Editorial

Headache phenotypes in insomnia, obstructive sleep apnea, and COMISA: Impact on diagnosis and therapy

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Headache associated with comorbid insomnia and sleep apnea (COMISA) may represent a distinct clinical phenotype. Its severity, refractoriness and unique characteristics necessitate a comprehensive, integrative therapeutic approach.

Headache and sleep disorders frequently coexist and interrelate, but are often managed in silos despite overlapping neurophysiological pathways.[1] The relationships between insomnia, obstructive sleep apnea (OSA) and primary headache disorders – particularly migraine[2] and tension-type headache (TTH)[3] – have long been observed, but remain poorly characterized. More recently, the comorbidity of insomnia and OSA, termed COMISA (comorbid insomnia and sleep apnea), has emerged as a distinct and clinically relevant phenotype,[4] yet its implications for headache diagnosis and therapy are still underexplored.[5] A recent large trial regarding COMISA and neurological comorbidities excluded headaches from the data analysis, reporting a lack of information on sleep disorders from headache clinics.[5] The International Classification of Headache Disorders, 3rd edition (ICHD-3), includes several types of sleep-related headache, but ones associated with insomnia and COMISA are not yet clearly defined as distinct headache categories.[1,6]

According to the recently revised International Classification of Sleep Disorders (ICSD-3-TR), insomnia is marked by difficulty initiating or maintaining sleep despite adequate opportunity, leading to daytime impairment.[7] It is closely associated with increased cortical excitability, sympathetic nervous system overactivation and the dysregulation of the hypothalamic–pituitary–adrenal axis.[8] These alterations heighten pain perception and are strongly implicated in central sensitization, contributing to increased vulnerability to TTH and migraine attacks.[9] Insomnia increases the risk of both TTH and migraine, the frequency of both types of headaches, as well as the disability associated with them.[10] Hyperarousal mechanisms in insomnia interfere with descending pain inhibitory pathways, often rendering headaches more resistant to pharmacological preventive treatment.[11]

In OSA, recurrent upper airway obstruction during sleep results in intermittent hypoxia, sleep fragmentation and sympathetic surges.[12] Headaches

associated with OSA tend to be mild to moderate, of the dull/pressure type, bilateral (bifrontal), and occur upon awakening.[12] Although these 'morning headaches' are generally short-lived and respond to treatment, their mechanism of action is debatable.[12] They were originally thought to be due to hypoxia-induced cerebral vasodilation and the resulting changes in intracranial pressure; however, recent studies have not found any such association.[13] In some individuals, particularly those with higher apnea–hypopnea index scores, OSA has also been associated with migraine-like presentations,[14] and even cluster headache,[15] although the mechanistic pathways have not been fully elucidated.[14]

COMISA occurs in 30–50% of OSA patients, and 30–40% of chronic insomnia patients have OSA.[16] People with COMISA exhibit greater sleep disruption, psychological distress and daytime impairment than individuals with either disorder alone. From a headache perspective, COMISA may reflect a compounded pathophysiological burden involving both hyperarousal and hypoxemia, likely increasing susceptibility to more frequent, prolonged and refractory headache episodes.[16] Headaches in COMISA may blend the characteristics of both the insomnia and OSA phenotypes, such as early morning onset with extended duration, increased severity, or the overlapping features of migraine and TTH.[17] Also, COMISA has been associated with higher rates of medication-overuse headache and psychiatric comorbidities, factors that further complicate treatment.[16]

Screening for sleep disorders should be mandatory in cases of chronic or high-frequency headaches. Validated tools, such as the Insomnia Severity Index (ISI), the STOP-Bang Questionnaire, the Epworth Sleepiness Scale (ESS), or overnight oximetry, could aid in identifying sleep-related contributors to chronic or treatment-resistant headaches. Moreover, understanding the patient's chronotype and circadian alignment can offer additional insight into headache patterns during a 24-hour period.[18]

From a therapeutic standpoint, tailored interventions are necessary. In patients with insomnia and headache, cognitive behavioral therapy for insomnia (CBT-I) has been shown to reduce the frequency of headaches and improve sleep quality.[19] In OSA-related headache, the continuous positive airway pressure (CPAP) therapy or mandibular advancement devices (MADs) can offer significant symptom relief,[17,20] with documented improvement in both headache and sleep indices. For COMISA, however, monotherapy is often inadequate. These patients may require a combination of CBT-I and CPAP, or other multimodal strategies, such as pharmacological agents that could simultaneously address sleep and pain, e.g., amitriptyline or melatonin. Behavioral strategies targeting sleep hygiene and circadian rhythms, including light therapy and sleep–wake scheduling, may also be beneficial, particularly in cases with misalignment or shift work involvement.[21]

To improve care in the COMISA population, future research should prioritize longitudinal studies exploring headache progression, neuroimaging studies of shared pathways between sleep, pain and emotional regulation, and trials testing integrated interventions in patients with comorbid sleep disorders and headache.

In conclusion, headaches associated with insomnia, OSA and COMISA represent overlapping but distinguishable clinical phenotypes that demand integrated diagnostic and therapeutic approaches. COMISA in particular should be recognized as a high-risk, underdiagnosed condition in patients with chronic or refractory headaches. Systematic screening for sleep disturbances and cross-specialty collaboration may significantly enhance outcomes, reduce pain burden and improve quality of life (QoL) in this complex clinical population.

Beyond OSA and insomnia

In addition to the well-established roles of insomnia and OSA in headache pathogenesis, a broader spectrum of sleep-related breathing disorders (SRBDs) may contribute to headache presentations and should be considered in differential diagnosis. Conditions such as upper airway resistance syndrome (UARS), central sleep apnea (CSA) and treatment-emergent CSA can also result in fragmented sleep, nocturnal hypoxia and autonomic dysregulation – each a potential driver of head pain. For instance, UARS, although subtler in its polysomnographic presentation than OSA, can induce significant sympathetic activation and micro-arousals, leading to non-restorative sleep and tension-type or migraine-like secondary headaches.[9] Similarly, central apneas may cause abrupt fluctuations in carbon dioxide levels, cerebrovascular reactivity and intracranial pressure, each capable of contributing to morning or nocturnal headaches.[13] Differentiating among these SRBDs is crucial, as their therapeutic responses vary significantly, ranging from positional therapy and expiratory pressure relief to adaptive servo-ventilation.

A growing body of research underscores the importance of considering insomnia not as a unitary condition, but as a heterogeneous group of phenotypes, some of which may coexist with SRBDs in more complex constellations. For example, paradoxical insomnia – characterized by the misperception of sleep – can overlap with milder forms of OSA or UARS, complicating the clinical picture and delaying an appropriate intervention.[22] Conversely, sleep-maintenance insomnia with frequent awakenings may reflect unrecognized respiratory arousals or limb movement disorders. In these contexts, careful use of ambulatory monitoring or full polysomnography is warranted, particularly in patients whose headache patterns correlate with disturbed or fragmented sleep.

The relevance of recognizing coexisting sleep disturbances extends beyond diagnostic clarity; it directly influences therapeutic outcomes. A patient presenting with

Table 1. Sleep disorder features potentially influencing headache presentation and management

Sleep disorder	Impact on headache	Associated mechanisms	Treatment relevance	Phenotypic headache expression	Diagnostic implications
Insomnia	increases the frequency and chronification of primary headache, especially migraine, TTH	hyperarousal, sleep fragmentation, central sensitization	CBT-I and agents targeting both sleep and headache often needed	often aggravates migraine and TTH	sleep history crucial; rule out comorbid SRBDs
OSA	may induce morning headaches; vascular instability may worsen migraine	intermittent hypoxia, sympathetic activation, vasodilation	CPAP or MAD may reduce headache severity; screen for other causes	morning headaches; a possible trigger in predisposed individuals	screen for morning headaches and other secondary causes
COMISA	dual influence – hyperarousal and hypoxia may potentiate headache burden	additive mechanisms: inflammation; impaired pain modulation	combined therapy (CBT-I + CPAP/MAD); treat both sleep disorders to improve headache control	aggravates primary headache; may complicate diagnosis and increase medication overuse	consider COMISA in refractory headache with poor sleep and mixed symptoms

The table summarizes current clinical tendencies and proposed mechanisms linking sleep disorders to headache characteristics. Rather than indicating strict phenotypes, the table outlines how insomnia, OSA and COMISA may influence headache presentation, chronification and treatment response. The data is based on clinical observations and hypotheses; further research is needed to define population-level patterns.
OSA – obstructive sleep apnea; COMISA – comorbid insomnia and sleep apnea; TTH – tension-type headache; CBT-I – cognitive behavioral therapy for insomnia; CPAP – continuous positive airway pressure; MAD – mandibular advancement device; SRBDs – sleep-related breathing disorders.

chronic migraine or TTH may show a partial response to analgesic prophylaxis or behavioral interventions if an underlying SRBD remains unaddressed.[9] Similarly, patients treated with CPAP for OSA may continue to experience headaches if comorbid insomnia or circadian misalignment is left untreated.[18] This interdependence highlights the necessity for a comprehensive sleep assessment in all patients with persistent or refractory headaches, particularly when temporal patterns suggest a sleep-related trigger.

In practice, incorporating a sleep-focused evaluation into the headache diagnostic process is warranted. Clinicians should routinely screen for symptoms such as non-restorative sleep, loud snoring, witnessed apneas, excessive daytime sleepiness, difficulty falling or staying asleep, and morning headaches. Questionnaires like the Berlin Questionnaire, STOP-Bang, ISI, and the Munich Chronotype Questionnaire (MCTQ) offer quick, validated insights. For selected patients, especially those with complex or overlapping symptoms, overnight studies are indispensable. Importantly, the use of wearable technology, including home oximetry and actigraphy, is making such evaluations more accessible and scalable.

Integrating these insights into clinical workflows not only facilitates the accurate phenotyping of sleep-related headache, but also guides rational therapeutic strategies. For instance, a patient with COMISA and mixed headache features may benefit from concurrent CBT-I and MAD, especially when CPAP adherence is poor. Another patient with CSA and chronic daily headache may respond to pharmacological agents that modulate the respiratory drive, such as acetazolamide, in conjunction with headache prophylactics. In all cases, the personalization of therapy based on the sleep and headache phenotype maximizes the likelihood of symptom resolution and QoL improvement. Table 1 summarizes the potential influences of insomnia, OSA and COMISA on headache presentation and therapeutic response, highlighting overlapping mechanisms and the need for tailored interventions.

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