▪ Headache Medicine 2022, 13(3):192-200 ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

▪ DOI: 10.48208/HeadacheMed.2022.20

Review

The importance of addressing sleep disorders in migraine treatment

Pablo Guarisco Ferreira[1], Lara Henriqueta Bussolaro Ricardi[1], Edivarley Rodrigues da Costa Júnior[2], Alcântara Ramos de Assis Cesar[1]

[1]Universidade Federal do Parana, Toledo, Parana, Brazil
[2]Universidade Federal de São Paulo, Sao Paulo, Brazil

Pablo Guarisco Ferreira
pabloguarisco@ufpr.br

Edited by:
Marcelo Moraes Valença

Keywords:
Migraine
Sleep Disorders
Treatment
Triggers
Prodromal Symptoms

Abstract

Migraine is one of the most common complaints in the clinical practice of neurology. It is multifactorial, with insomnia being a predisposing factor present in almost 50% of cases. The pathophysiology of migraine is complex and involves alterations in several areas of the CNS that share common pathways with sleep disorders. These include hypotha¬-lamic connections, hormones, and neuropeptides such as orexin and monoaminergic. Furthermore, there are other specific sleep disorders associated with migraine. Currently, treatment is individualized and lifestyle changes and sleep adjustment are recommended in addition to medication. In view of the above, the association between sleep and migraine represents a therapeutic opportunity that can be exploited based on a detailed clinical approach during clinical examination.

Received: September 21, 2022
Accepted: September 23, 2022

Introduction

Insomnia is the sleep disorder found in almost 50% of patients diagnosed with migraine.[1] It is also true that there is a higher prevalence of migraine in individuals with insomnia, compared to individuals without this sleep disorder.[2]

While migraine can awaken the patient in the middle of sleep, sleep disruption comply as a trigger for the attack in cases where the pathophysiological mechanisms are shared.[3] Interestingly, a higher occurrence of arousal from migraine attacks can be observed during REM sleep. Some attacks of nocturnal headache occur during dreams, and occasionally the aura of classic migraine attacks is incorporated into the content of a dream preceding awakening with severe headache.[4]

Changes in sleep, such as sleep deprivation, have been identified as triggering factors for single attacks.[5] It is also described that the periodicity of crises follows the circadian cycle, with most seizures occurring in the early morning hours[6], probably related to the activity of monoaminergic neurotransmitters that interfere with REM sleep.[7,8] Also, chronic exposure to insufficient sleep induces changes in pain inhibitory processes, favoring the chronification of the disease.[9]

As soon, by presenting the common pathophysiology, this article purpose to report the complaints of sleep disturbance and migraine, by direct or indirect mechanisms, demonstrating the relevance of addressing the theme on diagnostic routine, as well as in management of the therapy. It also intends to differentiate triggers from prodromes, which often, although associated, have different mechanisms of action and therapeutics.

Sleep and Migraine

Epidemiology

Currently, migraine affects 12 to 15% of the general population.[8,10] It is more common in women between the ages of 30 and 39, with migraine without aura being more prevalent.[11] Migraine, although not fatal, is disabling and ranks 2nd in the ranking that relates illness and years of life lived with disability.[10,12]

On the other hand, in men sleep disturbances related to respiratory alterations and fragmentary myoclonias were more prevalent, while in women insomnia was common.[13,14]

The main sexual differences in sleep shows up with the first menstrual cycle.[15] Progesterone looks to decrease the incidences of environment-related sleep disruption by improving the duration and quality of slow-wave sleep.[16] Also, corroborating the relationship between prodromes of migraine and the menstrual cycle are the localization of estrogen and progesterone receptors in the sleep/wake regulatory nuclei, including the basal prosencephalon, hypothalamus, dorsal raphe nucleus, and locus coeruleus.[17]

In addition, workers with journey more than 40 hours per week had a higher prevalence of short sleep duration, while the lowest prevalence was found in the oldest age group (>65 years), followed by the youngest one (18-25 years).[18]

These factors helps to explain the predominance of migraine among females and in productive age people. Moreover, how it is seems that the population has been reducing their sleep time[18,19] this may serve as an alert to clinicians for the increase in the incidence of headache over the years.

Diagnosis

Migraine is a primary headache[20] and its diagnosis is defined by the International Classification of Headache Disorders (ICHD-3). Likewise, sleep disorders can be systematized by the International Classification of Sleep Disorders.[21]

A good anamnesis is essential for the diagnosis of migraine[22], as well as for sleep disorders[23], since they may be related and interfere with the therapeutic strategy and prognosis of the disease. Thus, during the investigation, it is important to ask about the duration and intensity of migraine, prodromes, and possible triggers; questions such as the time of onset and awakening sleep, frequency and duration of awakenings, duration of naps, daytime sleepiness symptoms, fatigue, and sleep environment.[24] Suggesting the patient to keep a sleep diary for a period of two weeks or more, as well as during the headache investigation, contributes to the diagnosis and possibilities correlations. Around the medications, the excess use drugs for acute headache treatment, oral contraceptives, postmenopausal hormone replacement, nasal decongestants, selective serotonin reuptake inhibitors, and proton pump inhibitors can be reported as the trigger the crises.[26]

Migraine Pathophysiology

It has been proposed that migraine would have vascular characteristics, being caused mainly by vasodilation, while aura would arise from vasoconstriction. Nowadays, it is known that it is a complex disorder with genetic, anatomical, physiological and pharmacological components.[27] Also, sleep can be disturbed by musculoskeletal factors or concomitant depression.[28]

Alterations in several areas of the CNS may be linked to prodromal and migraine attacks. For example, the increase in light sensitivity experienced may be secondary to increased activity in the occipital cortex[29]; while brainstem activation can cause nausea.[30] On the other hand, hypothalamic hyperfunction could trigger polyuria, mood and appetite changes and if this occurs in the connecting circuits thalamus to the cortex, the symptom is cutaneous allodynia.[31] The importance of these findings lies in the possibility of defining new therapeutic targets for drugs and neuromodulators, such as transcranial magnetic stimulation.[32]

Anatomical variabilities in the nerve roots may also influence the migraine pattern. Branches of the trigeminal nerve may reach the neck muscles through the skull, suggesting a possible role for these afferents in migraine-related neck pain. Patients with these causes would benefit from local therapies of suboccipital injections of anesthetics and steroids.[33]

Neurotransmitters

To associate sleep disorders and migraine, is fundamental the elucidation of the role of neurotransmitters. Orexins, melatonin, pituitary adenylate cyclase activating polypeptide, serotonin, dopamine, and adenosine are the molecules that represent a possible role as mediators of this relationship.[3] In addition, diencephalic and brainstem anatomical regions are involved in both the pathogenesis of migraine and the regulation of the sleep-wake cycle[9,34] as is shown in Table 1.

Table 1. Anatomical regions and neurotransmitters related to migraine and sleep modulation

Anatomical Region	Migraine	Sleep
Cortex	Pain processing: thalamo-cortical ascending projections synapse on a diffuse network of cortical regions, including the primary and secondary somatosensory motor cortex and visual cortex for pain processing Pain modulation: through direct and indirect descending projections from the cortex to the trigeminocervical complex	Promotion of wakefulness: through ascending inputs from monoaminergic neurons, hypothalamus and basal prosencephalon.
Thalamus	Processing and transmission of nociceptive information from the trigeminocervical complex	Promotion of wakefulness and integration of sub-cortical sleep-wakefulness inputs
Hypothalamus - posterior (dopamine) - lateral (orexin)	Pain processing, transmission, and modulation of the ascending pathway of the brainstem nuclei and trigeminocervical complex The dopaminergic nucleus A11 is responsible for the prodromal symptoms of migraine Orexinergic neurons facilitate or inhibit the trigeminocervical complex by specific receptors and regulate the sleep-wake cycle Orexinergic neurons are also related to the premonitory phase of a migraine attack. It generates symptoms such as yawning, food cravings, and changes in wakefulness.[25]	Promotion of wakefulness, regulation of circadian rhythm and control of sleep-wakefulness transition Promotion of wakefulness by activation of the monoaminergic system of the brainstem, basal prosencephalon, and cortex Sleep-wakefulness transition control- participates in the flip-flop system for sleep-wakefulness transition; maintains the stability of wakefulness; and prevents sudden and inappropriate onset of sleep Significant increases in orexin levels occur after partial sleep deprivation.[35]
Brainstem - Periaqueductal (dopamine) - Dorsal raphe nucleus (serotonin) - Locus coeruleus (norepinephrine)	Transmission of pain by afferent fibers from the trigeminocervical complex to the thalamus Modulation of pain through the descending input of the thalamus and hypothalamus The circadian rhythm of serotonin and the discharge of serotoninergic neurons may influence the production of endogenous opioids and the activity of the trigeminal system.[36] Concentrations of calcitonin gene-related peptide (CGRP) are persistently elevated in patients with chronic migraine, and are released during exacerbation.[37]	Promotion of wakefulness: ascending activation pathways projecting from the brainstem to the thalamus and basal prosencephalon Stabilization of wakefulness: it receives the orexinergic excitatory projections and sends inhibitory inputs to sleep promoting ventrolateral preoptic nucleus to reinforce wakefulness Sleep transition control: inhibition of this nucleus by the ventrolateral preoptic nucleus promotes sleep. Noradrenergic and serotoninergic neurons inhibit REM sleep Increased activity in the trigeminal nuclei during sleep may precipitate a seizure and awaken the patient.[38] Onset of sleep by stimulation of monoaminergic cells in the locus coeruleus.[39]

Adapted from: Tiseo C, Vacca A, Felbush A, et al. **Migraine and sleep disorders: a systematic review**. *J Headache Pain* 2020. 21(1):1-13. The other references are indicated in the table.

Common pathway between the pathophysiology of migraine and sleep disorders

The hypothalamus is involved in the regulation of several physiological processes, such as sleep, circadian cycle, thermal regulation, appetite, cardiovascular and endocrine functions, modulation of the trigeminal nociceptive system, and others. In migraine, many of these functions, as well as their control pathways, are dysfunctional.

In the modulation of pain in migraine, the hypothalamus has a direct action, through connections with the trigeminal-cervical complex; and indirect, through connections with other structures that help in this modulating process, such as the periaqueductal gray matter (PAG) and the locus coeruleus (LC).[40] Migraine results from aberrant activation of the trigeminal-vascular system, promoting alteration of the nociceptive process. Also, there is a hyperactivation of the hypothalamus during the pain crisis[40,41] and prodromal symptoms.[40,42]

Patients with migraine also have alterations in sleep-related neuropeptides, such as orexins. Produced by the lateral hypothalamus, they control the transition between wakefulness and sleep stages. Patients with chronic or episodic migraine present altered levels of these neuropeptides in the cerebrospinal fluid.[40] This may be associated with the reduced REM sleep period found in migraine patients, which in turn is related to more prominent allodynia during attacks.[43] In addition, these neuropeptides act in modulating trigeminal-vascular tone, with orexin A having anti-nociceptive components and orexin B having a pro-nociceptive action.[44] Melatonin also seems to play a role in the association between migraine and sleep disorders, exerting anti-nociceptive effects through the activation of MT2 receptors; but its production, regulated by the hypothalamus, is altered in sleep disorders.[45] Other hormones related to hypothalamic activity, such as cortisol, are also modified.[46]

Triggers and prodromal symptoms related to sleep disorders

In the natural history of migraine disease, two stages precede the pain crisis: exposure to migraine triggers, stimuli believed to precipitate the crisis; and the prodromal stage of the disease, which consists of symptoms that precede the crisis by 2 to 48 hours, occurring before the aura (in migraine with aura) or before the onset of headache (in migraine without aura).[47]

It is estimated that about 75% to 95% of patients report specific triggers for migraine attacks[48] with sleep disturbances among the most important, reported by at least 50% of patients.[1,49-50] Other common triggers are: stress, hormonal changes in women, fasting, bright lights, and odors (such as perfume).[1,9,40,43,45,48,49,51] Patients may have a single trigger or multiple triggers, such as stress and sleep disturbance.[1,48] They may change throughout a lifetime[1] and such characteristics do not seem to vary according to ethnicity or demographic region.[48] Also, the adequate recognition of the migraine attack trigger in each patient plays an important role in the prevention of the disease, through strategies that aim to avoid, as much as possible, the known triggers.[1]

Changes in sleep pattern and other hypothalamic functions are also among the main prodromal symptoms of migraine. Examples are excessive sleepiness, repetitive yawning, mood and appetite variations, fatigue, nausea, and vomiting.[40,47,52] These symptoms appear to be due to hypothalamic hypersensitivity to dopamine.[40,52] This hypothesis was demonstrated experimentally in which the administration of a dopamine agonist increased the incidence of prodromal symptoms in migraine patients[53] and, in another study, in which the administration of domperidone 30g (dopaminergic antagonist), early in the prodromal phase, reduced the incidence of the migraine attack by 61% compared to the placebo group.[54] Other studies have demonstrated, by functional neuroimaging examination, a hyperactivation of the hypothalamus in the prodromal phase.[42] Therefore, the identification of prodromal symptoms offers an important therapeutic window for the prevention of migraine pain attacks.

It is also observed an important correlation between the identified trigger and the prodromal symptom that will be followed.[55] Some examples are shown in Table 2. Thus, some authors suggest the possibility that some triggers may be early manifestations of the prodromal phase of the disease.[55,52]

Table 2. Relationship between trigger perception and the corresponding prodromal symptom.

Reported trigger	Prodromal symptom
Light Stimuli	Photophobia
Sound stimuli	Phonophobia
Skipping meals	Food cravings
Stress	Mood swings, neck stiffness
Dehydration	Excessive thirst
Poor sleep	Fatigue, drowsiness

Adapted from: Karsan N, et al. **Are some patient-perceived migraine triggers simply early manifestations of the attack?**. *J Neurol* 2021. 268(5):1885-1893. DOI:10.1007/s00415-020-10344-1

Sleep disorders, besides serving as triggers, negatively

influence migraine in several ways: poor sleep quality is considerably more frequent in adults with migraine; it increases the frequency and intensity of attacks, as well as favoring the chronification of the disease, regardless of the presence of psychiatric comorbidities, such as depression and anxiety.[9,43,56,57]

Migraine and specific sleep disorders

Migraine and sleep disorders are often associated comorbidities and, individually, very prevalent. It is known that patients with inadequate sleep routine present cognitive impairment, short attention span, irritability, daytime sleepiness, mood swings, stress, and even increased appetite and hunger perception.[58-61] These symptoms are present both in acute sleep deprivation and in chronic impairment of its quality or duration.[59] It is worth noting the intersection between these symptoms and those present in migraine, as shown in Table 3.

Table 3. symptoms related to sleep pattern changes compared to prodromal symptoms of migraine

Symptom of insufficient sleep	Prodromic Symptom of Migraine
Mood swings, irritability	Mood swings
Increased perception of hunger	Food cravings
Daytime sleepiness, reduced attention span	Fatigue, drowsiness

However, the mechanisms by which each sleep disorder influences the onset and development and evolution of migraine are still unknown. In Table 4, the main categories of these disorders and their possible correlations with migraine are compiled, according to the ICSD.[21]

Table 4. The major categories of sleep disorders and correlations with migraine.

Sleep disturbance category	Correlations with migraine
Insomnia	Studies suggest a bidirectional relationship between migraine and insomnia, in which insomnia is a risk factor and promotes worsening of the clinical presentation and course of migraine with increased pain intensity, frequency of attacks, and chronicity of the disease; individuals with migraine have a higher risk of developing insomnia .[9]
Sleep-Related Respiratory Disorders	
Obstructive sleep apnea (OSA)	Although there is no clear association between the two comorbidities [9,41], some evidence suggests that obstructive sleep apnea may play a trigger role in migraine in predisposed patients and may promote exacerbation of headache frequency and severity.[9]
Sleep-Related Movement Disorders	
Restless legs syndrome (RLS)	The presence of RLS in patients with migraine is associated with greater severity of the disease, with increased frequency of attacks, occurrence of photophobia, phonophobia, nausea, and higher anxiety and depression scores than in individuals without RLS. It is theorized that the association between migraine and RLS is due to a dopaminergic dysfunction in the hypothalamic nucleus A11.[9,62] The presence of RLS is more common in patients with the chronic form of migraine than with the episodic form.[45]
Central hypersomnia disorders	
Narcolepsy	Patients with narcolepsy have a higher prevalence of migraine.[9] Although the association between both comorbidities is controversial, narcolepsy stems from a dysfunction of the orexinergic system, which also appears to be related to migraine.[9]
Circadian rhythm disorders	Some studies have reported an association between migraine and the circadian cycle.[9,45,44] Migraine attacks occur more frequently in the morning and those that occur in this period are more severe.[45] There is no clear association between both comorbidities.[9]
Parasomnias	
Sleepwalking	Adults with migraine appear to have a higher prevalence of sleepwalking in childhood[45] and adults with sleepwalking have a higher risk of developing migraine or any other headache, regardless of associated comorbidities such as depression, chronic insomnia, and daytime sleepiness.[9] Possibly stems from alterations in the serotonergic and orexinergic pathways.[46]
REM sleep behavior disorder	The presence of dream staging was associated with greater migraine-related disability and poorer sleep quality.[9,63] More studies should be done to evaluate the possible correlation between behavioral REM sleep disorder and migraine.[9,45]

Conclusion

Migraine and sleep disorders are common clinical conditions in the general population, often associated with other diseases. This fact is likely due to overlapping modulatory mechanisms. Thus, for the treatment of migraine, it is essential the analysis of triggers during anamnesis and management through lifestyle changes, such as: regularizing sleep patterns, weight loss and increased physical exercises; avoidance of alcohol and caffeine consumption; control of comorbidities (such as hypertension, psychiatric, endocrine, and others).

Although current preventive therapies are effective for mild cases, there is a significant need for safer treatments.[64] Triptans, nonsteroidal anti-inflammatory drugs, and antiemetics remain mainstays in acute migraine therapy. However, in view of the recognition of the neurotransmitters involved in the crises, drugs that interfere in these pathways may be effective in the treatment. Drugs with action on neurotransmitters common to sleep disorders and migraine, such as CGRP antagonists and modulators of central monoaminergic pathways and orexins, may also be effective.[65-67] Also, migraine attacks with different clinical features may respond differently, and the management of specific exacerbating factors and the personalization of acute and preventive therapeutic approaches should be considered.[26] Therefore, in this article, we emphasize the importance of looking for disturbances and changes in sleep patterns during the clinical examination of migraine patients, especially when headache is difficult to control.

Conflict of interest: The authors report no conflict of interest

Funding: No

Author's contributions: PGF, LHBR, ERCJr, research and writing; ERCJr, ARAC, review and correction

Pablo Guarisco Ferreira
https://orcid.org/0000-0002-8842-6190
Lara Henriqueta Bussolaro Ricardi
https://orcid.org/0000-0001-6883-5459
Edivarley Rodrigues da Costa Júnior
https://orcid.org/0000-0002-3130-327X
Alcântara Ramos de Assis Cesar
https://orcid.org/0000-0002-7390-7282

References

1. Kelman L. **The triggers or precipitants of the acute migraine attack.** *Cephalalgia* 2007;27(5):394-402 Doi:10.1111/j.1468-2982.2007.01303.x
2. Kim J, Cho SJ, Kim WJ, Yang KI, Yun CH and Chu MK. **Impact of migraine on the clinical presentation of insomnia: a population-based study.** *J Headache Pain* 2018;19(1):86 Doi:10.1186/s10194-018-0916-5
3. Dodick DW, Eross EJ, Parish JM and Silber M. **Clinical, anatomical, and physiologic relationship between sleep and headache.** *Headache* 2003;43(3):282-292 Doi:10.1046/j.1526-4610.2003.03055.x
4. Dexter JD and Weitzman ED. **The relationship of nocturnal headaches to sleep stage patterns.** *Neurology* 1970;20(5):513-518 Doi:10.1212/wnl.20.5.513
5. Wöber C, Brannath W, Schmidt K, Kapitan M, Rudel E, Wessely P and Wöber-Bingöl C. **Prospective analysis of factors related to migraine attacks: the PAMINA study.** *Cephalalgia* 2007;27(4):304-314 Doi:10.1111/j.1468-2982.2007.01279.x
6. Alstadhaug K, Salvesen R and Bekkelund S. **Insomnia and circadian variation of attacks in episodic migraine.** *Headache* 2007;47(8):1184-1188 Doi:10.1111/j.1526-4610.2007.00858.x
7. Drake ME, Pakalnis A, Andrews JM and Bogner JE. **Nocturnal sleep recording with cassette EEG in chronic headaches.** *Headache* 1990;30(9):600-603 Doi:10.1111/j.1526-4610.1990.hed3009600.x
8. Othmer E, Hayden MP and Segelbaum R. **Encephalic cycles during sleep and wakefulness in humans: a 24-hour pattern.** *Science* 1969;164(3878):447-449 Doi:10.1126/science.164.3878.447
9. Tiseo C, Vacca A, Felbush A, et al. **Migraine and sleep disorders: a systematic review**. *J Headache Pain* 2020. 21(1):1-13. DOI:10.1186/s10194-020-01192-5
10. Pavlova MK and Latreille V. **Sleep Disorders.** *Am J Med* 2019;132(3):292-299 Doi:10.1016/j.amjmed.2018.09.021
11. Ashina M, Katsarava Z, Do TP, Buse DC, Pozo-Rosich P, Özge A, . . . Lipton RB. **Migraine: epidemiology and systems of care.** *Lancet* 2021;397(10283):1485-1495 Doi:10.1016/s0140-6736(20)32160-7
12. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML and Stewart WF. **Migraine prevalence, disease burden, and the need for preventive therapy.** *Neurology* 2007;68(5):343-349 Doi:10.1212/01.wnl.0000252808.97649.21
13. **Global, regional, and national burden of migraine**

and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018;17(11):954-976 Doi:10.1016/s1474-4422(18)30322-3

14. Auer M, Frauscher B, Hochleitner M and Högl B. **Gender-Specific Differences in Access to Polysomnography and Prevalence of Sleep Disorders.** *J Womens Health (Larchmt)* 2018;27(4):525-530 Doi:10.1089/jwh.2017.6482
15. Zhang B and Wing YK. **Sex differences in insomnia: a meta-analysis.** *Sleep* 2006;29(1):85-93 Doi:10.1093/sleep/29.1.85
16. Pengo MF, Won CH and Bourjeily G. **Sleep in Women Across the Life Span.** *Chest* 2018;154(1):196-206 Doi:10.1016/j.chest.2018.04.005
17. Caufriez A, Leproult R, L'Hermite-Balériaux M, Kerkhofs M and Copinschi G. **Progesterone prevents sleep disturbances and modulates GH, TSH, and melatonin secretion in postmenopausal women.** *J Clin Endocrinol Metab* 2011;96(4):E614-623 Doi:10.1210/jc.2010-2558
18. Mong JA, Baker FC, Mahoney MM, Paul KN, Schwartz MD, Semba K and Silver R. **Sleep, rhythms, and the endocrine brain: influence of sex and gonadal hormones.** *J Neurosci* 2011;31(45):16107-16116 Doi:10.1523/jneurosci.4175-11.2011
19. Luckhaupt SE, Tak S and Calvert GM. **The prevalence of short sleep duration by industry and occupation in the National Health Interview Survey.** *Sleep* 2010;33(2):149-159 Doi:10.1093/sleep/33.2.149
20. Knutson KL, Van Cauter E, Rathouz PJ, DeLeire T and Lauderdale DS. **Trends in the prevalence of short sleepers in the USA: 1975-2006.** *Sleep* 2010;33(1):37-45 Doi:10.1093/sleep/33.1.37
21. **Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition.** *Cephalalgia* 2018;38(1):1-211 Doi:10.1177/0333102417738202
22. Sateia MJ. **International classification of sleep disorders-third edition: highlights and modifications.** *Chest* 2014;146(5):1387-1394 Doi:10.1378/chest.14-0970
23. Cutrer FM, Bajwa ZH and Sabahat A. **Pathophysiology, clinical manifestations, and diagnosis of migraine in adults.** *Up to Date* 2012;
24. Judd BG and Sateia MJ. **Classification of sleep disorders.** *Up to Date* 2021;
25. Martin VT and Behbehani MM. **Toward a rational understanding of migraine trigger factors.** *Med Clin North Am* 2001;85(4):911-941 Doi:10.1016/s0025-7125(05)70351-5
26. Lipton RB, Serrano D, Nicholson RA, Buse DC, Runken MC and Reed ML. **Impact of NSAID and Triptan use on developing chronic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study.** *Headache* 2013;53(10):1548-1563 Doi:10.1111/head.12201
27. Giffin NJ, Ruggiero L, Lipton RB, Silberstein SD, Tvedskov JF, Olesen J, . . . Macrae A. **Premonitory symptoms in migraine: an electronic diary study.** *Neurology* 2003;60(6):935-940 Doi:10.1212/01.wnl.0000052998.58526.a9
28. Charles A. **The pathophysiology of migraine: implications for clinical management.** *Lancet Neurol* 2018;17(2):174-182 Doi:10.1016/s1474-4422(17)30435-0
29. Schulte LH, Jürgens TP and May A. **Photo-, osmo- and phonophobia in the premonitory phase of migraine: mistaking symptoms for triggers?** *J Headache Pain* 2015;16:14 Doi:10.1186/s10194-015-0495-7
30. Maniyar FH, Sprenger T, Schankin C and Goadsby PJ. **The origin of nausea in migraine-a PET study.** *J Headache Pain* 2014;15(1):84 Doi:10.1186/1129-2377-15-84
31. Wang T, Chen N, Zhan W, Liu J, Zhang J, Liu Q, . . . Gong Q. **Altered effective connectivity of posterior thalamus in migraine with cutaneous allodynia: a resting-state fMRI study with Granger causality analysis.** *J Headache Pain* 2015;17:17 Doi:10.1186/s10194-016-0610-4
32. Andreou AP, Holland PR, Akerman S, Summ O, Fredrick J and Goadsby PJ. **Transcranial magnetic stimulation and potential cortical and trigeminothalamic mechanisms in migraine.** *Brain* 2016;139(Pt 7):2002-2014 Doi:10.1093/brain/aww118
33. Kemp WJ, 3rd, Tubbs RS and Cohen-Gadol AA. **The innervation of the cranial dura mater: neurosurgical case correlates and a review of the literature.** *World Neurosurg* 2012;78(5):505-510 Doi:10.1016/j.wneu.2011.10.045
34. Jouvet M. **Neurophysiology of the states of sleep.** *Physiol Rev* 1967;47(2):117-177 Doi:10.1152/physrev.1967.47.2.117
35. Hoffmann J, Supronsinchai W, Akerman S, et al. **Evidence for orexinergic mechanisms in migraine.** *Neurobiology of disease*, 2015. 74:137-143. DOI:10.1016/j.nbd.2014.10.022
36. Yaksh TL. **Direct evidence that spinal serotonin and noradrenaline terminals mediate the spinal antinociceptive effects of morphine in the periaqueductal gray**. *Brain Research*, 1979 160(1):180–185. DOI:10.1016/0006-8993(79)90616-4
37. Marcus R, et al. **BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo**

controlled, dose-ranging trial. *Cephalalgia*, 2014. 34(2):114-125. DOI:10.1177/0333102413500727

38. Blau JN. **Resolution of migraine attacks: sleep and the recovery phase.** *Journal of Neurology, Neurosurgery & Psychiatry*, 1982. 45(3):223-226. DOI:10.1136/jnnp.45.3.223
39. Smart D, Jerman JC. **The physiology and pharmacology of the orexins**. *Pharmacology & therapeutics*, 2002. 94(1-2):51-61. DOI:10.1016/S0163-7258(02)00171-7
40. Strother LC, Srikiatkhachorn A and Supronsinchai W. **Targeted Orexin and Hypothalamic Neuropeptides for Migraine.** *Neurotherapeutics* 2018;15(2):377-390 Doi:10.1007/s13311-017-0602-3
41. Denuelle M, Fabre N, Payoux P, Chollet F and Geraud G. **Hypothalamic activation in spontaneous migraine attacks.** *Headache* 2007;47(10):1418-1426 Doi:10.1111/j.1526-4610.2007.00776.x
42. Maniyar FH, Sprenger T, Monteith T, Schankin C and Goadsby PJ. **Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks.** *Brain* 2014;137(Pt 1):232-241 Doi:10.1093/brain/awt320
43. Stanyer EC, Creeney H, Nesbitt AD, Holland PR and Hoffmann J. **Subjective Sleep Quality and Sleep Architecture in Patients With Migraine: A Meta-analysis.** *Neurology* 2021;97(16):e1620-e1631 Doi:10.1212/wnl.0000000000012701
44. Baksa D, Gecse K, Kumar S, Toth Z, Gal Z, Gonda X and Juhasz G. **Circadian Variation of Migraine Attack Onset: A Review of Clinical Studies.** *Biomed Res Int* 2019;2019:4616417 Doi:10.1155/2019/4616417
45. Song TJ, Kim BS and Chu MK. **Therapeutic role of melatonin in migraine prophylaxis: Is there a link between sleep and migraine?** *Prog Brain Res* 2020;255:343-369 Doi:10.1016/bs.pbr.2020.05.014
46. Peres MF, Sanchez del Rio M, Seabra ML, Tufik S, Abucham J, Cipolla-Neto J, . . . Zukerman E. **Hypothalamic involvement in chronic migraine.** *J Neurol Neurosurg Psychiatr* 2001;71(6):747-751 Doi:10.1136/jnnp.71.6.747
47. Laurell K, Artto V, Bendtsen L, Hagen K, Häggström J, Linde M, . . . Kallela M. **Premonitory symptoms in migraine: A cross-sectional study in 2714 persons.** *Cephalalgia* 2016;36(10):951-959 Doi:10.1177/0333102415620251
48. Andress-Rothrock D, King W and Rothrock J. **An analysis of migraine triggers in a clinic-based population.** *Headache* 2010;50(8):1366-1370 Doi:10.1111/j.1526-4610.2010.01753.x
49. Bertisch SM, Li W, Buettner C, Mostofsky E, Rueschman M, Kaplan ER, . . . Mittleman MA. **Nightly sleep duration, fragmentation, and quality and daily risk of migraine.** *Neurology* 2020;94(5):e489-e496 Doi:10.1212/wnl.0000000000008740
50. Andreou AP and Edvinsson L. **Mechanisms of migraine as a chronic evolutive condition.** *J Headache Pain* 2019;20(1):117 Doi:10.1186/s10194-019-1066-0
51. Casteren DS, Verhagen IE, Onderwater GL, MaassenVanDenBrink A and Terwindt GM. **Sex differences in prevalence of migraine trigger factors: A cross-sectional study.** *Cephalalgia* 2021;41(6):643-648 Doi:10.1177/0333102420974362
52. Kelman L. **The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs.** *Headache* 2004;44(9):865-872 Doi:10.1111/j.1526-4610.2004.04168.x
53. Cerbo R, Barbanti P, Buzzi MG, Fabbrini G, Brusa L, Roberti C, . . . Lenzi GL. **Dopamine hypersensitivity in migraine: role of the apomorphine test.** *Clin Neuropharmacol* 1997;20(1):36-41 Doi:10.1097/00002826-199702000-00004
54. Amery WK and Waelkens J. **Prevention of the last chance: an alternative pharmacologic treatment of migraine.** *Headache* 1983;23(1):37-38 Doi:10.1111/j.1526-4610.1983.hed2101037.x
55. Karsan N, Bose P, Newman J and Goadsby PJ. **Are some patient-perceived migraine triggers simply early manifestations of the attack?** *J Neurol* 2021;268(5):1885-1893 Doi:10.1007/s00415-020-10344-1
56. Walters AB, Hamer JD and Smitherman TA. **Sleep disturbance and affective comorbidity among episodic migraineurs.** *Headache* 2014;54(1):116-124 Doi:10.1111/head.12168
57. Ødegård SS, Engstrøm M, Sand T, Stovner LJ, Zwart JA and Hagen K. **Associations between sleep disturbance and primary headaches: the third Nord-Trøndelag Health Study.** *J Headache Pain* 2010;11(3):197-206 Doi:10.1007/s10194-010-0201-8
58. Goel N, Rao H, Durmer JS and Dinges DF. **Neurocognitive consequences of sleep deprivation.** *Semin Neurol* 2009;29(4):320-339 Doi:10.1055/s-0029-1237117
59. Banks S and Dinges DF. **Behavioral and physiological consequences of sleep restriction.** *J Clin Sleep Med* 2007;3(5):519-528
60. Killgore WD. **Effects of sleep deprivation on cognition.** *Prog Brain Res* 2010;185:105-129 Doi:10.1016/b978-0-444-53702-7.00007-5
61. Schmid SM, Hallschmid M, Jauch-Chara K, Born J and Schultes B. **A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men.** *J Sleep Res* 2008;17(3):331-334 Doi:10.1111/j.1365-

2869.2008.00662.x

62. Freedom T, Evans RW. **Headache**. *Headache: The Journal of Head and Face Pain* 2013. 53:1358-1366. DOI:10.1111/head.12178
63. Suzuki K, Miyamoto T, Miyamoto M, Suzuki S, Watanabe Y, Takashima R and Hirata K. **Dream-enacting behaviour is associated with impaired sleep and severe headache-related disability in migraine patients.** *Cephalalgia* 2013;33(10):868-878 Doi:10.1177/0333102413477742
64. Wijeratne T, Kuan WS, Kelly AM, Chu KH, Kinnear FB, Keijzers G, . . . Laribi S. **Migraine in the Emergency Department: A Prospective Multinational Study of Patient Characteristics, Management, and Outcomes.** *Neuroepidemiology* 2022;56(1):32-40 Doi:10.1159/000520548
65. Cernuda-Morollón E, Larrosa D, Ramón C, Vega J, Martínez-Camblor P and Pascual J. **Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine.** *Neurology* 2013;81(14):1191-1196 Doi:10.1212/WNL.0b013e3182a6cb72
66. Voss T, Lipton RB, Dodick DW, Dupre N, Ge JY, Bachman R, . . . Michelson D. **A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine.** *Cephalalgia* 2016;36(9):887-898 Doi:10.1177/0333102416653233
67. Goadsby PJ and Sprenger T. **Current practice and future directions in the prevention and acute management of migraine.** *Lancet Neurol* 2010;9(3):285-298 Doi:10.1016/s1474-4422(10)70005-3