# Sleep and Headache

M. O’Hare, R.P. Cowan  
Department of Neurology and Neurological Sciences, Palo Alto, CA, USA

## Outline

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>202</td>
</tr>
<tr>
<td>The Clinical Relationship between Sleep and Headache Disorders</td>
<td>202</td>
</tr>
<tr>
<td>Migraine is Clinically Related to Sleep</td>
<td>202</td>
</tr>
<tr>
<td>Cluster Headache is Clinically Related to Sleep</td>
<td>203</td>
</tr>
<tr>
<td>Hypnic Headache is Clinically Related to Sleep</td>
<td>204</td>
</tr>
<tr>
<td>The Shared Neurobiological Substrate of Sleep and Headache</td>
<td>205</td>
</tr>
<tr>
<td>The Hypothalamus is a Key Structure Linking Headache and Sleep</td>
<td>206</td>
</tr>
<tr>
<td>The Brainstem Contains Key Structures Linking Headache and Sleep</td>
<td>208</td>
</tr>
<tr>
<td>Abnormal Serotonin Signaling in the Brainstem may Link Headache and Sleep</td>
<td>208</td>
</tr>
<tr>
<td>The Homeostatic and Circadian Drives to Sleep</td>
<td>209</td>
</tr>
<tr>
<td>The Role of Adenosine in Primary Headache Pathophysiology</td>
<td>210</td>
</tr>
<tr>
<td>The Role of Melatonin in Headache Pathophysiology</td>
<td>210</td>
</tr>
<tr>
<td>The Role of Orexin in Headache and Sleep</td>
<td>212</td>
</tr>
<tr>
<td>Cortical Spreading Depression may Link Headache and Sleep</td>
<td>212</td>
</tr>
<tr>
<td>Headache Itself can Result in Sleep Disturbances</td>
<td>213</td>
</tr>
<tr>
<td>Psychiatric Comorbidities are Common in Headache Patients, and may Further Disturb Sleep</td>
<td>214</td>
</tr>
<tr>
<td>Sleep Disorders can Cause or Exacerbate Headache</td>
<td>214</td>
</tr>
<tr>
<td>The Relationship Between Sleep Apnea and Headache</td>
<td>215</td>
</tr>
<tr>
<td>Could Sleep Apnea Cause or Exacerbate Primary Headache Disorders?</td>
<td>215</td>
</tr>
<tr>
<td>Milder Forms of Sleep-disordered Breathing may Also be Associated with Headache</td>
<td>215</td>
</tr>
<tr>
<td>The Pathophysiology of Headaches Related to Sleep-disordered Breathing is Unclear</td>
<td>216</td>
</tr>
<tr>
<td>CPAP Therapy may Improve Headache Associated with Sleep-disordered Breathing</td>
<td>216</td>
</tr>
<tr>
<td>Cluster Headache is Strongly Associated with OSA</td>
<td>216</td>
</tr>
<tr>
<td>Conclusions</td>
<td>217</td>
</tr>
<tr>
<td>References</td>
<td>218</td>
</tr>
</tbody>
</table>
INTRODUCTION

Sleep and headache share a well-recognized, bidirectional relationship, with complex and incompletely understood interactions. The physiology of sleep shares many features with the pathophysiology of headache disorders, both in terms of the neuroanatomical pathways and the neurotransmitters that are involved. This may explain features of primary headache disorders like migraine, cluster headache and hypnic headache; all conditions whose clinical phenotype is intrinsically related to sleep.

Moreover, the painful experience of headache itself disrupts sleep, potentially creating a vicious circle of reinforcement. Both sleep disturbance and chronic pain also greatly increase the risk of depression and anxiety, further affecting the complex relationship between sleep and headache. Similarly, sleep disorders such as sleep apnea can lead to secondary headaches, and may in turn affect the expression of various primary headache disorders.

THE CLINICAL RELATIONSHIP BETWEEN SLEEP AND HEADACHE DISORDERS

Certain primary headache disorders are closely related to sleep by their phenotype, including migraine, cluster headache, and hypnic headache. The clinical features of these particular disorders suggest a relationship to sleep pathology. Shared neuroanatomical and neurotransmitter pathways may explain the mechanisms underlying this relationship.

Migraine is Clinically Related to Sleep

Migraine is a recurring headache disorder characterized by attacks of unilateral, pulsating head pain, that is, moderate to severe in intensity, with associated photophobia and phonophobia, and/or nausea and vomiting.\(^1\) The complex relationship between migraine and sleep was noted as early as 1873, when Liveing described the therapeutic effects of sleep on a migraine attack—“the pain is […] relieved […] by sleep when the sufferer is fortunate enough to procure it.” Liveing also described the propensity for migraine attacks to begin on waking and to be precipitated by disturbances of sleep patterns.\(^2\)

This phenomenon is still observed, with sleep reported by many migraineurs as a reliable abortive therapy for acute migraine. There is also clear evidence that changes in sleep patterns (e.g., decreased sleep, increased sleep, or changing time zones) can precipitate migraine attacks.\(^3\)\(^-\)\(^7\) In addition, sleep disorders contribute to the evolution of episodic migraine into its chronic form.\(^8\) The use of behavioral sleep modification techniques may result in an improvement in migraine frequency, and may be an effective adjunctive therapy in reverting chronic migraine back to its episodic form.\(^3\)\(^,\)\(^4\)

Sleep complaints are prevalent among migraineurs, with difficulty initiating or maintaining sleep reported by over half of patients, and frequent difficulty reported by a third of patients.\(^9\) This is particularly striking in chronic (transformed) migraine, where patients almost invariably report modifiable poor sleep habits, nonrestorative sleep, and shorter sleep durations.\(^9\)\(^,\)\(^10\) Evidence from a case-control study suggests that excessive daytime sleepiness is more common in migraineurs than controls, with an odds ratio of 3.1.\(^11\) However, a more
recent study did not support this, suggesting that although migraineurs are more likely to report sleepiness, they do not score higher on the Epworth sleepiness scale (ESS), a common objective measurement of recent sleepiness.\textsuperscript{12}

Migraine attacks exhibit clear circadian timing, with attacks more likely to occur between the hours of 4 a.m. and 9 a.m.\textsuperscript{13} A disturbance of circadian rhythms in migraine is also supported by “circa-septan” and circannual patterns that vary according to localization in the northern or southern hemisphere.\textsuperscript{14} Parasomnias such as sleep terrors, somnambulism, sleep bruxism, restless legs syndrome (RLS), and nocturnal enuresis are also seen more commonly in migraineurs.\textsuperscript{15} The mechanisms underlying the association of these disorders with migraine are poorly understood. European case-control observational studies have estimated the prevalence of RLS in migraineurs at 22–26\%, compared with a prevalence of 5–8\% in the general population.\textsuperscript{16,17} The comorbidity of migraine and RLS appears to be associated with higher migraine attack frequency, greater migraine-related disability, and increasing impairment in subjective sleep quality.\textsuperscript{18} The mechanism underlying this association remains obscure, and pathology relating to the hypothalamus or to dopaminergic signaling has been proposed.\textsuperscript{18,19} Migraine-induced sleep disruption may also play a role in RLS severity. For a complete review of the subject see the review by Mitsikostas et al.\textsuperscript{20}

Migraine attacks may be related to specific sleep stages, although the exact mechanisms remain unclear. Nocturnal arousal from sleep with migraine may be more likely during REM sleep.\textsuperscript{21,22} In addition, migraine appears more likely to occur following a night’s sleep with excessive durations of slow wave and REM sleep.\textsuperscript{23} Some patients report that daytime napping can trigger migraine attacks, and this has been reported to occur following naps in which slow wave or REM sleep is obtained.\textsuperscript{23} However, these findings were not supported by more recent polysomnographic (PSG) studies of migraineurs by Goder et al.\textsuperscript{22} Findings consistent with reduced cortical activation were observed the night preceding a migraine (reduced number of arousals, reduced beta power in slow wave sleep and reduced REM density).\textsuperscript{22} Similarly, studies of migraineurs during pain-free periods have demonstrated reduced cortical arousal.\textsuperscript{24,25}

Engstrom et al. compared sleep patterns in migraineurs during both interictal and peri-ictal phases to healthy controls.\textsuperscript{12} Migraineurs reported greater subjective sleep complaints such as insomnia, tiredness or pain-related sleep difficulties. However, the difference between the migraine population and healthy controls was much less significant when looking at PSG data, which demonstrated increased amounts of slow wave sleep and reduced fast arousals in the interictal migraine group.

Cluster Headache is Clinically Related to Sleep

Cluster headache (CH) is a distinct primary headache disorder characterized by attacks of excruciating pain, typically in a unilateral retro-orbital distribution, with associated ipsilateral autonomic features.\textsuperscript{1} It occurs more commonly in males.\textsuperscript{26} In its typical episodic form, patients experience “clusters” of headaches occurring up to 8 times per day, with periods of remission in between, each lasting between 20 and 180 minutes.\textsuperscript{27} CH is a disorder intricately associated with sleep, often with a predictable chronobiological pattern.\textsuperscript{28} CH often awakens the patient at the same time each night (circadian rhythmicity), and tends to occur in clusters in the same season each year (circannual periodicity).\textsuperscript{29}
A causal relationship between REM sleep and cluster attacks has been postulated. Headache waking CH patients from sleep occurred more frequently during REM sleep in a number of case series. However, this data has since been challenged by more recent studies that have reported no such relationship. In fact, these more recent case series demonstrate headache onset occurring more predominantly during stage 2 non-REM (NREM) sleep in both episodic and chronic CH patients. There also appears to be a reduction in the duration of slow wave sleep and REM sleep duration in these cases. Overall, it appears that a specific sleep stage abnormality is insufficient in explaining CH attack onset, and the relationship is more complicated than previously hypothesized.

CH is also strongly associated with obstructive sleep apnea (OSA). OSA prevalence of up to 80% has been reported in a CH population. This association will be further discussed later in this chapter, along with neuroimaging and neuroendocrine evidence supporting a pathophysiological link between sleep and CH.

Hypnic Headache is Clinically Related to Sleep

Hypnic headache is the only primary headache disorder, that is, defined specifically in relation to sleep. The most recent International Classification of Headache Disorders (ICHD 3-beta) diagnostic criteria require that hypnic headaches occur only during sleep, and result in awakening from sleep. The presence of cranial autonomic features or restlessness exclude the diagnosis according to ICHD 3-beta criteria, and are more suggestive of a trigeminal autonomic cephalgia. However, some authors dispute this, reporting “mild” autonomic features in several cases.

Hypnic headache is a rare condition, accounting for only 0.07–0.35% of headaches seen in specialist clinics. The underlying pathophysiology remains poorly understood. It has been proposed that hypnic headache may in fact represent an age-related phenotypic change of another sleep-related primary headache disorder such as migraine. Hypnic headache may also coexist with other primary headache conditions such as migraine or tension-type headache. In a recent case series of 23 patients, 16 had a preceding diagnosis of migraine.

Hypnic headaches typically begin in the 5th decade of life, more often in females, and are generally moderate to severe in intensity and bilateral in distribution. Migrainous features have been reported. Given the advanced age at headache onset, the diagnosis of hypnic headache should only be made after a careful evaluation for other causes of nocturnal headache such as elevated intracranial pressure, space-occupying lesion, arterial hypertension, and OSA. However, hypnic headache may also coexist with OSA, thus the presence of a sleep disorder does not exclude the primary headache diagnosis. The prevalence of OSA is high in hypnic headache patients; however, this is reflective of the age distribution, and OSA prevalence is normal when compared to age-matched controls.

Hypnic headaches tend to occur at a specific time each night, earning the nickname “alarm clock headache.” This points strongly toward an underlying disorder of chronobiology. Hypnic headache may be associated with age-related alterations in sleep physiology. There is a reduction in slow wave sleep seen in the elderly, as well as increasingly fragmented
sleep, with increased daytime napping and increased nocturnal waking, and this may predispose patients to this disorder. Hypnic headache does not appear to be strictly associated with a specific sleep phase, and attacks can occur in both REM and non-REM sleep, even within the same individual.

Structural neuroanatomical changes reported in hypnic headache patients further support a circadian disorder, with decreased gray matter volume in the posterior hypothalamus, a key structure in sleep physiology. Similar structural changes have been reported in narcolepsy patients. Age-related melatonin deficiency has also been proposed as a pathophysiological mechanism in this condition; the possible role of melatonin will be discussed later in this chapter.

Summary of Headache Disorders and Their Associated Sleep Disorders

<table>
<thead>
<tr>
<th>Headache disorder</th>
<th>Associated sleep disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>• Insomnia</td>
</tr>
<tr>
<td></td>
<td>• Parasomnias (sleep terrors, somnambulism, sleep bruxism, restless leg syndrome)</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>• Obstructive and central sleep apnea</td>
</tr>
<tr>
<td>Hypnic headache</td>
<td>• Associated with disturbed sleep by definition</td>
</tr>
<tr>
<td>Tension-type headache</td>
<td>• Insomnia</td>
</tr>
<tr>
<td>Chronic daily headache</td>
<td>• Insomnia</td>
</tr>
<tr>
<td></td>
<td>• Obstructive sleep apnea, snoring</td>
</tr>
</tbody>
</table>

THE SHARED NEUROBIOLOGICAL SUBSTRATE OF SLEEP AND HEADACHE

The transition between wake and sleep is controlled by the interaction between arousal and sleep-promoting pathways in the brain. Many of the structures, pathways, and neurotransmitters involved in this process are also implicated in headache pathophysiology. The convergence between sleep and headache pathways primarily localizes to diencephalic and brainstem structures (Fig. 11.1).

Sensory afferents mediating headache pain converge on the trigeminal nucleus caudalis (TNC) of the brainstem, which then project to the ventral posteromedial nucleus of the thalamus. These TNC projections interact with numerous brainstem and diencephalic nuclei as they ascend through the midbrain, including the periacqueductal grey matter (PAG), locus coeruleus, hypothalamus, limbic system, and autonomic brainstem centers such as the solitary nucleus and the parabrachial nucleus.

Of equal importance in headache pathophysiology are the descending pathways that modulate nociceptive pathways in the TNC. Brainstem structures including the rostroventromedial medulla, nucleus raphe magnus, locus coeruleus, and PAG modulate the trigeminovascular pathway and are influenced by descending inputs from the thalamus and hypothalamus.
The Hypothalamus is a Key Structure Linking Headache and Sleep

Hypothalamic structures are vital for maintaining wakefulness, and significant lesions of the posterolateral hypothalamus result in an unremitting sleep-like state. The importance of the hypothalamus in this regard was first recognized by von Economo, who described how inflammation in this region, “encephalitis lethargica,” produced profound disturbances of sleep/wake control. In particular, the posterior hypothalamus is a critical wake-promoting area. Histaminergic neurons of the tuberomammillary nuclei project widely to cortical and diencephalic structures to promote wakefulness.

In the lateral hypothalamus, a specific population of orexin-containing neurons reciprocally excite many activating monoaminergic systems, and also project to the basal forebrain and cortex. These orexinergic projections are thought to have a specific role in coordinating the activity of other activating systems, maintaining the stability of the waking state, and preventing inappropriate sudden onset of sleep. Orexin-containing neurons are deficient in patients with narcolepsy, a condition characterized by inappropriate sleep onset as well as intrusion of a REM-like-state into waking hours.

In migraine, hypothalamic involvement has long been hypothesized, as premonitory symptoms (e.g., changes in appetite or mood, yawning, and autonomic features) suggest...
localization to this region. Functional imaging studies support this hypothesis, demonstrating activation of the hypothalamus, midbrain PAG, and dorsal pons during the early premonitory phase of migraine. In addition, the comorbidity of migraine and nocturnal enuresis suggests a shared hypothalamic pathological substrate because the hypothalamus plays an important role in micturition. Adolescents with migraine are more likely to report a history of nocturnal enuresis (41% in episodic and 49% in chronic migraine compared to 12% of controls), and also achieve bladder control at a later age than controls.

The distinctive rhythmicity of CH and hypnic headache is also highly suggestive of hypothalamic involvement. In addition, secondary CH has been shown to arise from suprasellar invasion of a pituitary adenoma, further supporting a role for the hypothalamus in the development of CH. Neuroendocrine abnormalities provided the first objective evidence supporting hypothalamic dysfunction in CH. The pronounced gender discrepancy in CH patients, a disorder with a male to female ratio of 9:1, prompted sex hormone studies. These revealed lower testosterone levels in CH patients, with altered rhythmicity of secretion. In addition, abnormalities in the secretion of prolactin, gonadotrophins, growth hormone, thyroid-stimulating hormone, and cortisol have also been reported. Challenge testing of the hypothalamic-pituitary axis (with the insulin tolerance test) results in blunted responses, consistent with hypothalamic dysfunction—even in comparison to a population of chronic back pain patients. Similarly, studies of hypothalamic function in chronic migraine patients have revealed blunted profiles of prolactin secretion, and increased cortisol levels. Measurements of growth hormone secretion were normal in this population.

Radiological evidence also supports hypothalamic dysfunction in CH, with positron emission tomography (PET) scans demonstrating increased regional cerebral blood flow in the ipsilateral posterior hypothalamus during cluster attacks, as well as other less specific pain-processing areas such as the anterior cingulate cortex. This suggests a role for the hypothalamus as a generator of CH. Hypothalamic activation does not occur after injection of capsaicin into the forehead, suggesting a CH-specific association. MRI scans of episodic and chronic CH patients show increased volume of the inferior posterior hypothalamus bilaterally, in the region correlating to the area of specific activation seen on PET imaging. In addition, proton MR spectroscopy studies in CH patients demonstrate abnormal metabolite ratios consistent with loss or dysfunction of neurons and myelin in the hypothalamus.

Functional MRI (fMRI) studies confirm ipsilateral activation of the posterior hypothalamus in the cluster headache ictal phase. Resting state fMRI studies also demonstrate abnormal connectivity during cluster attacks between the hypothalamus and other brain regions typically involved in the “pain matrix” (such as the anterior and posterior cingulate cortex). Abnormal connectivity between the hypothalamus and regions of the frontal, parietal, and temporal cortex persists interictally. Hypothalamic activation was initially thought to be specific to CH genesis, but has also been demonstrated on PET scanning of spontaneous migraine attacks. Similarly, abnormal functional connectivity of the hypothalamus in migraineurs has been reported, particularly to regions such as the locus coeruleus and other areas controlling autonomic tone.

In addition, hypothalamic activation has been demonstrated in various other trigeminal autonomic cephalgias (TACs), including hemicranias continua, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), and paroxysmal hemicranias. The pronounced circadian rhythmicity of CH is absent in these other TACs, and
the persistence of posterior hypothalamic activation suggests that hypothalamic activation may in fact be more indicative of pain than specific circadian circuitry. Deep brain stimulation (DBS) of the posterior inferior hypothalamus has been effective in intractable cases of chronic CH, with improvement in sleep architecture and quality after treatment, as well as pain relief. However, there have been two case reports associating posterior hypothalamus DBS with disruption of sleep patterns. In both cases, patients with intractable CH and SUNCT as well as comorbid sleep disorders (REM behavioral disorder in one; non-REM parasomnia in the other) underwent DBS implantation of the posterior hypothalamus. In both cases, headache control improved, but this correlated temporally with both objective and subjective evidence of worsening sleep disturbance.

In summary, there is an abundance of structural and functional neuroimaging data supporting a role for the hypothalamus in headache pathogenesis. Dysfunction of the hypothalamus may result in disinhibition of the PAG and TNC, resulting in uncontrolled trigeminovascular activation.

The Brainstem Contains Key Structures Linking Headache and Sleep

Key structures in the overlap between headache and sleep localize to the brainstem, including the locus coeruleus, ventral PAG, and dorsal raphe nucleus. These cell bodies send monoaminergic projections to thalamic nuclei, the lateral hypothalamus, basal forebrain, and cortex. They are important in maintaining arousal, and are highly active during wakeful hours. In addition, the ventrolateral PAG (vlPAG) plays a specific role in switching off REM sleep (i.e., it is a REM-off zone), and is innervated by orexigenic neurons of the lateral hypothalamus. As well as their role in arousal, these brainstem structures also play an important role in the modulation of headache perception, acting as an endogenous “antinociceptive system.”

Abnormal Serotonin Signaling in the Brainstem may Link Headache and Sleep

The main CNS serotoninergic nucleus is the dorsal raphe nucleus. This is a key antinociceptive structure that is also involved in promoting wakefulness. A significant role for serotonin in migraine pathophysiology has long been suspected. This theory is supported by a wealth of indirect evidence. Serotonin metabolism in migraineurs is abnormal, both during and between attacks. Plasma serotonin is abnormally low in the interictal phase in migraineurs, and increases during attacks, while the inverse is observed in plasma measures of plasma 5-HIAA, the principle metabolite of serotonin. CSF 5-HIAA is increased (which may reflect increased central serotonin turnover), and the capacity for serotonin synthesis is increased in migraineurs.

In addition, the mechanism of action of many pharmacologic agents involved in provoking, aborting, and preventing migraine attacks relates to serotonin (e.g., reserpine, triptans, selective serotonin reuptake inhibitors). One unifying theory explaining the altered serotonin metabolism observed in migraineurs proposes that migraine is a condition of central serotonin dysregulation, leading to a cycle of recurrent headaches and reduced pain threshold.
Serotoninergic activity of the dorsal raphe nucleus is characterized by circadian rhythmicity. Waking hours are associated with tonic activity of the serotoninergic neurons, which decreases during slow wave sleep, becoming almost totally quiescent during REM sleep. These fluctuations in serotoninergic activity may also contribute to the relationship between migraine and sleep.

The Homeostatic and Circadian Drives to Sleep

Many ascending activating pathways projecting from the brainstem to the thalamus and basal forebrain promote a state of wakefulness. These arousal systems are counterbalanced in a controlled manner by an endogenous drive to sleep, which leads to arousal pathways being “switched off” by inhibition arising from the ventrolateral preoptic nucleus (VLPO). GABAergic inhibitory neurons of the VLPO project to the tuberomammillary nucleus, locus coeruleus, and the dorsal and median raphe nuclei. Bilateral lesions of the VLPO in animal models result in pronounced insomnia, with a dramatic reduction particularly of non-REM sleep.

These opposing systems are controlled by two separate processes, resulting in a consistent sleep–wake cycle. The first process, the homeostatic sleep drive, increases the longer while one is awake and decreases during sleep. The molecular basis of this “sleep homeostat” model is the accumulation of adenosine and other “somnogens,” metabolic by-products over the course of the waking hours. The existence of such a molecule was hypothesized as early as 1913, when Pieron reported inducing sleep in dogs by the intraventricular injection of CSF from sleep-deprived dogs. He explained this phenomenon by hypothesizing a “fatigue substance” or “hypnotoxin” produced by physiological exertion. Adenosine is the molecule now understood to fill that role, and is considered an endogenous somnogen, that is, thought to activate sleep-promoting pathways in the VLPO and inhibit wakefulness-promoting pathways in the basal forebrain. The soporific effects of adenosine are counteracted by caffeine, an antagonist of adenosine receptors.

The second process is the circadian rhythm. This daily rhythm is established by a “circadian pacemaker” in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, which is entrained to light-dark periodicity by inputs from photosensitive melanopsin-containing retinal ganglion cells. The SCN predominantly projects to the subparaventricular zone, which in turn projects to the dorsal medial hypothalamus (DMH). GABAergic neurons in the DMH project to the lateral hypothalamus while glutamatergic neurons project to the VLPO, thus promoting the sleep state. The multiple relays within the hypothalamus may explain how factors other than simple light–dark entrainment of the SCN can influence circadian sleep regulation, including other environmental stimuli such as food availability.

The SCN also projects to the paraventricular hypothalamic nucleus, controlling melatonin release from the pineal gland. Melatonin may then feedback and modulate SCN activity, as evidenced by the ability of melatonin to entrain circadian rhythms in blind patients, with animal models demonstrating this effect only in the presence of an intact SCN. Other SCN inputs that can modulate the circadian rhythm include those related to locomotor activity and sleep states.
The Role of Adenosine in Primary Headache Pathophysiology

Adenosine plays a role in both pain and sleep, acting primarily on A1 and A2A receptors in the CNS. The pain-related effects of adenosine vary in a receptor-dependent manner, with A1 stimulation having antinociceptive effects, and A2A stimulation resulting in pain. The sleep-promoting effects of adenosine are primarily mediated via A1 receptor activation, with some contribution from A2A receptor activation. Administration of adenosine can cause migraine in susceptible patients, and elevated circulating levels of adenosine have been recorded during migraine attacks. Adenosine also facilitates the effects of vasoactive intestinal peptide (VIP) and calcitonin-related gene peptide (CGRP), molecules known to be important in migraine pathophysiology.

Adenosine exerts its somnogenic effect via inactivation of the CaV2.1 channel, which is mutated in a form of familial hemiplegic migraine, the CACNA1A sub-type. In addition, a specific haplotype of the A2A receptor has been identified, that is, associated with the development of migraine with aura. In addition to a genetic predisposition to migraine, CACNA1A mutant mice have altered sleep phenotypes, with more rapid adjustment of circadian rhythm to phase shifts of the light–dark cycle. They are also less susceptible to the somnogenic effects of adenosine.

Given the association between adenosine, sleep, and nociception, therapeutic applications of both adenosine agonists and antagonists have been investigated in primary headache disorders. Selective A1 receptor agonists reduce CGRP release in response to dural stimulation and reduce trigeminovascular activation, and are of interest in the development of novel treatments for migraine and CH. Caffeine, widely used as a neurostimulant drug, acts as an antagonist at both A1 and A2A receptor types, and is also useful as a treatment adjunct in headaches. Interestingly, caffeine is often therapeutically effective in the treatment of hypnic headache, and caffeine withdrawal itself may also cause headache.

The Role of Melatonin in Headache Pathophysiology

Melatonin secretion from the pineal gland is regulated by the SCN and begins at dim-light onset, with hypnotic effects. Melatonin may also have analgesic effects, and disordered melatonin secretion may result in headache. Mechanisms underlying the interaction between melatonin and headache may include potentiation of GABAergic inhibition of pain pathways, modulation of 5-HT signaling, reduced production of proinflammatory cytokines, inhibition of nitric oxide synthase, antioxidant effects, and the induction of cytokines acting at opioid receptors (melatonin-induced-opioids).

Pineal cysts are common incidental findings on imaging, and are associated with an increased incidence of headache, with a migrainous phenotype predominating. Disordered melatonin secretion, rather than mass effect, is thought to underlie this phenomenon because the association is unrelated to cyst size. Abnormal melatonin secretion profiles have been described as a result of structural pineal disease associated with headache, with resolution of headache and normalization of melatonin secretion after surgical resection.

Melatonin secretion profiles are also abnormal in primary headache disorders. However, it should be noted that this finding lacks specificity, and has also been demonstrated in conditions such as alcohol ingestion, fibromyalgia, and depression. Initial studies by
Claustrat et al. indicated that plasma melatonin levels were lower in migraine patients when compared to controls, a difference that was more pronounced in those with comorbid depression. Subsequent studies of urinary melatonin concentrations demonstrated lower levels in migraineurs during the interictal period, with more pronounced decreases during migraine attacks. In patients with chronic migraine, nocturnal melatonin secretion was not found to be significantly different than healthy controls, however there was a significant phase delay in the peak melatonin concentration, similar to that seen in patients with delayed sleep phase syndrome. Those with chronic migraine and comorbid insomnia exhibited significantly lower melatonin levels in addition to the phase delay.

Nocturnal plasma melatonin levels in CH are abnormally low in comparison to controls, particularly in smokers, and are lower during cluster attacks than in the interictal phase. Melatonin levels in these patients are persistently low throughout the calendar year, with no clear circannual or seasonal rhythm identified. Melatonin secretion declines with age, and because hypnic headache is a disease of the middle-aged to elderly population, melatonin deficiency has been proposed as a pathophysiological explanation. The administration of exogenous melatonin is therefore of interest as a therapeutic option in a range of primary headache disorders.

Evidence for the use of melatonin in the treatment of migraine is limited, with conflicting reports. It is regarded as “Level U” quality evidence. An open label study of melatonin (3mg) in 34 episodic migraine patients reported an improvement in headache frequency, severity, and duration with treatment. In a subsequent randomized controlled trial of 179 episodic migraine patients, the response to melatonin (3mg) exceeded the response to placebo and was equivalent to amitriptyline therapy, although with better tolerability. However, another randomized controlled trial of melatonin therapy (2mg) in episodic migraine (n = 48) showed no improvement in attack frequency or sleep quality compared to treatment with placebo.

The migraine population included in this study had measures of sleep quality that were almost normal at baseline, and the possibility remains that melatonin may be helpful in selected migraineurs with comorbid sleep disorders and abnormal melatonin production. It should be noted that melatonin therapy is typically extremely well tolerated and that higher doses of up to 10 mg have been evaluated in nonheadache disorders.

A small randomized controlled trial investigating the efficacy of melatonin in CH prophylaxis also demonstrated a benefit, with a significant reduction in the number of daily attacks. Of the 10 treated patients, 5 patients (all episodic) had a clear response. The two patients in the group with chronic CH had no response. Subsequent anecdotal evidence has suggested a therapeutic effect of melatonin in chronic CH. Another trial investigating the use of melatonin as an adjunctive therapy in nine patients with episodic and chronic CH showed no improvement in attack frequency or analgesic use; however, the dose used (2 mg) was much lower than that used in the earlier positive trial (10 mg).

Agomelatine is an antidepressant drug acting as an agonist at the MT1 and MT2 melatonin receptor and as a selective 5-HT2C receptor antagonist. Its use in the treatment of patients with migraine and comorbid depression has been reported in a case series with encouraging results. Lithium, which is used in the effective treatment of CH and hypnic headaches, may exert its effect in part by increasing melatonin concentrations. Melatonin has been anecdotally effective in treatment of hypnic headache. Ramelteon, a selective melatonin MT1/MT2 receptor agonist with a longer half-life than melatonin, is also anecdotally effective.
Hemicrania continua (HC) is defined in part by its responsiveness to indomethacin, however the tolerability of long-term indomethacin therapy can be problematic. The benign side-effect profile of melatonin is very appealing in these instances. The efficacy of melatonin in HC treatment has been suggested by a number of case reports. Tapering indomethacin therapy following the introduction of melatonin was attempted in a recent study of 11 HC patients, with two patients achieving total freedom from pain on melatonin alone, three partial responders who were able to reduce their indomethacin dose, and no response to melatonin in six cases.

The Role of Orexin in Headache and Sleep

The orexin system of the hypothalamus is activated in response to stimuli such as emotion and stress via inputs from the insular cortex and amygdala, the biological clock via inputs from the dorsomedial nucleus of the hypothalamus, and sleep–wake transitions via inputs from the VLPO and dorsal raphe nucleus. Activation of the orexinergic system results in behavioral changes including increased wakefulness, feeding, and sympathetic tone.

Orexinergic neurons from the posterolateral hypothalamus interact in a complex manner with the TNC, and may facilitate or inhibit TNC nociception by receptor-specific pathways. Manipulation of orexinergic signaling has been evaluated for its therapeutic implications in migraine as well as in sleep disorders. Orexin signaling is also involved in appetite regulation, reward pathways, and even the pathology of anxiety and depression. Orexinergic pathways are known to promote feeding behaviors, and dysregulation of this system may contribute to the increased prevalence of obesity in migraineurs.

Evidence from animal migraine models suggests that systemic treatment with a dual antagonist of orexin receptors 1 and 2 acts both peripherally and centrally to reduce neurogenic dural vasodilation, cortical spreading depression, and TNC activation. This suggests a primarily facilitatory role of orexin in TNC nociception. Orexin levels are increased in the initial stages of a migraine attack, and CSF orexin concentrations are higher in patients with chronic migraine or medication overuse headache compared to controls. Although a recent randomized controlled trial of a dual orexin antagonist as a migraine prophylactic agent was negative, future avenues for clinical trials may include the study of these agents in CH.

There is an increased incidence of migraine in narcolepsy patients, a population known to be deficient in orexinergic neurons of the hypothalamus. However, this relationship remains controversial. A case-control study failed to demonstrate any relationship between migraine and narcolepsy, instead demonstrating a higher prevalence of “unspecific” headaches in narcolepsy patients, predominantly tension-type.

Cortical Spreading Depression may Link Headache and Sleep

Cortical spreading depression (CSD) is a spreading wave of neuronal and glial depolarization that is thought to correlate with the aura preceding migraine headache in a subset of patients. It results in neurogenic inflammation, as well as activation of meningeal nociceptors and the TNC. CSD also affects the physiology of subsequent sleep, with pronounced changes persisting for hours. As the percentage of non-REM sleep increases, REM sleep decreases, and slow-wave activity is increased ipsilateral to the side of CSD stimulus.
These changes may be related to CSD-induced alteration of ionic conductance, or to CSD-induced disruption of cortical cholinergic transmission.\textsuperscript{158} CSD completely silences wakefulness-promoting basal forebrain cholinergic projections\textsuperscript{159} and may also promote increased non-REM sleep via induction of COX-2 activity and increased prostaglandin production.\textsuperscript{160}

A genetic model of the relationship between sleep disorders and migraine has been identified in one family with familial hemiplegic migraine (FHM) and familial advanced sleep phase syndrome (FASPS). A missense mutation was identified in the gene encoding CK1 delta, a kinase known to be involved in circadian rhythm control. Knock-out mice for this mutation exhibited a markedly lower threshold for CSD initiation, and greater dilation of pial arterioles during CSD,\textsuperscript{161} thus acting similarly to transgenic models of familial hemiplegic migraine.\textsuperscript{162} Nitroglycerin-induced migraine models in these mice also demonstrate an increased propensity to nociception and TNC activation.\textsuperscript{161}

Given this information, screening for circadian rhythm sleep disorders (CRSD) has been proposed in migraine patients.\textsuperscript{163} CRSD are conditions in which there is a failure of synchronicity between the external day/night and the internal biological clock, and include delayed sleep phase syndrome, “jet lag,” and shift worker syndrome.\textsuperscript{51} Timing of the circadian system can be evaluated with salivary measurements of the onset of melatonin secretion in the evening, which may guide the timing of exogenous melatonin therapy in treating comorbid headache and CRSD.\textsuperscript{163} Stronger evidence in the form of a randomized-controlled trial is needed to adequately assess the clinical utility of routine screening and treatment of CRSD in the migraine population.

**HEADACHE ITSELF CAN RESULT IN SLEEP DISTURBANCES**

Sleep disturbance is increasingly prevalent with increasing headache frequency,\textsuperscript{53} and can be predicted by other headache-related factors including headache severity and headache-related disability.\textsuperscript{164} Pain makes restful sleep very difficult because it is associated with a state of stress and heightened alertness.\textsuperscript{165} However, painful stimuli alone do not explain the sleep disturbance reported by patients with pain disorders, as painful stimuli during sleep in healthy subjects result in only brief cortical arousals and postural adjustments without significant sleep disruption or recollection of disrupted sleep the following day.\textsuperscript{166} Chronic pain, however, has been associated with increased activity of systems modulating ascending activation as well as nociception, such as the raphe magnus.\textsuperscript{165,166} Pain has been shown experimentally to alter sleep microarchitecture, with an overall arousal effect of decreased delta activity and increased high frequency activity.\textsuperscript{167}

Behavioral factors may also play a role and chronic pain may be considered to condition a patient toward insomnia by maladaptive strategies such as increased daytime napping and spending increased amounts of time in the bedroom while alert and in pain.\textsuperscript{165,168} A bidirectional relationship between sleep and pain has been illustrated in female fibromyalgia patients, with a poor night’s sleep predictive of a bad pain day, and vice versa.\textsuperscript{169} It is difficult to establish direction or causality in the relationship between sleep and headache, and both processes are very likely to feed into one another.\textsuperscript{170} The relationship between pain and sleep is complex, and while increasing severity of pain correlates with worsening sleep, the association is even stronger for cognitive factors such as low mood and rumination.\textsuperscript{165}
Psychiatric Comorbidities are Common in Headache Patients, and may Further Disturb Sleep

Depression and anxiety disorders are highly prevalent in headache patient populations, and can further disrupt sleep. However, the association of sleep disturbance in migraineurs persists despite correction for psychiatric comorbidities, and cannot be entirely explained by psychological factors.

A recent cross-sectional population-based Danish study investigated the epidemiology of headache and sleep disorders. The percentage of individuals reporting both complaints was 18.1%. The presence of severe comorbid headache and sleep disorders was strongly associated with stress, depression, and anxiety, as well as significantly impaired quality of life. Engstrom et al. demonstrated that increasing levels of anxiety were associated with more superficial sleep in both migraineurs and healthy controls. However, migraineurs appeared to be more vulnerable to this effect, with reduced slow wave sleep and higher reported insomnia associated with anxiety.

SLEEP DISORDERS CAN CAUSE OR EXACERBATE HEADACHE

Typically healthy people who do not experience regular headaches will develop sleep deprivation headaches when provoked; these tend to be dull, frontal, and aching in nature. Paiva et al. found that patients presenting with early morning headache were more likely to have an underlying sleep disorder, and that treatment of the latter resulted in improvement in headache. Patients with insomnia have a 3.2-fold increased risk of reporting migraine, and a 2.3-fold increased risk of reporting tension type headache (TTH), after adjusting for anxiety and depression. The presence of sleep disorders other than sleep disordered breathing, such as insomnia, was associated with an increased incidence of new-onset migraine in a large longitudinal population-based study.

Sleep disturbances are also strongly suspected to be a risk factor for the development of chronic daily headache (CDH), although a causal relationship has not been demonstrated. Patients with CDH are more likely to report sleep complaints than those with episodic headache or the general population.

A correlation between sleep disturbance and pain is not only seen in headache, but has also been reported in many diverse chronic pain conditions. Evidence suggesting that sleep disturbance contributes to pain initially came from animal studies demonstrating that sleep deprivation resulted in a reduced pain threshold. In humans, experimentally interfering with slow wave sleep results in increased musculoskeletal tenderness reminiscent of fibromyalgia, as well as a reduced pain threshold.

Impaired sleep may result in disordered pain processing. Specifically, disrupted REM sleep has been shown to impair the antinociceptive effect of the endogenous opioid system in animal models. Reduced serotoninergic signaling after sleep deprivation may also contribute to a state of hyperalgesia. Lack of sleep has been reported as a precipitating factor for both migraine and TTH, and has been reported to worsen existing TTH. Patients with migraine and to a lesser extent TTH are significantly more likely to complain of severe sleep disturbance than headache free patients, with just a marginal reduction in the strength
of association after controlling for depression and anxiety.\textsuperscript{33} Two consecutive nights of self-reported poor sleep in chronic migraine patients is highly predictive of increased headache activity,\textsuperscript{180} and reduced sleep duration is associated with increased headache severity. This effect appears to be synergistic with that of high stress levels,\textsuperscript{180} and may suggest a protective effect of a regular sleep schedule during periods of high stress.\textsuperscript{181}

**The Relationship Between Sleep Apnea and Headache**

The prevalence of OSA has dramatically increased over the last two to three decades, in tandem with the rising prevalence of obesity.\textsuperscript{182} Recent estimates of prevalence suggest that polysomnographic evidence of a significant number of apnea/hypnoea episodes is found in 33.9\% of males and 17.4\% of females in the 30–70 age group; with evidence of moderate to severe disease in 13 and 5.6\%, respectively.\textsuperscript{182}

Sleep apnea and sleep-disordered breathing may interact with headache disorders in a number of ways.

According to ICHD-3 beta criteria, the diagnosis of sleep apnea-related headache requires the presence of headache on awakening, in association with a diagnosis of sleep apnea. Evidence of causality is required, either by the headache developing soon after the onset of OSA, or by the headaches improving or worsening in parallel with OSA.\textsuperscript{1} The nature of the headache is described as typically bilateral, lasting less than 4 h after waking, and lacking in migrainous features.\textsuperscript{1} However, this clearly defined syndrome does not describe the various other ways in which sleep apnea may modulate other primary headache disorders.

**Could Sleep Apnea Cause or Exacerbate Primary Headache Disorders?**

The relationship between OSA and primary headache disorders was examined in a large cross-sectional population-based Norwegian study. This data did not support a relationship between migraine and OSA in the general population,\textsuperscript{183} and furthermore did not demonstrate any dose-response relationship between severe OSA and migraine severity. Similarly, no relationship between TTH and OSA was identified.\textsuperscript{184} This is consistent with previous studies reporting the prevalence of OSA in a headache population to be similar to that of the general population.\textsuperscript{185} Therefore, while the evidence may not support an increased prevalence of primary headache disorders in OSA patients, the question of whether the frequency and severity of headaches may be influenced by the presence of OSA remains to be answered.

Refractory CDH may be associated with OSA. In one study, patients attending a headache clinic were referred for polysomnography if they were experiencing CDH that was refractory to standard treatment, and in addition reported one of the following: headaches predominantly occurring during sleep or in the morning, snoring, or daytime somnolence.\textsuperscript{58} Of the 72 patients studied, 29.2\% received a diagnosis of OSA (13.7\% of women and 66.6\% of men).\textsuperscript{58} Patients without OSA who simply snore habitually also appear to be at increased risk of CDH.\textsuperscript{59}

**Milder Forms of Sleep-disordered Breathing may Also be Associated with Headache**

Morning headache may be a relatively nonspecific finding for sleep apnea.\textsuperscript{186,187} In one study of patients undergoing PSG for snoring, the prevalence and characteristics of headache
(including morning headache and an ICHD diagnosis of migraine) did not differ significantly between the group ultimately diagnosed as having sleep apnea and those who were just “snorers”. Of note, headache was strongly correlated with measures of depression in both groups. Despite this lack of specificity, headaches in the group with sleep apnea did respond to treatment with continuous positive airways pressure (CPAP). This is at odds with the recent Norwegian epidemiological data, which demonstrates that the presence of morning headache is predictive of OSA in the general population, and was present in 11.8% of PSG-confirmed OSA cases. The relationship persisted after correction for potential confounders, including depression and BMI.

The Pathophysiology of Headaches Related to Sleep-disordered Breathing is Unclear

Episodic hypoxia is one hypothesis that has been proposed to explain OSA-related headache. Experimental induction of arterial oxygen desaturations to 75–80% have been demonstrated to trigger migraine in migraineurs, and headache is highly prevalent in those ascending to high altitudes. However, the duration or severity of oxygen desaturation in OSA patients studied by Kristiansen et al. was not predictive of the presence of OSA-related headache. Similarly, a study by Sand et al. did not identify a dose-response relationship between the severity of apnea, oxygen desaturation, and headache.

Alternatively, hypercapnia secondary to respiratory insufficiency may result in altered pH, vasodilation and trigeminal activation. “Turtle headaches” are described as bilateral, generalized headaches occurring in a patient who wakes up, pulls the bedclothes over their head, and goes back to sleep again. The proposed mechanism in this instance is the induction of mild hypoxia and hypercapnia.

CPAP Therapy may Improve Headache Associated with Sleep-disordered Breathing

In one study of 11 patients with comorbid sleep apnea and migraine, treatment with CPAP resulted in a marked improvement in migraine frequency and a significant reduction in medication use. Similarly, nonspecific headache in a sleep apnea population is more likely to improve in those who are compliant with CPAP therapy. However, Mitsikostas et al. reported an improvement in headache frequency with CPAP therapy in just 23.8% of patients with comorbid OSA and CDH, with a worsening of headache frequency in 66.6%. Of note, this particular population was one of refractory CDH, with patients having already failed to respond to at least two different prophylactic pharmacotherapies.

Cluster Headache is Strongly Associated with OSA

OSA has been reported in up to 80% of the CH population. The association is strengthened by evidence demonstrating that in the cluster-free period CH patients have significantly fewer apneic and desaturation episodes, and the diagnosis of OSA is less likely to be made. Interestingly, both central and obstructive apneas have been observed during cluster attacks, even though central apneas were not present outside the cluster period.
The mechanism underlying this relationship is poorly understood. The two processes may be associated with a shared neurobiological substrate in the hypothalamus. Alternatively, a causal relationship may exist, possibly secondary to hypoxia. This latter theory is suggested by the therapeutic effect of oxygen administration in the abortion of a cluster headache attack. However, central hypothalamic dysregulation of both processes appears more likely in light of the recently reported central apnea occurring in association with cluster attacks. Evidence that CPAP therapy improves CH is limited and conflicting, with a lack of prospective studies.

Sleep and headache disorders are intricately related, both in clinical presentation and physiology. Shared anatomical pathways may help to explain this relationship, and recent functional imaging studies suggest that the hypothalamus, long suspected on clinical grounds, may be involved in both processes. The roles of shared neurotransmitters such as serotonin, adenosine, melatonin, and orexin lend further support to this relationship.

These physiological intersections not only provide insights into the underlying headache pathology but also suggest novel therapeutic approaches. Of particular interest for future research is the potential role of melatonin in the treatment of selected headache patients. Given its benign side-effect profile, even modestly positive effects in this medication-sensitive population would be welcomed. Future research may focus on the therapeutic effect of melatonin in migraine patients stratified by sleep quality indices. Screening selected patients for circadian rhythm sleep disorders (as proposed by Rovers et al.), to further personalize melatonin therapy is also appealing; however, further evidence is needed before widespread adoption of this approach.

Sleep and headache disorders cause or exacerbate each other in a complex, bidirectional manner, perhaps as a reflection of their shared neurobiological substrate. The common comorbidities of depression and anxiety further modify and complicate this relationship, and are associated with lower quality of life indices. The importance of these relationships may be overlooked or underestimated in clinical practice, resulting in potentially avoidable distress.

Rains et al. propose general guidelines for approaching comorbid sleep and headache disorders. These include taking a careful history to clarify the way in which headache and sleep interact in an individual. Standardized sleep questionnaires have also been suggested as a screening tool in all headache patients. Sleep apnea should be suspected and screened for, not only in those with morning headaches or with signs and symptoms of OSA but also in those with specific headache diagnoses that may be associated with higher risk of comorbid OSA (i.e., CH, hypnic headache, chronic migraine, and chronic TTH). Screening for depression and anxiety is also recommended.

The presence of comorbid sleep disorders in a headache patient, with or without coexisting OSA, depression, or anxiety, will influence the choice of pharmacotherapy in that individual. Bidirectional treatment with a single agent targeting both depression and headache may be helpful in some patients.

Impressive results in reducing headache frequency have been reported with behavioral sleep modifications in a migraine population. The behavioral intervention used in this study
consisted of five components: scheduling a consistent bedtime allowing for 8 h in bed; elimination of TV, reading, or music in bed; the use of a visualization technique to shorten time to sleep onset; moving the evening meal ≥4 h before bedtime and limiting fluid intake within 2 h of bedtime; and the discontinuation of naps.\textsuperscript{1} At a minimum, patients should be counselled on pragmatic lifestyle modifications including adherence to a consistent sleep/wake schedule, avoiding “screen time” before going to sleep, and reducing caffeine and alcohol intake.\textsuperscript{199} There is no evidence at present to support a reduction in headache frequency in insomniac migraineurs treated with hypnotic agents.\textsuperscript{200}

The intersection between sleep and headache is clinically complex, remains incompletely understood, and provides many pathophysiological insights and novel therapeutic targets. In addition, it affords the conscientious physician an opportunity to consider his or her patient in a holistic light, bearing in mind the high prevalence of comorbid headache, sleep and psychiatric disorders, and how these factors may influence one another.

**References**


REFERENCES


