

# Current Perspectives on the Impact of Chronic Migraine on Sleep Quality: A Literature Review

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**Objective:** Recent studies have shown that sleep problems occur in migraineurs and poor sleep causes chronification, but the mechanisms by which chronic migraine affects sleep quality are still unknown. This review aims to analyze commonly reported sleep disturbances in chronic migraine (CM) and determine the effect of CM on sleep quality.

**Materials and Methods:** We conducted a comprehensive review of all published articles on CM and sleep quality from inception to March 2022 in the literature. Clinical trials, observational studies, and case series ( $\geq 20$  cases) were included. Two reviewers and a supervisor reviewed the titles and abstracts of all search results with predefined inclusion and exclusion criteria. PubMed search for randomized controlled trials and open studies on CM and sleep quality reported in English between 1983 and 2022 was conducted using the keywords including chronic migraine, sleep, insomnia, sleep quality, polysomnography, and Pittsburgh Sleep Quality Index.

**Results:** A total of 535 potentially relevant articles were found. A total of 455 articles and reviews, meta-analyses published in any language other than English, with other exclusion criteria, were excluded from the review. In the remaining articles, 36 clinical studies, reviewing sleep quality and its association with migraine, were identified and reviewed. Evidence from this review shows that poor sleep and migraine chronicity are intertwined with other accompanying comorbidities and dysregulation of circadian rhythm that innovative treatments promise to bring relief to both poor sleep as well as migraine.

**Conclusion:** Sleep disorders are common in CM and the association between migraine chronification and sleep quality is bidirectional. Comorbid conditions with accompanying frequent attacks in migraine may impair sleep quality. While the maladaptive pain process worsens sleep, poor sleep quality also negatively affects migraine pain. Sleep disturbance, which is affected by worsening migraine attacks, causes deterioration in the quality of life, loss of workforce, and economic burden.

**Keywords:** chronic migraine, sleep, sleep quality, insomnia, sleep disorders

## Introduction

Chronic migraine (CM) is a headache emerging 15 days or more per month for more than three months, which is migraine-like for at least eight days or more per month. It could lead to complications such as work disability, loss of workforce, and deteriorating quality of life.<sup>1</sup> Global studies show that ~1.4–2.2% of the world's population is diagnosed with CM.<sup>2</sup> Clinical studies involving the diagnosis and management of chronic pain are important because of various symptomatology, comorbidities, and risk of disability.<sup>3</sup>

Sleep is one of the most important physiological processes and it is considered a period of rest and recovery for the body.<sup>4,5</sup> Sleep supports cognitive functions, mood, and memory, and ensures the proper functioning of the endocrine and immune systems.<sup>5,6</sup> In addition, sleep is a sensitive regulator of the circadian rhythm, in which biological, environmental (eg exposure to natural light), and behavioral factors are regulated.<sup>7</sup> The association between sleep and migraine is complex and bidirectional, as changes in sleep may trigger migraine and be important in its symptom and treatment.<sup>8</sup>

There is a relationship between migraine and sleep, which has not been fully understood yet in terms of pathogenesis.<sup>9</sup> Insomnia can trigger migraine attacks, and sleep is disrupted during attacks.<sup>10–12</sup> Sleep disorders and headaches overlap clinically and have pathophysiological, anatomical, and physiological similarities.<sup>13</sup> The increasing number of evidence

suggests that there may also be a common underlying etiology. Sleep deprivation, which is associated with migraine pathology,<sup>11</sup> results in decreased pain inhibition and dysfunction of the pathway, leading to the development of central sensitization and pain amplification.<sup>14,15</sup>

Certain lifestyle factors and comorbidities have also been confirmed as risk factors for the development of CM<sup>16</sup> and sleep disturbances are well-known risk factors for migraine chronification.<sup>6,17</sup> Changes in sleep-wakefulness patterns, such as sleep deprivation, and disorders such as insomnia, restless leg syndrome, sleep apnea, and poor sleep quality-duration are also common migraine triggers.<sup>11,18–20</sup> Conditions that disrupt the cycle, such as shift work, may also contribute to the exacerbation of migraine attacks.<sup>21</sup>

Patients with CM have reported shorter nighttime sleep duration compared to those with episodic migraine (EM) and have been more likely to initiate sleep, maintain sleep, and show sleep-inducing headaches. Also, complaints of insomnia symptoms were at least three times more common than in the general population.<sup>22</sup> In contrast, targeted behavioral sleep intervention can provide improvement in headache frequency and conversion from CM to EM.<sup>23</sup>

Poor sleep is often found during the premonitory or postdrome migraine stages.<sup>24,25</sup> Poor sleep quality is associated with the developmental process of CM.<sup>26</sup> Sleep disturbance impairs endogenous pain-relieving function and increases spontaneous pain, especially headache.<sup>27</sup> Studies reported in the literature have tried to explain possible associations between chronic pain and sleep by common biochemical mediators such as serotonin, melatonin, orexins, dopamine, and adenosine, which play a role in both migraines and sleep disorders.<sup>6,28</sup>

Neuroimaging studies on CM have found functional and microstructural changes in the brainstem, hypothalamus, basal ganglia, and cortex, which are involved in pain processing. Changes may be associated with headache frequency and/or duration, insomnia, and other comorbidities such as depression and anxiety.<sup>29–32</sup>

The purpose of this review is to review the effect of CM on sleep quality in light of current scientific literature. Studies will be generally presented in the form of the relationship between CM and sleep, the relationship between etiological causes, and the analysis of sleep quality after migraine treatment. In the literature, there is an increasing number of studies on the relationship between migraine and sleep disorders in contrast to fewer studies discussing the subject of chronic migraine and sleep quality, with most focusing on how poor quality sleep leads to migraine being transformed into its chronic form. In our review, we investigated how sleep-related diagnostic scales or methods can affect sleep as well as treatment interventions.

## Materials and Methods

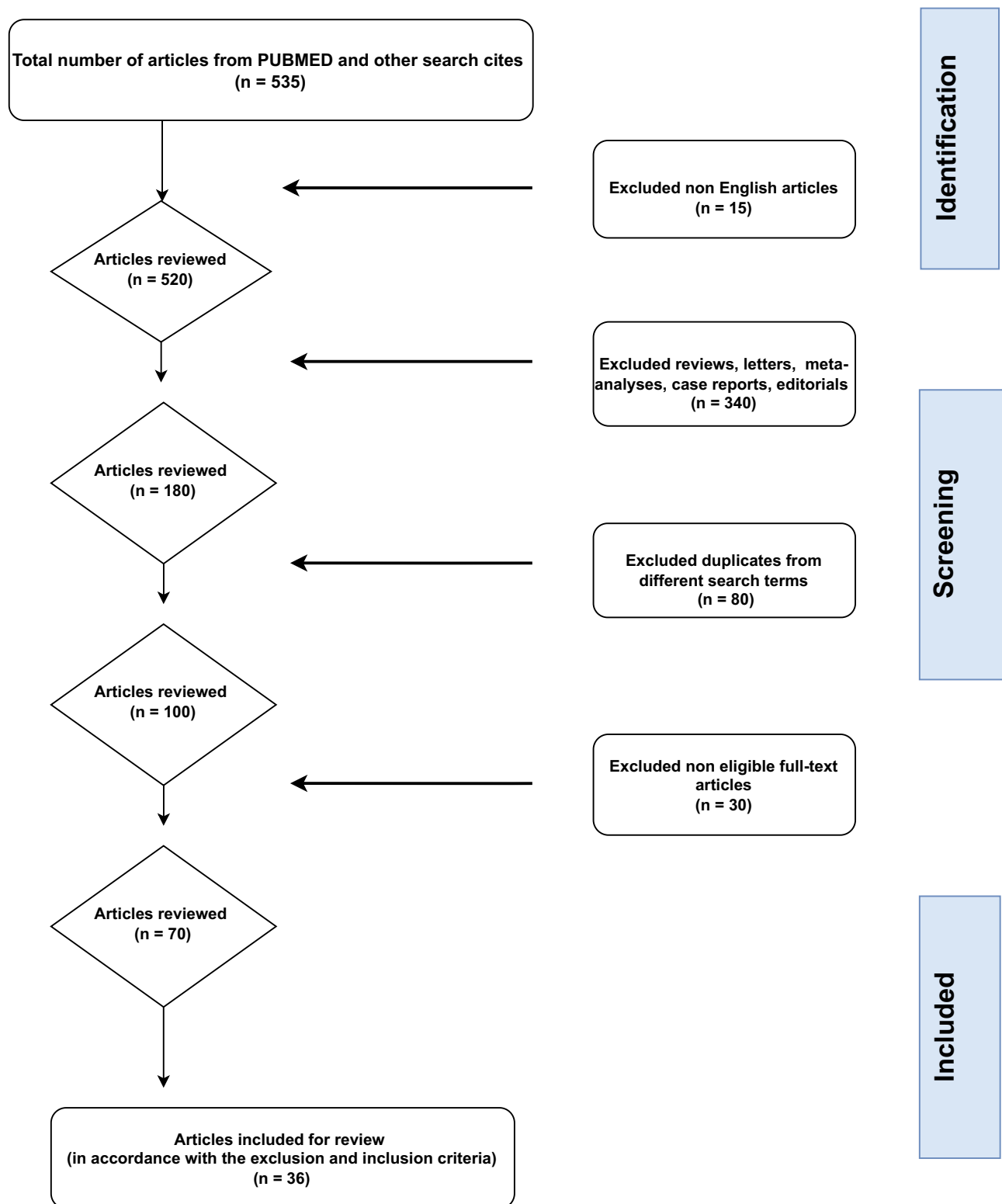
To study the interaction between CM and sleep quality, sleep studies conducted with CM patients older than 18 years of age with no structural lesions in the brain and pregnancy excluded were reviewed. The search was conducted on PubMed and Google Scholar for research articles with  $\geq 20$  cases, and relevant observational studies published between 1983 and 2022 using the keywords chronic migraine, sleep, sleep quality, insomnia, insufficient sleep, insomnia, sleep disorders, polysomnography, actigraphy. The last search date used was March 2022. Articles were selected through an independent, unbiased selection of articles using appropriate keywords. Studies were also distinguished for the initial evaluation by examining the references of the articles. Unpublished studies the full versions of which were unavailable, those that did not diagnose CM according to the “International Classification of Headache Disorders” for the diagnosis of migraine and did not meet the criteria for sleep disorders according to the “International Classification of Sleep Disorders” were excluded.

All abstracts of the articles in English meeting search criteria were reviewed. Figure 1 shows the progress of article selection and the number of articles in each step. The review was conducted with a focus on CM and sleep quality and sleep disorders.

Our article exclusion criteria consisted of review articles, meta-analyses, letters, editorials, case reports or studies with  $< 20$  patients, opinion articles, and abstracts with no full articles published.

## Questionnaires, Scales Used in Studies

In this review, the studies that used the following scales, the validity, and reliability of which was ensured for the respective studies, were analyzed: “Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), International Restless Legs Syndrome study group consensus criteria (IRLSSG), Epworth Sleepiness Scale (ESS), Somatic symptom qualitative and quantitative questioning, Medical Outcomes Study (MOS) Sleep scale, tests six dimensions of sleep,



**Figure 1** Participant flow diagram for sleep updates in chronic migraine patients for this review.

including initiation, maintenance (eg staying asleep), quantity, adequacy, somnolence (eg drowsiness), and respiratory impaired breaths (eg shortness of sleep problems), Sleep quantity score, Sleep Condition Indicator (SCI), Stanford Sleepiness Scale (SSS), SLP6 index, which is a summary of sleep problems based on adequacy, shortness of breath, and somnolence, Dysfunctional Beliefs, and Attitudes about Sleep (DBAS), Pre-sleep arousal scale, Berlin Questionnaire”.

## Results

As a result of the search conducted on electronic databases, 535 articles published between 1983 and 2022 were found for review of titles and abstracts (Figure 1).

The search was completed with a total of 36 articles meeting the search and inclusion criteria for full-text review. These eligible articles were reviewed by two reviewers for eligibility based on the relationship of title, abstract, and statistical results review. Thirty articles could not be accessed even through the library of our university.

The studies reviewed were performed in multiple geographic regions and included case-control, prevalence study, prospective cohort study, and sleep assessment after intervention with interventional-behavioral-digital or drug therapy. The review was carried out by focusing on the studies conducted in the field of CM and sleep and the studies in which we obtained significant statistical results from the relevant research. Studies that did not provide specialized statistics for CM patients among general migraine patients were excluded from the review. In the study, studies in which the relationship between scales and sleep quality was evaluated in general are presented in Table 1, while studies in which sleep was evaluated by applying migraine treatment with medication or other treatments are summarized in Table 2.

## The Role of Sleep in the Chronicity Process and Accompanying Comorbidities

Headache, a progressive form characterized by increases in frequency, severity, duration, and resistance of migrainous attacks may evolve into CM<sup>33</sup> and chronicity occurs in about 3% of EM patients.<sup>34,35</sup> The coexistence of neural pathways involved in pain processing and genetic factors is responsible for this course.<sup>36</sup>

Various comorbidities and risk factors associated with migraine chronification are well defined.<sup>16,35</sup> Identified triggers and aggravating factors appear as emotional and physical stress, nutrition, and sleep disturbances.<sup>37,38</sup> Poor sleep plays an important role in the chronicity process.<sup>39</sup> Lifestyle and behavioral changes, and acute and prophylactic treatments should be planned together to reduce the frequency, severity, and duration of migraine attacks.<sup>40</sup>

Understanding specific comorbidities in migraine is important for several reasons. First, recognition of migraine comorbidities may help understand the genetic or biological mechanisms that support the development of new treatments and facilitate disease management, and may also improve prognosis.<sup>41</sup> The identification of migraine comorbidities can also help in the development of new treatments for subgroups and the recognition of underlying biological diseases.<sup>42</sup>

## Sleep Disorders and the Importance of Circadian Rhythm in Chronic Migraine

Previous studies evaluated a wide spectrum of sleep disorders commonly seen in migraine patients, including insomnia, increased daytime sleepiness, poor sleep quality, prolonged sleep latency, sleep apnea, restless legs syndrome, and parasomnia.<sup>6,43</sup> In patients with CM, headache is highly accompanied by insomnia, poorer sleep, sleep disturbances, and sleep insufficiency.<sup>44</sup>

It has been suggested that excessive sleep and sleep deprivation are the most common causes of morning migraine attacks.<sup>45</sup> Problems such as sleep deprivation, excessive sleeping, or inability to sleep regularly may be an important factor in the transition from the episodic to the chronic form of migraine.<sup>9</sup> Most of the available data in the literature comes from self-administered self-report scales. In our review, by PSQI, ISS, IRLSSG, ESS, qualitative and quantitative questioning of somatic symptoms, we observed a high rate of concomitant sleep disorders, insomnia, RLS, and increased daytime sleepiness, impaired sleep quality, and snoring in CM patients.<sup>41,46–53</sup> However, it is noteworthy that there are differences in the studies conducted. Rothrock et al's study of a quantitative investigation of migraine triggers showed that too much or little sleep was not a trigger with increased risk for chronic migraineurs, contrary to expectations. They identified a correlation between having more frequent migraine headaches or longer exposure to the disease and improved ability to identify and compensate for triggers.<sup>54</sup> Viana et al found insomnia comorbidity severe enough to require hypnosis in the CM-drug overuse headache (MOH) group. They also found the rate of snoring to be higher in the chronic group than in the EM group.<sup>49</sup>

**Table I** Summary of Results from Published Studies of CM and Sleep Without Treatment Intervention

First Author, Year, Center, Title	Number – Gender of Patients	Study Design	Sleep Scales	Results
Pedron et al, 2022, Spain “Predictive factors of sleep quality in patients with chronic migraine”	Included: 50 CM patients, 92.6% patients were female	An observational, cross sectional study	PSQI	Depressive symptoms, pain, and headache-related disability were found to be predictors of poor sleep quality (33%).
Stefano et al, 2021, Italy “Social Distancing in Chronic Migraine during the COVID-19 Outbreak: Results from a Multicenter Observational Study”	Included: Total 261 patients, 186 (71.3%) had CM, 227 (87%) patients were female	An observational study, May 2020–July 2020	ISI	Median total ISI score increased ( $p < 0.001$ ), monthly headache days increased ( $p < 0.001$ ) during social distancing in all groups.
Curro et al, 2021, Italy “Chronic migraine in the first COVID-19 lockdown: the impact of sleep, remote working, and other life/psychological changes”	Included: 92 CM patients, 85.9% patients were female	An observational cross-sectional study	PSQI	Increased migraine attack/frequency, decreased sleep duration/ quality, prolonged sleep latency and higher PSQI score were associated with worsening depression/anxiety.
Yin et al, 2020, Taiwan “Prevalence and association of lifestyle and medical-, psychiatric-, and pain-related comorbidities in patients with migraine: A cross-sectional study”	Included: 1257 participants, 179 controls; (311 CM and 946 EM patients)	A cross-sectional observational study	Participants were questioned in terms of sleep and other comorbidities in a structured interview	Insomnia was detected in 46% in CM patients and 30.7% in EM patients ( $p < 0.001$ ).
Buse et al, 2019, USA “Sleep Disorders Among People With Migraine: Results From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study”	Included: 1111 with CM (8.7%) patients, 11,699 with EM (91.3%) patients	CaMEO Study, longitudinal design with web-based cross-sectional surveys	Berlin Questionnaire for Sleep Apnea, MOS Sleep Measures	MOS sleep scale components values showed worse sleep quality among those with CM ( $p < 0.001$ ). 37.0% were at “high risk” for sleep apnea based on the Berlin Questionnaire those with CM.
Ceylan et al, 2019, Turkey “Coexistence of Symptoms Associated with Trigeminal Pathways in Chronic and Episodic Migraine and the Effects on Quality of Life”	Included: 183 CM patients, 897 EM patients, 893 (82.8) were female	A cross sectional study, March 2013–August 2015	PSQI	Sleep latency was longer in 16.7% of EM patients. However, in CM, it was found to be 39.3% ( $p < 0.001$ ).
Ong et al, 2018, Chicago “Can Circadian Dysregulation Exacerbate Migraines?”	Included: 20 CM patients, 20 controls, all of patients female	A prospective observational pilot study	Wrist actigraphy, MEQ, DLMO	In CM, the number of painful days per month was significantly correlated with DLMO and later sleep episode ( $p < 0.05$ ).

(Continued)

Table 1 (Continued).

First Author, Year, Center, Title	Number – Gender of Patients	Study Design	Sleep Scales	Results
Tommaso et al, 2018, Italy “Circadian rhythms of migraine attacks in episodic and chronic patients: a cross sectional study in a headache center population”	Included: 196 CM patients, 590 EM patients, females prevailed in both groups	A cross sectional study, January 2015–January 2017	MOS2, headache diaries for 3 months	CM patients did not differ in circadian rhythm pattern in migraine attacks compared to EM group with their attacks.
Viana et al, 2018, Italy “Factors associated to chronic migraine with medication overuse: A cross-sectional study”	Included: 156 EM patients, 63 from CM-MOH	A cross-sectional study	Insomnia and snoring were questioned quantitatively	Snoring was high in CM-MO patients and severe insomnia requiring the use of hypnotic was associated with CM-MOH.
Lin et al, 2016, Taiwan “Prevalence of restless legs syndrome in migraine patients with and without aura: a cross-sectional, case-controlled study”	Included: 372 patients; 57 CM-133 controls; 39 (68.4%) were female in CM group	A cross-sectional, case-controlled study, January 2014–December 2015	IRLSSG consensus criteria, PSQI	RLS frequency was higher in the chronic migraine frequency group than the control group, and total PSQI scores were also associated with higher RLS prevalence.
Smitherman et al, 2016, USA “Randomized Controlled Pilot Trial of Behavioral Insomnia Treatment for Chronic Migraine With Comorbid Insomnia”	Included: 16 CM patients, 15 controls	A single site, prospective, randomized controlled pilot trial, June 2011–March 2013	Behavioral insomnia treatment, Actigraphy, PSQI, ESS,	Total sleep time and sleep efficiency as measured by actigraph and PSQI scoring improved after treatment ( $p < 0.05$ ).
Lucchesi et al, 2016, Italy “Fatigue, sleep–wake pattern, depressive and anxiety symptoms and body-mass index: analysis in a sample of episodic and chronic migraine patients”	Included: 75 CM, 75 EM without aura	A cross-sectional study	ESS, PSQI	PSQI score was found to be higher in patients with CM ( $p < 0.015$ ) ESS score was similar between groups (0.727).
Verma et al, 2016, India “Study of Sleep Disorders and Polysomnographic Evaluation among Primary Chronic Daily Headache Patients”	Included: Total 83 patients, 31 (37.3%) were CM patients, 50 (60.2%) were CTTH patients	A prospective, hospital-based observational study	Overnight PSG, Sleep diaries, ESS and insomnia symptom score.	Sleep efficiency and stage 3 sleep were lower in CM group compared to the CTTH. There was no significant relationship between PSG parameters in patients with sleep disorders in both groups.
Tommaso et al, 2014, Italy “Sleep features and central sensitization symptoms in primary headache patients”	Included: 2135 Primary headaches patients were analyzed in 10 groups, 333 CM patients, 280 patients were female	A case-control study, January 2012–December 2013	MOS, Sleep Problems Index II (9 items) and the Sleep Problems Index I (six items), Sleep quantity	CM patients, short sleep time, central sensitivity symptoms and the amount of sleep reduced according to other groups. MOS scores did not show results related to the correlation with the symptoms of the central sensitization between the groups.

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Table 1 (Continued).

First Author, Year, Center, Title	Number – Gender of Patients	Study Design	Sleep Scales	Results
Barbanti et al, 2013, Italy “A case-control study on excessive daytime sleepiness in chronic migraine”	Included: 100 CM patients (92 92% female), 100 controls	A case-control study, June 2010–May 2011	ESS, MIDAS, PSQI	Total PSQI and subscale analysis scores were higher in patients than in controls ( $p < 0.01$ ).
Houle et al, 2012, USA “Stress and Sleep Duration Predict Headache Severity in Chronic Headache Sufferers”	Included: 33 CM and 22 CTTH	A reanalysis of a previously published, observational, paper-pencil diary study	Stress ratings, duration of previous nights' sleep	Modeled data suggest that two consecutive days of sleep reduction is associated with an increased risk of headaches; Headache severity ratings were inversely related to sleep duration.
Lucchesi et al, 2012, Italy “Evidence of increased restless legs syndrome occurrence in chronic and highly disabling migraine”	Included: 102 patients CM, 175 patients EM, 200 controls	A case-control study, January 2011–September 2011	IRLSSG criteria (2003), PSQI	RLS was diagnosed in 28 (16%) of 175 EM patients and 35 (34.3%) of 102 CM patients ( $p = 0.0006$ )
Rothrock et al, 2010, USA “An Analysis of Migraine Triggers in a Clinic-Based Population”	Included: 200 patients, 144 (72%) had CM, others EM	A sub-study of a larger project	Migraine triggers investigated quantitatively (much or little sleep)	Patients with CM and EM were similarly affected by the more or less as a sleep trigger.
Maizels et al, 2004, CA “Somatic Symptoms in Headache Patients: The Influence of Headache Diagnosis, Frequency, and Comorbidity”	Included: 289 patients, 162 CM, others EM	Sixth month follow-up questionnaires were mailed to all study participants.	Somatic symptoms questioned with PHQ-15	Insomnia was more common in the CM group compared to EM group ( $p < 0.001$ ).
Peres et al, 2001, Brazil “Hypothalamic involvement in chronic migraine”	Included: 17 patients with CM and nine age and sex matched healthy volunteers were included.	Longitudinal cross-sectional study in which hormone determinations were performed hourly for 12 hours	Melatonin, prolactin, growth hormone, and cortisol concentrations were determined every hour for 12 hours.	A delayed nocturnal melatonin peak in patients with CM and lower melatonin concentrations in patients with CM with insomnia.

**Note:**  $p < 0.05$  is statistically significant.

**Abbreviations:** CM, chronic migraine; EM, episodic migraine; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; MOS, Medical Outcomes Study; MEQ, Morningness-Eveningness Questionnaire; DLMO, dim light melatonin onset; MOS, MOS2 sleep quantity score; IRLSSG, International Restless Legs Syndrome Study Group consensus; ESS, Epworth Sleepiness Scale; MOH, medication overuse headache; CTTH, chronic tension type headache; PHQ-15, Patient Health Questionnaire-15 (Somatic Symptom Severity Scale); PSG, polysomnography.

## Insomnia, RLS in Chronic Migraine

Insomnia-related mechanisms emphasize hyperalgesic state resulting from reduced inhibition of the pain pathway, caused by sleep deprivation and fragmented sleep, as well as the importance of desensitization of nociceptors by increased proinflammatory cytokine cascade.<sup>49</sup> Again, in the CaMEO study, the study in which extensive web-based analysis was performed, the rates of both snoring and insomnia were high in CM, compared to EM, according to the MOS sleep scale and Berlin questionnaire.<sup>18</sup> Similarly, Lucchesi et al and Ceylan et al reported a higher PSQI score in CM compared to EM, but Lucchesi et al found similar levels of daytime sleepiness in the EM and CM groups.<sup>50,51</sup>

In another study investigating RLS and sleep quality in CM and EM, the rate of RLS was high in CM patients, and sleep quality worsened in patients with RLS.<sup>52</sup> For this study, CM patients were overweight, which is a risk factor for



**Table 2** Summary of Findings from Studies Evaluating the Effect of Various Treatments for CM on Sleep Quality

First Author, Year, Center, Title	Number – Gender of Patients	Study Design	Applied Treatments and Sleep Scales	Results
Icco et al, 2021, Italy “Anodal transcranial direct current stimulation in chronic migraine and medication overuse headache: A pilot double-blind randomized sham-controlled trial”	Included: 20 patients CM and MOH, 16 (80%) patients were female	A randomize, double blind, sham controlled trial	Transcranial direct stimulation, SCI, PSQI, SSS	Sleep disturbances (SCI and PSQI scores) were significantly improved in the overall population ( $p < 0.05$ ) after treatment.
Saçmacı et al, 2021, Turkey “Clinical success of greater occipital nerve blockade in improving sleep quality of chronic migraineurs: a prospective observational study”	Included: 37 CM patients, 31 (84%) patients were female	A prospective observational study, December 2018–February 2020	GON-B (for three months), PSQI, ESS, DBAS, ISI, Pre-sleep arousal scale	Improvement in all sleep scales after treatment ( $p < 0.001$ ), monthly headache days decreased ( $p < 0.001$ ).
Russo et al, 2020, Italy “Multidimensional assessment of the effects of erenumab in chronic migraine patients with previous unsuccessful preventive treatments: a comprehensive real-world experience”	Included: 70 CM patients, 55 (78.6) patients were female	An observational, prospective, non randomized, open-label study, February 2019–July 2019	Monthly erenumab 70 mg sc or 140 mg dose for six months, MOS Sleep Scale	Sleep quality improved significantly after treatment ( $p < 0.05$ ).
Crawford et al, 2020, US “Digital Cognitive Behavioral Therapy for Insomnia in Women With Chronic Migraines”	Included: 35 CM patients, all of them were female	A case control observational study	Digital Cognitive Behavioral Therapy for 12 weeks, ISI, Sleep Diaries	ISI was significantly reduced at post treatment ( $p < 0.05$ ).
Ulusoy et al, 2020, Turkey “The effect of greater occipital nerve blockade on the quality of life, disability and comorbid depression, anxiety, and sleep disturbance in patients with chronic migraine”	Included: 84 CM patients, 72 (85.71%) patients were female	A prospective, cross-sectional study June 2018–March 2019	GON-B (for three months), PSQI	PSQI scores decreased clinically significantly after treatment and between monthly treatments ( $p < 0.001$ ).
Packard et al, 2020, USA “Effect of circadian rhythm on the pain associated with preventive onabotulinumtoxinA injections for migraines”	Included: 61 CM patients, 34 (87%) patients were female	Injector blind randomly selected study, October 2018–December 2019	BotulinumtoxinA (circadian time dependent-injection; morning or afternoon) as chronotherapeutics	The study found that chronotherapeutically, BTA injection in the morning was more painful than in the afternoon ( $p < 0.05$ ).



Blumenfeld et al, 2019, USA “Effects of onabotulinumtoxinA treatment for chronic migraine on common comorbidities including depression and anxiety”	Included: 373 CM patients, most of the group were female	COMPEL study was a multicentre, open-label, prospective study	OnabotulinumtoxinA 155U for nine treatment cycles, PSQI	PSQI score decreased significantly after treatment, fatigue symptom improved ( $p < 0.0001$ ).
Barad et al, 2019, USA “Response to BotulinumtoxinA in a Migraine Cohort with Multiple Comorbidities and Widespread Pain”	Included: 402 CM patients, 83% patients were female	A sequential retrospective observational cohort study	OnabotulinumtoxinA injections, Sleep Impairment and Disturbance assessed by querying with NIH PROMIS scale	This study demonstrates that patients with medically complex migraine may be particularly resistant to treatment with onabotulinumtoxinA. Attention was drawn to the need for a multidisciplinary approach
Loeb et al, 2018, Brasil “Botulinum toxin A (BT-A) versus low-level laser therapy (LLLT) in chronic migraine treatment: a comparison”	Included: 36 CM patients (each groups 18 patients), 30 patients were female	A preliminary pilot study	Botulinum toxin A (BT-A), LLLT, Sleep quality were qualitative score on a scale	Sleep quality increased more significantly in the LLLT group than in the BT-A group.
Rodrigo et al, 2017, Spain “Occipital Nerve Stimulation for Refractory Chronic Migraine: Results of a Long-Term Prospective Study”	Included: 37 refractory CM patients, 33 were female	An uncontrolled open label design, June 2002–June 2013	ONS, Sleep quality (Normal, bad, very bad)	Sleep quality returned to normal in 91% of patients, and pain intensity and drug use decreased.
Aydinlar et al, 2017, Turkey “OnabotulinumtoxinA effectiveness on chronic migraine, negative emotional states and sleep quality: a single-center prospective cohort study”	Included: 190 CM patients, 167 (87.9%) patients female	A single-center prospective cohort study, May 2012–May 2016	OnabotulinumtoxinA (for 48 weeks), PSQI	While no significant changes were noted in overall sleep quality, patients who were not initially depressed showed significant improvement in sleep quality.
Lin et al, 2016, Taiwan “Associations Between Sleep Quality and Migraine Frequency A Cross-Sectional Case-Control Study”	Included: 357 patients, 34 CM patients and the remaining migraine groups according to monthly pain frequency numbers and 134 controls	A cross sectional controlled study, June 2015–May 2015	Cognitive-behavioral therapy, actigraphy, PSQI	PSQI total scores were highest for the high frequency and CM groups, high migraine frequency and RLS screening scores were identified as independent factors of poor sleep.

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**Table 2** (Continued).

First Author, Year, Center, Title	Number – Gender of Patients	Study Design	Applied Treatments and Sleep Scales	Results
Kinfe et al, 2015, Germany “Cervical non-invasive vagus nerve stimulation (nVNS) for preventive and acute treatment of episodic and chronic migraine and migraine-associated sleep disturbance: preliminary findings from a prospective observational cohort study”	Included: 20 patients, 10 patients were CM, 10 patients were EM, 16 (80%) were female	An open label, prospective, observational cohort study	Non-invasive vagus nerve stimulation PSQI	Global PSQI score was reduced (sleep latency, daytime dysfunction).
Calhoun et al, 2007, USA “Behavioral Sleep Modification May Revert Transformed Migraine to Episodic Migraine”	Included: 43 women with transformed migraine	A randomized, single-blind, placebo-controlled pilot study	Patients were randomized to receive behavioral sleep instructions and placebo behavioral instructions	Behavioral sleep therapy resulted in improvement in headache frequency and reversal of episodic migraine ( $p = 0.001$ ).
Peres et al, 2006, Brazil “Chronic migraine prevention with topiramate”	Included: 50 CM patients, 40 (80%) had female	An observational evaluation study of treatment success methodologically	Effective dose topiramate therapy (for 12 weeks), Insomnia side effect qualitatively investigated	Insomnia was detected (2 patients, 4%).
Saper et al, 2001, New England “Nefazodone for Chronic Daily Headache Prophylaxis: An Open-Label Study”	Included: 52 patients, 48 (92%) had CM	A two center, open-label study	Nefazodone 300 mg (5HT2 antagonist) 16 weeks treatment, Visual analog score assessment in terms of sleep	Significant improvement in sleep score after treatment ( $p < 0.00001$ )

**Note:**  $p < 0.05$  is statistically significant.

**Abbreviations:** CM, chronic migraine; EM, episodic migraine; MOH, medication overuse headache; SCI, Sleep Condition Indicator; SSS, Stanford Sleepiness Scale; GON-B, greater occipital nerve block; ESS, Epworth Sleepiness Scale; DBAS, Dysfunctional Beliefs and Attitudes about Sleep; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; MOS, Medical Outcomes Study Sleep Scale; LLLT, low level laser therapy; ONS, occipital nerve stimulation.

apnea. Shortness of breath as poor sleep quality with a high risk of chronification (17.0 vs 9.5), and daytime somnolence (33.2 vs 21.9), sleep adequacy (38.7 vs 60.5) were less in these patients compared to those with episodic migraine.

## Central Sensitization, Circadian Rhythm, Melatonin in Chronic Migraine

Tommaso et al investigated central sensitization in the form of detailed interviews in all primary headache groups (including CM) with MOS, the Sleep Problems Index (SLP6), sleep quantity (SLPQRAW) scales and found that sleep duration was decreased in the CM group about short sleep duration, central sensitivity symptoms, and chronicity in CM patients. However, MOS scores did not correlate with central sensitization symptoms between the different groups.<sup>53</sup> The study also emphasized that the relationship between allodynia, pericranial sensitivity, and short sleep characterizes chronic migraine more than other primary headaches. Increased frequency of headaches and unexpected nocturnal or early morning awakenings may cause sleep fragmentation; difficulty falling asleep and lack of sleep are triggers for the majority of patients with migraine.<sup>55</sup> Cutaneous allodynia, which is a prominent symptom during migraine attacks, has been shown to worsen in response to REM sleep deprivation,<sup>56</sup> which may indicate the importance of allodynia in the wakefulness-REM-NREM transitions in migraine. They discussed that the triggering mechanism between chronic pain attack and sleep may be due to the interaction between the circadian rhythm influence and the inhibition of the nociceptive pathway as a result of increased expression in orexin receptors.<sup>53</sup>

In their study investigating the circadian rhythm difference in attacks using MOS, and sleep quantity score, the authors did not find a rhythm difference in the time of onset of headache in CM patients compared with EM.<sup>57</sup> In another study evaluating the circadian periodicity of migraine patients, migraine attacks were frequently in the early morning hours, and the study characterized patients with an early chronotype.<sup>58</sup> However, Tommaso et al<sup>57</sup> discussed the inadequacy of the consistency of headache diaries and the inclusion of only chronically followed patients as limitations in their study.

In the majority of studies, circadian differences found in patients with headache showed the greatest pain sensitivity at night and in the early morning,<sup>59,60</sup> and CM patients who received botox as their headache treatment also found that morning therapy was more painful.<sup>61</sup> Among the studies conducted to show the place and importance of the circadian rhythm in CM, in a pilot study comparing EM and CM patients, Ong et al conducted wrist actigraphy and Dim light melatonin onset (DLMO) measurements. In CM, the number of headache days per month was significantly associated with DLMO and later sleep episodes.<sup>62</sup> There was no evidence that individuals with CM would have a delayed circadian phase compared to healthy subjects. They pointed out that circadian dysregulation may be an explanatory bridging mechanism between CM and insomnia and other comorbidities. Melatonin to be used in the treatment of migraine may improve the circadian phase and provide positive bidirectional interaction for both headaches and sleep.<sup>62</sup>

Peres et al collected serum for hourly hormone determination for 17 hours and 12 hours in CM and the control group to monitor hypothalamic and pineal functions. As for one of the hormones tested, melatonin, they found a delayed nocturnal melatonin peak in patients with CM and lower concentrations of melatonin in patients with CM accompanied by insomnia.<sup>63</sup> Apart from the small sample size of the study, the fact that drug detoxification was provided and that patients with accompanying insomnia provided a clear diagnosis also provide valuable data. The circadian rhythm of melatonin secretion is regulated by the suprachiasmatic nucleus in the hypothalamus.<sup>64</sup> The results of the study supported the theory that hypothalamic involvement in CM causes a chronobiological dysfunction. While the interpretation of migraine as a cause or a result cannot be made, it has also been discussed that it may be related to sleep disorders. This study emphasized that melatonin is an endogenous scavenger and may be an alternative in treatment.

For circadian periodicity of pain, ion channels involved in pain responses are thought to be managed by circadian variations in the expression and activity levels. Pro-inflammatory cytokines, chemokines secreted by control genes of non-clock gene expressions and hormone concentrations as well as glial activity levels regulate the circadian rhythm.<sup>65</sup> In addition, prodromal insomnia with an increase in the number of nighttime awakenings before the migraine attack has been reported. Disruption of REM sleep is among the findings discussed as an underlying mechanism of untimely awakening and nocturnal migraine attacks.<sup>12</sup>

## Predictors of Sleep Disturbance in Chronic Migraine

Sleep disturbance, increased headache frequency, analgesic overuse, and depression are the strongest risk factors for the new onset of CM.<sup>44,66</sup> In a recent study investigating the predictors of sleep quality, Pedrón et al showed that depressive symptoms, pain, and headache-related disability had a 33% role in affecting sleep quality.<sup>67</sup>

Another study investigating the effect of isolation of the COVID process on insomnia recently demonstrated that there was an increase in monthly headache frequency and ISI score with isolation in migraine groups, most of which comprised CM patients.<sup>68</sup> Currò et al showed that in CM sufferers during the COVID quarantine period, decreased sleep duration and quality, prolonged sleep latency, and ultimately higher PSQI values were associated with worsening depression/anxiety and increased migraine attack frequency. This study showed that reduced sleep duration is associated with an increase in migraine attack duration and pain.<sup>69</sup>

Stress is the trigger for poor sleep and migraine chronification.<sup>21,70</sup> Quarantine is a lifestyle that increases stress.<sup>71</sup> Ultimately, different circadian habits and decreased physical activity associated with stress, anxiety, or depression may affect patients' sleep disturbances, leading to a potential increase in migraine attack frequency.<sup>72</sup> A previous review suggested that conditions such as stress levels increasing with disruption of the sleep-wakefulness cycle, and shift work may also contribute to an exacerbation of migraine attacks.<sup>21</sup>

High attack frequency in CM was associated with poor and weak sleep; sleep with incomplete restoration is seen as poor sleep habits, short sleep time, and longer sleep latency.<sup>44</sup> Fragmented sleep is generally not restorative and negatively affects daytime performance; moreover, reduced sleep efficiency and increased waking up after sleep onset have recently been identified as a trigger for migraine.<sup>73</sup>

Regarding the effects of migraine on sleep quality, we examined the vulnerabilities that should be emphasized because both of them create a negative interaction with each other. Anxiety, stress, depression, pain and sleep problems negatively affect the daily living activities and lives of individuals and become a great burden on both sleep and CM in terms of providing treatment modalities always in cooperation with different disciplines.

## Common Pathophysiological Mechanisms in Migraine and Sleep

Insomnia is the most common sleep disorder among migraine sufferers and the relationship appears to be bidirectional.<sup>74</sup> Many studies in the literature discussed that insomnia triggers migraine. However, it has also been noted that migraine is a precursor to insomnia.<sup>75</sup> Fragmented sleep caused by migraine headaches can lower the pain threshold, as well as increase the risk of migraine attacks due to their role in the pathophysiology of monoaminergic disorders such as serotonin and dopamine that occur in sleep disorders. As a result, migraine and sleep disorders have been hypothesized to have a possible similar pathogenetic role.<sup>11</sup>

In addition, adenosine levels rise during migraine attacks and induce sensitivity to pain.<sup>76</sup> In the case of sleep deprivation, overstimulation of A1 receptors and adenosine overload is a possible mechanism that modulates neuronal activity and CSD because adenosine A1 receptor activation contributes to the persistent secondary phase of Leão's cortical spreading depression developing in the attack.<sup>77,78</sup>

Despite the emphasis on the effectiveness of orexinergic pathways and the importance of melatonin treatment in migraine patients, it is obvious that there is still a lack of sleep quality in migraine. This leads researchers to conduct further studies on sleep in migraine.<sup>79</sup> The hypothalamic orexinergic system plays a critical role in sleep/wakefulness transitions and stabilizing REM sleep and has been linked to migraine.<sup>80</sup>

Calcitonin gene-related peptide (CGRP), a neuropeptide known to be a major player in migraine, may play a role in regulating nighttime sleep maintenance.<sup>81,82</sup> A clear understanding of the etiological disorders can reduce the risk of chronicity with the identification and treatment of both sleep disorders and migraine.<sup>83</sup>

The varying volume of various regions of the prefrontal cortex, occipital lobe, right putamen, 4th ventricle, optic chiasm, and thalamus in migraine patients may indicate central plasticity in the pathogenesis and chronification of migraine.<sup>84</sup> Chen et al's study reported that basal forebrain volume was negatively associated with the sleep disturbance scale, supporting that altered basal forebrain may be associated with poorer sleep in migraine patients.<sup>84</sup> It should also be

noted that the deep gray matter structure and the thalamus, which is responsible for the modulation of visual information in migraine, have a role in regulating the sleep-wakefulness cycle.<sup>85</sup>

During sleep, the glymphatic system, which functions as a CNS waste clearance system and helps clear abnormal proteins, is responsible for a wide variety of homeostatic functions. Since glymphatic activity is primarily a sleep-related activity, dysregulation of sleep processes can result in the accumulation of CNS wastes with nociceptive properties; this supports the view that how sleep triggers migraine, how it relieves migraine, and how it contributes to migraine chronification.<sup>11</sup>

## Evaluation of Sleep Quality After Treatment of Chronic Migraine

Comorbid conditions complicate the treatment of migraine. Current migraine treatments either reduce pain or prevent the occurrence of migraine.<sup>86</sup> The treatment algorithm was arranged based on the relationships between migraine, sleep disorders, triggers, and psychiatric conditions. The sleep diary is the gold standard in headache management to identify triggers, confirm the diagnosis, guide behavioral therapy, and evaluate outcomes.<sup>74</sup> If there is accompanying insomnia, hypnotics, and cognitive behavioral treatment may be beneficial, if there is insomnia with accompanying anxiety - depression, migraine prophylaxis with sedative antidepressants or anticonvulsants may provide relief, while hypersomnia requires neutral or more stimulant drugs.

In studies investigating the role and place of treatments applied in CM in regulating sleep quality, transcranial direct stimulation, GON-B, monthly erenumab therapy, digital cognitive behavioral therapy, botulinum toxin, occipital nerve stimulation, cognitive-behavioral therapy, behavioral insomnia treatment, non-invasive vagus nerve stimulation (nVNS), effective dose topiramate therapy and nefazodone treatment as 5HT<sub>2</sub> antagonist have been examined in comparison with many other scales, especially PSQI, and actigraphy, and the quality of sleep was evaluated after the treatments applied. Groups have sometimes been studied in groups with medication overuse headache patients or chronic tension headache patients.

Starting with the most recent, Icco et al demonstrated that in the study of patients receiving double-blind controlled treatment, after transcranial direct stimulation procedure was evaluated with SCI, PSQI, and SSS scales, sleep quality improved with treatment.<sup>87</sup> In the studies of Saçmacı and Ulusoy, in which the effects of GON-B treatment in CM were evaluated, after 3 months of migraine treatment, sleep quality and insomnia improved with PSQI and other scales, and even according to Saçmacı et al's study, daytime sleepiness level decreased, pre-arousal states before sleep and even dysfunctional behaviors and attitudes towards sleep improved.<sup>88,89</sup> GONB treatment may be initially considered if comorbidities such as stress, depression and sleep disturbance are high in CM patients with few treatment options.<sup>88</sup>

Behavioral insomnia therapy accompanied by actigraphy was found to result in significant improvements in total sleep duration and sleep efficiency according to both actigraphy and PSQI in patients with CM accompanied by insomnia.<sup>90</sup> In the general migraine patient group with CM at a rate of 9.5%, the PSQI score was the highest in the group with CM. In addition, increased migraine frequency and RLS are independent risk factors for poor sleep.<sup>12</sup> Digital cognitive therapy was applied for 12 weeks to patients with insomnia and CM significantly improved insomnia.<sup>91</sup>

In a study of patients with large CM series,<sup>92</sup> Blumenfeld et al showed that sleep quality reported by PSQI improved after botox treatment, whereas Aydınlar et al's study with prospective series demonstrated that sleep quality did not significantly improve compared to PSQI in patients with initially intense depressive features.<sup>93</sup> Other comorbidities, such as accompanying depression, are obstacles to treatment success. Loeb et al found the therapeutic effect of Laser therapy and botox therapy on sleep in favor of LBBT in their group comprising patients with CM.<sup>94</sup> In a study, however, the successful ameliorative effects of botox treatment on pain frequency and severity and depression in the CM group with high comorbidities could not be demonstrated objectively on sleep, and the need for multidisciplinary treatment was emphasized.<sup>95</sup> Onabotulinumtoxin A treatment may help improve sleep in migraine patients by reducing the amount of activated CGRP.<sup>96</sup>

Rodrigo et al proved the success of occipital nerve stimulation therapy in improving sleep quality, finding that it resulted in improvement in 91% of 37 patients with refractory CM.<sup>97</sup> They showed that there was an overall improvement in the PSQI score in the "sleep delay and daytime dysfunction" subgroups in EM and CM patients treated with non-invasive vagus nerve stimulation (nVNS).<sup>98</sup>

In a study conducted to elucidate the possible side effects of topiramate therapy, used in the treatment of migraine, on sleep, they showed that only two (4%) of 50 patients who tried topiramate therapy had a side effect of insomnia.<sup>99</sup> In the

evaluation of the 5HT2 antagonist Nefazodone treatment in patients mostly with CM, post-treatment sleep score as a visual analog scale improved significantly.<sup>100</sup> Russo et al proved that after a 6-month monthly erenumab treatment, there was a significant improvement in sleep quality according to MOS Sleep Scale.<sup>101</sup> In conclusion, studies, consistent with the literature, show that preventive chronic migraine treatments, behavioral interventions such as BDT, and relaxation training also improve sleep in migraine patients.<sup>102</sup>

## Summary of a Sleep Disorder in CM

First of all, it is necessary to recognize the comorbidities associated with chronic migraine and to understand the importance of sleep and the way it interacts with other risk factors. Each of these diseases is intertwined. In our review, sleep was mainly analyzed using scale approaches, and it is noteworthy that especially there are a limited number of studies utilizing polysomnographic and biochemical methods. In addition, there are fewer studies investigating the effect of pure chronic migraine on sleep, with existing studies more commonly focused on treating chronic headaches or the episodic group. Some studies have mentioned a pathway that can adapt to the chronic process, while others have discussed the transformation of the chronic process into a maladaptive process. Also, more elaborative studies have not addressed all sleep disorders. Again, a more comprehensive evaluation has not been made for chronicity, whether it is poor sleep or frequent attacks. Although there are several experimental studies on pain pathways and sleep mediators for chronic migraine, there is no clear consensus on the importance of circadian rhythm and neurohypophyseal pathway studies. Many studies have emphasized how individual therapeutic methods for migraine headaches can improve sleep, ie, the importance of killing two birds with one stone.

## Limitations

There are inevitably limitations that need to be addressed in addition to the above-mentioned summary of findings. The studies included in this review had a small number of patients and different study designs. In addition, self-report scales were used to evaluate sleep quality in studies. The lack of PSG studies that objectively evaluate sleep architecture is an important shortcoming. This will be important in terms of fully understanding the sleep profile in CM and providing effective sleep interventions. In addition, more emphasis placed on functional and longitudinal studies investigating common neuroanatomical pathways for migraine and sleep will enrich the literature. Since sleep quality assessment appears as a side (sub) data in many studies, the effects of this on migraine frequency, severity, and duration have not been evaluated. Another limitation of the literature is that patients with CM were evaluated under treatment. Ultimately, it will be very important to evaluate the patients who receive and those who do not receive treatment together.

## Conclusion

This review aimed to analyze the association between migraine chronicity and sleep quality and the mutual effects of sleep and migraine on one another. The findings show that adults with CM achieve significantly higher scores on the PSQI than healthy controls or episodic patients and that treatments primarily intended for pain relief in CM also have a positive effect on sleep. However, there is a lack of more elaborate studies on sleep disorders. For example, a comprehensive analysis of all sub-titles such as parasomnias or the relationship of restless legs syndrome should have been conducted. Large biochemical studies and sleep analysis studies in larger populations have not addressed circadian rhythm disturbances also.

CM, as a disease, disrupts sleep quality with many triggering factors. It provokes the pain process again in disturbed sleep. Therefore, if this interaction chain is not broken in itself, the pathophysiology can continue in two directions. In general, although current studies provide guidance, further studies on sleep in migraine should be undertaken. Because there is no consensus on whether patients show objective changes in sleep architecture. We are likely to detect significant differences with further studies. Based on all the studies, a better insight into the relationship between migraine as a common and chronic disease, first of all, enables the provision of treatments before the conditions become more complicated and achievement of significant developments in the field of individual, mental, public health, and well-being.



## Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Author Contributions

All authors made a significant contribution to the work reported, either in all or part of the conception, study design, execution, acquisition of data, analysis, and interpretation phases, took part in drafting, revising, or critically reviewing the article, and gave final approval of the version to be published, agreed on the journal to which the article will be submitted and agreed to be accountable for all aspects of the work.

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