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The Role of Melatonin in the Treatment of Primary Headache Disorders

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Abstract

Objective—To provide a summary of knowledge about the use of melatonin in the treatment of primary headache disorders.

Background—Melatonin is secreted by the pineal gland; its production is regulated by the hypothalamus and increases during periods of darkness.

Methods—We undertook a narrative review of the literature on the role of melatonin in the treatment of primary headache disorders.

Results—There are randomized placebo-controlled trials examining melatonin for preventive treatment of migraine and cluster headache. For cluster headache, melatonin 10 mg was superior to placebo. For migraine, a randomized placebo-controlled trial of melatonin 3 mg (immediate release) was positive, though an underpowered trial of melatonin 2 mg (sustained release) was negative. Uncontrolled studies, case series, and case reports cover melatonin's role in treating tension-type headache, hypnic headache, hemicrania continua, SUNCT/SUNA and primary stabbing headache.

Conclusions—Melatonin may be effective in treating several primary headache disorders, particularly cluster headache and migraine. Future research should focus on elucidating the underlying mechanisms of benefit of melatonin in different headache disorders, as well as clarifying optimal dosing and formulation.

Keywords

melatonin; migraine; cluster headache; indomethacin

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Introduction

Melatonin is produced by the pineal gland and plays a role in regulating circadian rhythms, including initiating and sustaining sleep. Secretion of melatonin is increased in darkness and suppressed by light; the process is regulated by the suprachiasmatic nucleus of the hypothalamus[1].

Melatonin has been used to treat a number of primary headache disorders[2], including: migraine, cluster headache, tension-type headache, hypnic headache, hemicrania continua, SUNCT/SUNA and primary stabbing headache. The level of evidence supporting melatonin's efficacy in treating these disorders varies. For cluster headache and migraine there are randomized-placebo controlled trials, whereas for the rarer headache disorders the level of evidence consists of uncontrolled case series and case reports.

It is not clear what led clinicians to first try melatonin for the treatment of primary headache disorders, however circadian effects in cluster headache have been appreciated since at least the 1970s[3], and may have suggested a therapeutic role for melatonin. The mechanism of action of melatonin's benefit in headache disorders is not known, and may differ by headache disorder. Impact on the hypothalamus is one possibility, particularly in cluster headache and migraine where functional imaging studies have demonstrated the activation of the hypothalamus during attacks[4, 5], or hypnic headache where the occurrence of attacks exclusively out of sleep suggests chronobiological dysfunction and hypothalamic involvement. Notably there are melatonin receptors (MT1 and MT2) in the suprachiasmatic nucleus of the hypothalamus[6, 7], so direct action of exogenous melatonin at the hypothalamus is possible. During cluster periods, the timing and peak of endogenous melatonin release can become blunted or even absent[8–12]—exogenous melatonin supplementation may help by restoring these rhythms.

Alternatively melatonin's benefit may be mediated through improved sleep in some headache disorders. For example, there is a strong relationship between sleep and migraine. Regular sleep has been shown to be associated with a lower likelihood of having chronic migraine[13], and disrupted or inadequate sleep is often cited as a migraine trigger[14]. Sleep can also be used to terminate a migraine attack[14, 15].

Headache benefit from melatonin may be independent of sleep or the hypothalamus, as animal models and human data have demonstrated anti-inflammatory and anti-nociceptive properties of melatonin[16–18].

Lastly, melatonin and indomethacin share an indole structure, which may make it effective in indomethacin-responsive disorders[17], although this is a common structure in nature and appears in triptans and tetracylic ergolene derivatives, such as dihydroergotamine[19, 20]. Melatonin's comparatively favorable side effect profile compared to indomethacin makes it a desirable treatment candidate. The side effects of melatonin are generally few and mild, even at high dosages[17, 21, 22]; daytime tiredness and dizziness are possible[21–25].

This review will cover what is known about the use of melatonin in the treatment of primary headache disorders. We conclude with recommendations for future avenues of clinical investigation into melatonin's role in the treatment of primary headache disorders.

Migraine

Observational studies support a role for melatonin in the treatment of migraine. Adults with migraine have lower melatonin levels on migraine days compared to non-headache days and those with chronic migraine have lower melatonin levels than those with episodic migraine[26, 27]. Nocturnal melatonin levels are lower in women with migraine with aura whose attacks occur around menses compared to control women.

There is also experimental evidence supporting a therapeutic role for melatonin in migraine prevention, though with some conflicting data. In a double-blind, randomized, placebo-controlled, 3-arm trial with approximately 65 participants per arm, the efficacy of 3 mg of immediate release melatonin was superior to placebo and comparable to amitriptyline 25 mg nightly. The observed reduction in headache frequency at three months was: 2.7 in those treated with melatonin, 2.2 for amitriptyline (p=0.19), and 1.2 for placebo (p=0.009). The tolerability of melatonin was comparable to placebo and better than amitriptyline[25]. In contrast, in a smaller randomized, double-blind cross-over design study of 46 subjects, 2 mg of sustained release melatonin was not different from placebo for migraine prevention after 8 weeks of treatment[23]. Mean baseline migraine attack frequency (SD) was 4.2±1.2; during the placebo phase it was 2.9±1.4 vs. 2.8±1.6 during the melatonin treatment phase, p=0.75. Three participants (7%) had daytime tiredness and dizziness during melatonin treatment.

There are a number of possible reasons for the disparate findings between the two above trials, including differences in melatonin dose (3 mg vs. 2 mg) and formulation (immediate release vs. sustained release), trial design (parallel-group vs. crossover), treatment duration (3 months vs. 8 weeks), difference of outcome measures (headache days vs. migraine attacks) and possible under-powering in the smaller study. Crucially, the placebo response in the Peres and colleagues study was in-line with modern, adequately powered placebo-controlled migraine preventive studies, while the Alstadhaug and colleagues study placebo response was high. Additional randomized placebo-controlled trials are needed to clarify the role of melatonin in migraine prevention.

Uncontrolled studies have generally supported a therapeutic role for melatonin in migraine. In a pilot study of adult patients with migraine or tension-type headache, melatonin 4 mg appeared to be an effective dose for migraine prevention. Forty-nine patients were enrolled, of whom 37 had migraine, and 41 completed the 6-month treatment phase. Headache frequency, and Headache Impact Test scores were statistically significantly lower in the migraine group at 6-months of treatment compared to baseline[28].

Uncontrolled work in pediatrics also suggests melatonin may be useful in the treatment of pediatric and adolescent migraine. In one study, 60 pediatric and adolescent participants were treated with up to 6 mg melatonin nightly (formulation unspecified). At three months, mean(SD) migraine attack frequency decreased from 15.6±7.6 to 7.1±4.4 per month[29]. In a

smaller open-label pediatric study, 14 migraineurs were treated with 3 mg melatonin nightly. Ten (71%) had a ≥50% improvement in headache frequency at 3 months.[30] Melatonin was well tolerated in these pediatric studies: in the study where children received up to 6 mg of melatonin, 7(12%) had daytime sleepiness vs. 1(7%) in the smaller study where they received 3 mg[29, 30].

Tension-Type Headache (TTH)

Melatonin treatment for TTH has not been extensively studied. However some patients with TTH have been included in uncontrolled studies both in adults and pediatrics. In the uncontrolled adult study of melatonin 4 mg cited above, 12 tension-type headache patients were enrolled. The authors report a statistically significant decrease in both headache frequency and Headache Impact Test score in the TTH group[28].

There were eight children with chronic TTH in one of the uncontrolled studies of melatonin 3 mg for headache treatment in children. Four had a ≥50% reduction in headache attack frequency; none reported complete remission of headaches. The other four did not have a change in frequency from baseline[30].

Cluster Headache

In patients with episodic cluster headache, melatonin levels may have a reduced nocturnal peak during a cluster period[9, 11, 31] or even absent circadian rhythmicity[10, 11]. Low melatonin levels have been measured in cluster headache patients even during times of cluster remission[32, 33], though this has not been seen in all studies[12] and tobacco use may be confounding[33]. Cluster attacks often occur out of sleep[34]. Activation of the ipsilateral hypothalamus has been demonstrated during nitroglycerin-triggered cluster attacks[5]. Given all of the above, hypothalamic dysfunction has been hypothesized to play a pathophysiological role in cluster headache[35], and exogenous melatonin supplementation may help by repleting low endogenous levels during a cluster period, and/or helping to phase shift sleep.

In a randomized placebo-controlled trial consisting predominantly of episodic cluster headache patients (18/20 with episodic, 2/20 with chronic), melatonin 10 mg orally, when introduced early in a cluster period, i.e. 2nd to 10th day, was superior to placebo at decreasing cluster attack frequency. In the first week of treatment, mean (SD) attack frequency in the melatonin group vs. the placebo group was 1.9±1.5 vs. 2.7±0.9 (p<0.03), and in the second treatment week it was 1.5±1.7 vs. 2.5±0.9 (p=0.01). There were 10 patients per arm; five responded to melatonin and the other five did not. Improvement in the responders began within three days of treatment initiation and by five days none of the responders were still having cluster attacks. Given the small numbers, predictors of treatment response could not be identified. No significant side effects were noted[24].

Of note, the two chronic cluster headache patients were randomized to melatonin and both were non-responders[24]. However, there have been case reports of chronic cluster headache patients who have responded to melatonin—one responded within two days of initiation of

melatonin 9 mg, and another found melatonin 9 mg gave “immediate pain relief, with both daytime and nocturnal headaches completely abating.[36]”

Case reports have suggested lower dosages of melatonin might also be helpful in cluster headache. One patient with delayed sleep phase syndrome and episodic cluster responded to melatonin 5 mg nightly; although at one point he had to start taking it 2 hours earlier in order to phase shift his melatonin profile[8]. Cluster headache is rare in children, however a case has been reported where the child responded to melatonin 3 mg twice daily[37].

Hemicrania continua

Given the shared indole structure with indomethacin[38] and its comparatively more benign side effect profile, melatonin has been tried for the treatment of hemicrania continua(HC). As HC is a relatively rare headache disorder, the evidence supporting melatonin’s efficacy in its treatment is from case reports and case series. Therapeutic doses have ranged from 3–30 mg orally[39–41].

In a case series study from a single center, patients with HC underwent a protocol to attempt to transition over to melatonin treatment[39]. Melatonin was initiated at 3 mg nightly for 5 nights, followed by 6 mg nightly for 5 nights, followed by 9 mg thereafter. Patients were instructed to then try to taper down on their indomethacin dose, if they had not already started. Melatonin dosing could be increased up to 30 mg nightly, as needed, to try to maintain headache control as indomethacin was being lowered. However, some non-responders gave-up after trying only 9–12 mg. Of the eleven patients who went through this protocol; six (55%) did not have relief from melatonin at doses of 9–27 mg. Two (18%) had complete headache control on melatonin—one at a dose of 3 mg and one at a dose of 6 mg. Three patients (27%) had some relief from melatonin, thus they continued to require some indomethacin but were able to tolerate lower dosages. One developed a rash and had to stop melatonin; the other two were able to reduce indomethacin dosing by 75%—one using 9 mg of melatonin and the other 30 mg; however the one on 9 mg ultimately discontinued it due to nightmares. It was not possible in this small series to identify predictors of melatonin response in HC patients. Of note, in vitro evidence suggests melatonin may be able to protect against indomethacin-induced gastric ulcers by limiting gastric mucosal cell apoptosis; thus in addition to efficacy for HC, adding melatonin may lower the morbidity from long-term indomethacin exposure[39, 42].

In a separate series of three patients with HC by the same author, all responded to melatonin. One had developed presumed HC after a transplant, but as indomethacin was contra-indicated she could not undergo an indomethacin trial and thus did not meet ICHD criteria for HC. She became headache free on melatonin 9 mg nightly and headaches would return when melatonin was stopped. A second patient also became headache free on 9 mg melatonin, though rare breakthrough headaches would occur and respond to an extra dose of melatonin 6 mg. The third patient was able to reduce her indomethacin dose by 50% by adding melatonin 15 mg nightly[43].

In one case report, a woman with HC whose comorbid migraine had been worsened by indomethacin found effective HC control with melatonin 9 mg nightly[40]. Given there is RCT evidence supporting melatonin as a migraine preventive[25], it seems like an advantageous treatment choice for those patients who suffer from both HC and migraine.

Hypnic headache

Age-related dysfunction of the suprachiasmatic nucleus of the hypothalamus is thought to underlie why hypnic headache generally affects older individuals[44]. The body's release of melatonin may be impaired with age, in at least some individuals[45]. There are case reports of hypnic headache responding to melatonin, either as monotherapy[46] or as adjunctive therapy[47] though it has not been universally effective.

In a series of three patients with hypnic headache, two tried melatonin. One improved with 3 mg and became headache free on 6 mg. The other found melatonin 3 mg ineffective[46]. Another patient found melatonin 12 mg to be ineffective for hypnic headache[48]. In a series of twenty patients with hypnic headache, three were reported to have tried melatonin 3–5 mg as preventive therapy. One found it reduced frequency and intensity of headaches by half. One stopped melatonin because it reportedly aggravated symptoms[49]. Of note, there is a case report of a patient with hypnic headache who responded to ramelteon 8 mg, a selective melatonin receptor MT1/MT2 agonist.

Hypnic headache is extremely rare in children, however, a literature review has summarized the clinical characteristics of five published cases. Of the five, 2 underwent a treatment trial of melatonin and both reportedly responded. In one child, an initial dose of 2 mg nightly decreased headache intensity and frequency, and 4 mg rendered the patient asymptomatic. The other patient was treated with 3 mg melatonin nightly and also became headache-free[50, 51].

Other Primary Headache Disorders

Primary stabbing headache

In a series of 3 patients with primary stabbing headache, an indomethacin-responsive headache disorder, all 3 became pain free on melatonin doses of 3–12 mg nightly[52].

Paroxysmal hemicrania

As an indomethacin-responsive disorder it is conceivable that melatonin could be an effective treatment in some cases, however, we were not able to identify any case reports documenting the results of treatment trials of melatonin in patients with paroxysmal hemicrania.

SUNCT/SUNA: While we did not find published cases of primary SUNCT/SUNA treated with melatonin, there is a reported case of secondary SUNCT that developed following head and neck trauma and improved with a combination of treatments including: melatonin 10 mg daily, gabapentin, and physical and psychotherapy[53].

Future directions

Melatonin has shown promise in the treatment of several different primary headache disorders. Given its excellent safety and tolerability profile, further research into the role of melatonin in headache treatment is warranted. There are two priority areas of research:

1. Elucidation of the mechanism(s) of benefit of melatonin in different primary headache disorders

There are a number of possible mechanisms by which melatonin may benefit primary headache disorders, including improved circadian rhythm regulation and/or improved sleep. Melatonin also acts as an anti-oxidant, and has analgesic and anxiolytic properties—which may be mediated by its ability to enhance GABA signaling, increase beta-endorphin release, and inhibit nitric oxide production[18, 54–57].

Dysregulated expression of certain circadian genes has been found in exploratory analysis in cluster headache patients[58]. Additional research is needed in bother cluster headache and migraine to determine whether melatonin's therapeutic benefit is through improved sleep vs. improvement in circidan rhythm regulation more generally. Mobile actigraphy could be used in future research to monitor participants' sleep-wake cycles. If improvement in migraine frequency is mediated through improved sleep it would be helpful to identify which aspect of sleep—sleep onset latency, sleep efficiency or total sleep time—best correlates with improvement in headache frequency. As mobile health devices become increasingly available, such knowledge could allow for a "personalized medicine" approach to therapy as baseline circadian data that patients collect at home could be used to determine *a priori* whether they are likely to benefit from a melatonin treatment trial.

In cluster headache, pharmacokinetic data could help clarify whether melatonin benefit in a cluster period is most optimal when given at a particular time of the evening, or at a particular time of the cluster period, by systematic measurements of melatonin during the cluster period and with treatment.

In hypnic headache, the obvious mechanistic question is: is it only those who have low nocturnal melatonin levels who benefit from melatonin supplementation? As for the indomethacin-responsive headache disorders—why do some respond to melatonin while others do not? It is possible this is a question of dosing, an issue which segues into the second identifiable research priority for melatonin treatment in primary headache disorders.

2) Clarification of the optimal dose(s) and formulation of melatonin to be used in treatment of different primary headache disorders

Optimal melatonin dosing for treatment of each of these headache disorders may differ. Based on the range of doses reported to be effective for different disorders in this review, testing of broad dosing ranges may be needed to establish optimal dosing. Fortunately even at very high doses melatonin appears to be remarkably safe and without serious side effects. In healthy volunteers, melatonin doses of 20–100 mg orally have been given without adverse effects other than mild transient drowsiness[21]. In neonates doses of 10mg/kg intravenously[17] have been given without apparent toxicity in the treatment of procedural pain. Patients with

metastatic melanoma were treated with melatonin 700 mg/m^2/day for a median treatment follow-up of five weeks without apparent toxicity other than fatigue[22]. There has been some concern that elevated melatonin levels are associated with nocturnal asthma[59], however it is unclear to what extent this is of clinical significance[60]. Longer-term treatment trials have also supported melatonin's excellent safety profile—for example no serious adverse events occurred in the 8–12 week migraine preventive trials[23, 25], and longer term treatment durations of six months or more for migraine, sleep, and other indications have also not raised safety issues[28, 61–63].

For migraine, 3 mg appears to be the minimum effective dose in adults[25], and uncontrolled data suggest a slightly higher dose of 4 mg may also be helpful[28]. Further work is needed to determine whether there is a dose-response. Optimal dosing in pediatric migraine needs study in a randomized trial, but uncontrolled work suggests 3–6 mg may be an effective dosing range[29, 30].

For cluster headache, melatonin 10 mg[24] has been shown to be superior to placebo in treating cluster periods, however given that some patients with HC needed doses up to 30 mg to get benefit[39], it is possible that higher doses in cluster headache could further optimize responder rate.

The optimal formulation of melatonin to use in each headache disorder also needs to be clarified. It is often not explicitly stated whether immediate release or prolonged release melatonin is being used in treatment trials, though when not specified it is probably more likely to be immediate release melatonin. In migraine, the positive RCT used immediate release melatonin and the underpowered negative study used sustained release melatonin and also a lower dose[23, 25]. Hence, currently immediate release melatonin appears preferable in the treatment of migraine. As melatonin is a supplement it is not currently regulated by the FDA, thus product quality may vary between melatonin brands and even between batches of the same brand. Studies should therefore specify the brand of melatonin that was used so that clinicians can attempt to replicate benefits seen in trials, though a certain degree of uncertainty is unfortunately unavoidable.

It would also be worthwhile to establish the comparative efficacy of melatonin vs. melatonin receptor agonists, such as ramelteon, agomelatine and others. However, one of the potential advantages to a treatment like melatonin is that, if found to be effective, it can be easily accessed over the counter at relatively low cost—at least in the U.S.. Melatonin receptor agonists and, in some countries, prolonged release melatonin, would require a prescription and have potentially higher costs to the patient and the health care system. Thus accessibility and cost effectiveness argue for focusing research on immediate release melatonin as the first priority whenever it is medically appropriate to do so. Other strategies for improving circadian rhythms, such as early morning light therapy, could also be cost effective and merit study in primary headache disorders.

Conclusions

In randomized placebo-controlled trials, melatonin 3 mg (immediate release) orally nightly has been shown to be effective for migraine prevention and 10 mg melatonin nightly has been shown to be effective for episodic cluster headache. Sustained release melatonin at 2 mg nightly was not effective for migraine prevention in a small, randomized placebo-controlled trial. Uncontrolled trials and case reports support melatonin's efficacy in other primary headache disorders such as tension-type headache, hemicrania continua, hypnic headache SUNCT and primary stabbing headache. Additional randomized controlled trials are needed to establish optimal melatonin dosing and formulation in the treatment of each of the primary headache disorders, as well as to establish or confirm melatonin's efficacy and —where effective—to clarify the possibly distinct mechanisms underlying melatonin's treatment benefit in the different primary headache disorders.

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Abbreviations

HC	hemicrania continua
TTH	tension-type headache
SD	standard deviation
RCT	randomized controlled trial
ICHD	International Classification of Headache Disorders
MT1 and MT2	melatonin receptors

References

1. Brzezinski A. Melatonin in humans. The New England journal of medicine. 1997; 336:186–195. [PubMed: 8988899]

2. The International Classificatio of Headache Disorders, 3rd edition (beta version). Cephalalgia : an international journal of headache. 2013; 33:629–808. [PubMed: 23771276]

3. Ferrari E, Nappi G, Vailati A, Martignoni E, Bossolo PA, Polleri A. Circadian periodicity of plasma prolactin in some neurological diseases. International journal of chronobiology. 1979; 6:231–242. [PubMed: 162341]

4. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain. 2014; 137:232–241. [PubMed: 24277718]

5. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ. Hypothalamic activation in cluster headache attacks. Lancet. 1998; 352:275–278. [PubMed: 9690407]

6. Weaver DR, Stehle JH, Stopa EG, Reppert SM. Melatonin receptors in human hypothalamus and pituitary: implications for circadian and reproductive responses to melatonin. The Journal of clinical endocrinology and metabolism. 1993; 76:295–301. [PubMed: 8381796]

7. Wu YH, Ursinus J, Zhou JN, et al. Alterations of melatonin receptors MT1 and MT2 in the hypothalamic suprachiasmatic nucleus during depression. Journal of affective disorders. 2013; 148:357–367. [PubMed: 23357659]

8. Nagtegaal JE, Smits MG, Swart AC, Kerkhof GA, van der Meer YG. Melatonin-responsive headache in delayed sleep phase syndrome: preliminary observations. Headache. 1998; 38:303–307. [PubMed: 9595871]

9. Leone M, Frediani F, D'Amico D, et al. Dexamethasone suppression test, melatonin and TRH-test in cluster headache. Italian journal of neurological sciences. 1992; 13:227–232. [PubMed: 1624279]

10. Leone M, Lucini V, D'Amico D, et al. Twenty-four-hour melatonin and cortisol plasma levels in relation to timing of cluster headache. Cephalalgia : an international journal of headache. 1995; 15:224–229. [PubMed: 7553813]

11. Chazot G, Claustrat B, Brun J, Jordan D, Sassolas G, Schott B. A chronobiological study of melatonin, cortisol growth hormone and prolactin secretion in cluster headache. Cephalalgia : an international journal of headache. 1984; 4:213–220. [PubMed: 6518501]

12. Waldenlind E, Gustafsson SA, Ekbom K, Wetterberg L. Circadian secretion of cortisol and melatonin in cluster headache during active cluster periods and remission. Journal of neurology, neurosurgery, and psychiatry. 1987; 50:207–213.

13. Woldeamanuel YW, Cowan RP. The impact of regular lifestyle behavior in migraine: a prevalence case-referent study. Journal of neurology. 2016

14. Kelman L, Rains JC. Headache and sleep: examination of sleep patterns and complaints in a large clinical sample of migraineurs. Headache. 2005; 45:904–910. [PubMed: 15985108]

15. Ahn AH, Brennan KC. Unanswered questions in headache: how does a migraine attack stop? Headache. 2012; 52:186–187. [PubMed: 22221296]

16. El-Shenawy SM, Abdel-Salam OM, Baiuomy AR, El-Batran S, Arbid MS. Studies on the anti-inflammatory and anti-nociceptive effects of melatonin in the rat. Pharmacological research. 2002; 46:235–243. [PubMed: 12220966]

17. Gitto E, Aversa S, Salpietro CD, et al. Pain in neonatal intensive care: role of melatonin as an analgesic antioxidant. Journal of pineal research. 2012; 52:291–295. [PubMed: 22141591]

18. Marseglia L, Manti S, D'Angelo G, et al. Potential Use of Melatonin in Procedural Anxiety and Pain in Children Undergoing Blood Withdrawal. Journal of biological regulators and homeostatic agents. 2015; 29:509–514. [PubMed: 26122244]

19. Muller-Schweinitzer, E.; Weidmann, H. Basic Pharmacological Properties. In: Berde, B.; Schild, HO., editors. Ergot Alkaloids and Related Compounds. Berlin Heidelberg New York: Springer-Verlag; 1978. p. 180

20. Rodrigues T, Moreira R, Guedes RC, Iley J, Lopes F. Unanticipated acyloxymethylation of sumatriptan indole nitrogen atom and its implications in prodrug design. Archiv der Pharmazie. 2008; 341:344–350. [PubMed: 18442019]

21. Galley HF, Lowes DA, Allen L, Cameron G, Aucott LS, Webster NR. Melatonin as a potential therapy for sepsis: a phase I dose escalation study and an ex vivo whole blood model under conditions of sepsis. Journal of pineal research. 2014; 56:427–438. [PubMed: 24650045]

22. Gonzalez R, Sanchez A, Ferguson JA, et al. Melatonin therapy of advanced human malignant melanoma. Melanoma research. 1991; 1:237–243. [PubMed: 1823632]

23. Alstadhaug KB, Odeh F, Salvesen R, Bekkelund SI. Prophylaxis of migraine with melatonin: a randomized controlled trial. Neurology. 2010; 75:1527–1532. [PubMed: 20975054]
24. Leone M, D'Amico D, Moschiano F, Fraschini F, Bussone G. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. Cephalalgia : an international journal of headache. 1996; 16:494–496. [PubMed: 8933994]
25. Peres M, Goncalves A. Double-Blind, Placebo Controlled, Randomized Clinical Trial Comparing Melatonin 3 mg, Amitriptyline 25 mg and Placebo for Migraine Prevention. Neurology. 2013; 80:S40.005.
26. Masruha MR, de Souza Vieira DS, Minett TS, et al. Low urinary 6-sulphatoxymelatonin concentrations in acute migraine. The journal of headache and pain. 2008; 9:221–224. [PubMed: 18594760]
27. Masruha MR, Lin J, de Souza Vieira DS, et al. Urinary 6-sulphatoxymelatonin levels are depressed in chronic migraine and several comorbidities. Headache. 2010; 50:413–419. [PubMed: 19817880]
28. Bougea A, Spantideas N, Lyras V, Avramidis T, Thomaidis T. Melatonin 4 mg as prophylactic therapy for primary headaches: a pilot study. Functional neurology. 2016:1–5.
29. Fallah R, Shoroki FF, Ferdosian F. Safety and efficacy of melatonin in pediatric migraine prophylaxis. Current drug safety. 2015; 10:132–135. [PubMed: 24909684]
30. Miano S, Parisi P, Pelliccia A, Luchetti A, Paolino MC, Villa MP. Melatonin to prevent migraine or tension-type headache in children. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2008; 29:285–287.
31. Bruera O, Sances G, Leston J, et al. Plasma melatonin pattern in chronic and episodic headaches: evaluation during sleep and waking. Functional neurology. 2008; 23:77–81. [PubMed: 18671907]
32. Leone M, Lucini V, D'Amico D, et al. Abnormal 24-hour urinary excretory pattern of 6-sulphatoxymelatonin in both phases of cluster headache. Cephalalgia : an international journal of headache. 1998; 18:664–667. [PubMed: 9950622]
33. Waldenlind E, Ekbom K, Wetterberg L, et al. Lowered circannual urinary melatonin concentrations in episodic cluster headache. Cephalalgia : an international journal of headache. 1994; 14:199–204. [PubMed: 7954739]
34. Nesbitt AD, Goadsby PJ. Cluster headache. Bmj. 2012; 344:e2407. [PubMed: 22496300]
35. Leone M, Bussone G. A review of hormonal findings in cluster headache. Evidence for hypothalamic involvement. Cephalalgia : an international journal of headache. 1993; 13:309–317. [PubMed: 8242722]
36. Peres MF, Rozen TD. Melatonin in the preventive treatment of chronic cluster headache. Cephalalgia : an international journal of headache. 2001; 21:993–995. [PubMed: 11843873]
37. Arruda MA, Bonamico L, Stella C, Bordini CA, Bigal ME. Cluster headache in children and adolescents: ten years of follow-up in three pediatric cases. Cephalalgia : an international journal of headache. 2011; 31:1409–1414. [PubMed: 21911413]
38. Peres MF, Stiles MA, Oshinsky M, Rozen TD. Remitting form of hemicrania continua with seasonal pattern. Headache. 2001; 41:592–594. [PubMed: 11437897]
39. Rozen TD. How effective is melatonin as a preventive treatment for hemicrania continua? A clinic-based study. Headache. 2015; 55:430–436. [PubMed: 25711410]
40. Hollingworth M, Young TM. Melatonin responsive hemicrania continua in which indomethacin was associated with contralateral headache. Headache. 2014; 54:916–919. [PubMed: 24261314]
41. Spears RC. Hemicrania continua: a case in which a patient experienced complete relief on melatonin. Headache. 2006; 46:524–527. [PubMed: 16618278]
42. Maity P, Bindu S, Dey S, et al. Melatonin reduces indomethacin-induced gastric mucosal cell apoptosis by preventing mitochondrial oxidative stress and the activation of mitochondrial pathway of apoptosis. Journal of pineal research. 2009; 46:314–323. [PubMed: 19220725]
43. Rozen TD. Melatonin responsive hemicrania continua. Headache. 2006; 46:1203–1204. [PubMed: 16866728]
44. De Simone R, Marano E, Ranieri A, Bonavita V. Hypnic headache: an update. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2006; 27(Suppl 2):S144–S148.

45. Iguichi H, Kato KI, Ibayashi H. Age-dependent reduction in serum melatonin concentrations in healthy human subjects. The Journal of clinical endocrinology and metabolism. 1982; 55:27–29. [PubMed: 7200489]
46. Dodick DW. Polysomnography in hypnic headache syndrome. Headache. 2000; 40:748–752. [PubMed: 11091295]
47. Domitrz I. Hypnic headache as a primary short-lasting night headache: a report of two cases. Neurologia i neurochirurgia polska. 2005; 39:77–79. [PubMed: 15735995]
48. Ulrich K, Gunreben B, Lang E, Sittl R, Griessinger N. Pregabalin in the therapy of hypnic headache. Cephalalgia : an international journal of headache. 2006; 26:1031–1032. [PubMed: 16886944]
49. Holle D, Naegel S, Krebs S, et al. Clinical characteristics and therapeutic options in hypnic headache. Cephalalgia : an international journal of headache. 2010; 30:1435–1442. [PubMed: 20974580]
50. Silva-Neto RP, Almeida KJ. Hypnic headache in childhood: A literature review. Journal of the neurological sciences. 2015; 356:45–48. [PubMed: 26123200]
51. Cerminara C, Compagnone E, Coniglio A, et al. Hypnic headache in children. Cephalalgia : an international journal of headache. 2011; 31:1673–1676. [PubMed: 22025767]
52. Rozen TD. Melatonin as treatment for idiopathic stabbing headache. Neurology. 2003; 61:865–866. [PubMed: 14504346]
53. Rojas-Ramirez MV, Bertoli E, Smith JH. Short-Lasting Unilateral Neuralgiform Headache with Conjunctival Injection and Tearing Secondary to Head and Neck Trauma: Literature Review and Case Report. Journal of oral & facial pain and headache. 2016; 30:68–72. [PubMed: 26817035]
54. Esposito E, Paterniti I, Mazzon E, Bramanti P, Cuzzocrea S. Melatonin reduces hyperalgesia associated with inflammation. Journal of pineal research. 2010; 49:321–331. [PubMed: 20666977]
55. Cardinali DP, Golombek DA. The rhythmic GABAergic system. Neurochemical research. 1998; 23:607–614. [PubMed: 9566598]
56. Shavali S, Ho B, Govitrapong P, et al. Melatonin exerts its analgesic actions not by binding to opioid receptor subtypes but by increasing the release of beta-endorphin an endogenous opioid. Brain research bulletin. 2005; 64:471–479. [PubMed: 15639542]
57. Amir Aslani B, Ghobadi S. Studies on oxidants and antioxidants with a brief glance at their relevance to the immune system. Life sciences. 2016; 146:163–173. [PubMed: 26792059]
58. Costa M, Squassina A, Piras IS, et al. Preliminary Transcriptome Analysis in Lymphoblasts from Cluster Headache and Bipolar Disorder Patients Implicates Dysregulation of Circadian and Serotonergic Genes. Journal of molecular neuroscience : MN. 2015; 56:688–695. [PubMed: 25912293]
59. Sutherland ER, Ellison MC, Kraft M, Martin RJ. Elevated serum melatonin is associated with the nocturnal worsening of asthma. The Journal of allergy and clinical immunology. 2003; 112:513–517. [PubMed: 13679809]
60. Campos FL, da Silva-Junior FP, de Bruin VM, de Bruin PF. Melatonin improves sleep in asthma: a randomized, double-blind, placebo-controlled study. American journal of respiratory and critical care medicine. 2004; 170:947–951. [PubMed: 15306531]
61. Wade AG, Ford I, Crawford G, et al. Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: a randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety. BMC medicine. 2010; 8:51. [PubMed: 20712869]
62. Hoebert M, van der Heijden KB, van Geijlswijk IM, Smits MG. Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. Journal of pineal research. 2009; 47:1–7. [PubMed: 19486273]
63. Andersen LP, Gogenur I, Rosenberg J, Reiter RJ. The Safety of Melatonin in Humans. Clinical drug investigation. 2016; 36:169–175. [PubMed: 26692007]