients, ranging from -2.5 to +5 h. Most of the patients (69%) delayed the sleep phase (went to bed too late), as opposed to those (31%) who advanced it. Individuals who shifted by > 2 h represented 12.5% of the patients. There is evidence for the relevancy and effect of changes in biological rhythm experienced in migraine patients, and a possible correlation between migraine and the sleep schedule of patients.

Melatonin was first studied in migraine patients in 1989 [63]. It was shown that patients had lower levels of plasma melatonin in samples drawn at 23:00 h 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.* [64] also found that nocturnal urinary melatonin significantly decreased throughout the ovarian cycle in patients suffering from migraine without aura compared with controls. 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.

Brun *et al.* [65] studied urinary melatonin in women with attacks of migraine without aura that were associated with menses and controls. It was found that 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. This implicates melatonin in the pathogenesis of menstrual migraine.

Peres *et al.* [66] studied the plasma melatonin nocturnal profile, in which 13 samples were collected hourly from 19:00 to 07:00 h in chronic migraine patients and controls. Lower melatonin levels were observed in patients with insomnia compared with those without insomnia; there was a phase delay in the melatonin peak in patients versus controls, suggesting a chronobiological dysfunction in chronic migraineurs.

Only small studies showed a benefit in migraine patients from melatonin treatment. Claustrat *et al.* [67,71] looked at the nocturnal plasma melatonin profile and melatonin kinetics during melatonin infusion in six patients with status migrainous. Individual plasma profiles were disturbed in three migraine patients; two had a phase delay and one had a phase advance. Of the six patients, four reported headache relief the morning after the 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 migraines.

In another study, Nagtegaal *et al.* [68,72] investigated the effects of melatonin on varying headaches and their relation to the delayed sleep-phase syndrome (DSPS). A total of 30 DSPS patients were treated; one patient had migraine and his attacks dramatically decreased after the initiation of melatonin treatment. There was one successfully treated patient during a migraine attack by means of external (pT) magnetic fields [69].

An open-label trial has been performed using melatonin 3 mg for migraine prevention [70]. A total of 34 patients were included (of these, 27 women and 5 men completed the study), 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 significantly decreased when baseline was compared with the last month of treatment ($p < 0.001$). The medication was well tolerated. Only two patients dropped out of the study; one each due to daytime sleepiness and alopecia.

Melatonin may be implicated in the pathogenesis of migraine, as well as menstrual cyclic and chronic migraines. It may also play a role in migraine comorbid disorders, particularly depression and insomnia. Double-blind, placebo-controlled trials are necessary for an improved understanding of melatonin in migraine therapeutics.

6. Melatonin and cluster headaches

It has been suspected that melatonin may be involved in cluster headache genesis, primarily because melatonin is a sensitive marker of endogenous rhythms, which are disrupted in cluster headache [71].

In 1984, Chazot *et al.* [72] identified a decrease in nocturnal melatonin secretion and an abolished melatonin rhythm in cluster headache patients. Waldenlind *et al.* [73] also showed lower nocturnal melatonin levels during cluster periods compared with remissions. Determining urinary levels of 6-sulfatoximelatonin throughout the year, Waldenlind *et al.* [74] found higher melatonin levels in women than in men. The Swedish population had higher melatonin levels than Italian people, and smokers had lower levels than non-smoking cluster headache patients. Leone *et al.* [75] observed that melatonin and cortisol acrophases were significantly correlated in controls but not in cluster headache patients, indicating a chronobiological disorder in these patients.

Blau and Engel [86] found that an increase in body temperature resulting from exercise, a hot bath or elevated environmental temperature triggered cluster headaches in 75 out of 200 cluster headache patients. This finding shows that an increase in temperature was caused by a decrease in melatonin secretion [87]. It has recently been shown that (by a hypothalamic activation on positron emission tomography and functional magnetic resonance imaging) the suprachiasmatic nucleus may influence melatonin secretion. Melatonin for cluster headache prevention was subsequently studied in a double-blind, placebo-controlled trial [88], which showed 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 p.o. ($n = 10$) or placebo ($n = 10$) for 14 days. Of the 10 treated patients, 5 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 [82] did not respond to melatonin therapy, but Peres and Rozen [79] 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.* [89] 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 a small sample size) and the melatonin dose may explain the discrepancies in the results. Nagtegaal *et al.* [80] studied melatonin treatment in DSPS and identified a patient with episodic cluster headache in whom both disorders improved

after melatonin treatment. Melatonin plays an important role in the pathophysiology and treatment of cluster headaches.

7. Melatonin, hypnic headache and indometacin-responsive headaches

Hypnic headache is a benign, recurrent headache disorder that occurs only during diu- and nocturnal sleep. Headaches are often frequent, usually occurring every night, with striking consistency at the same time every night [81]. Hypnic headache is typical in the elderly and because melatonin secretion significantly declines with ageing, one may speculate that a melatonin deficiency is a possible cause of hypnic headache [82]. 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 so far [83].

Peres *et al.* [85] described a patient with a seasonal variation in hemicrania continua, proposing that the melatonin's chemical structural similarity to indometacin, could be one of the possible mechanisms of action that is involved in indometacin-responsive headaches. Rozen [86] reported a hemicrania continua patient who responded to melatonin 9 mg, and described three idiopathic stabbing headache patients treated with melatonin who showed an excellent clinical response and side-effect profile [87]. A recent study showed hypothalamic activation in paroxysmal hemicranias. If a similar mechanism occurs during a cluster headache, the paroxysmal hemicranias may be potential candidates for melatonin treatment. Future studies will clarify the role of melatonin in indometacin-responsive headaches or TACs and hypnic headaches.

8. Headaches and chronobiological disorders

Several chronobiological disorders have been described to date. Jet lag is a travel-induced circadian rhythm phenomenon that afflicts healthy individuals following long-distance flights through several time zones. Typical symptoms are daytime sleepiness, fatigue, impaired alertness, headaches, irritability, loss of appetite, decrease in physical performance, and trouble initiating and maintaining sleep. This syndrome is attributed to transient desynchronisation of the circadian rhythm until the internal biological clock is rephased to the new environmental conditions [88]. Headache features, diagnosis and impact have never been thoroughly studied in patients with jet lag syndrome. Peres *et al.* [62] found that most (79%) of the migraine patients who report frequently travelling across time zones endured an increase in headache severity or frequency.

Shift work involves a substantial employed population worldwide. Pucci *et al.* [90] studied 157 employees and found primary headaches in 26.7% with shift work being a major risk factor. Ho and Ong [91] studied 2096 individuals in a randomised survey in Singapore and found that individuals who performed shift work had more frequent headaches. Peres *et al.* [62] found that 86% of migraineurs had their headaches worsen after shift work.

DSPS and advanced sleep-phase syndrome are chronic, long-term circadian schedule disorders. Various primary headaches were found in 30 DSPS patients [80]; three women had chronic tension-type headaches, one had patient migraine with aura, one a cluster headache. In each case, their headaches decreased dramatically after melatonin 5 mg/night.

9. Expert opinion

The connection between headache disorders and circadian biology and melatonin is fascinating, but is only in its first steps towards a more definitive understanding. Future studies in several directions are obligatory for the field to develop a more careful clinical examination of circadian and circannual variation in primary and secondary headaches. A study of different latitudes is needed, as is the study of headache diagnosis, effect and treatment response in chronobiological disorders.

Animal models, the genetics involved in chronobiological rhythms, neuroimaging, neurophysiology and laboratory measures are important tools for further research. Urinary 6-sulfatoxymelatonin levels may be the easiest, non-invasive method for melatonin secretion analysis, but a profile over 12 – 24 h could provide more detailed information. There is still uncertainty regarding the best biological marker for circadian rhythmicity; to date, the nocturnal melatonin peak, dim light melatonin onset and dim light melatonin offset have been proposed.

Melatonin treatment of headache disorders is promising, particularly in cluster headaches, hypnic headaches, indometacin-responsive headaches and migraine. Melatonin may also be important in migraine comorbidity. Insomnia in headache patients is the most likely associated condition that could respond to melatonin therapy. Lower melatonin levels may predict the response to melatonin treatment, which also occurs in the insomnia that is associated with other diseases [92]. Other chronobiotic agents, such as melatonin receptors agonists, light therapy and magnetic fields, can also be tested. In several conditions, melatonin dosing may be in the range of 0.1 – 100 mg and there is no data on which brand would be the safest or most effective. Contraindications and precautions for its use may include pregnancy, certain autoimmune disorders and daytime administration. Ramelteon (TAK-375), a selective melatonin-1 or -2 receptor agonist, has been approved for the treatment of insomnia [93]. At present, its possible efficacy in headache disorders is only speculative. Agomelatine (S-20098) is another agonist showing efficacy in the treatment of major depressive disorder [94] and it may also be a candidate for migraine prevention.

Melatonin has played an important role in headache disorders and it may have great therapeutic potential for use in the treatment of primary headache disorders.

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