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Clinical Review

Sleep and anti-calcitonin gene related peptide (CGRP) drugs: current evidence and perspectives

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ABSTRACT

Migraine and sleep share a bidirectional relationship: sleep disruption can trigger migraine attacks, while migraine impairs sleep continuity and quality. Calcitonin gene-related peptide (CGRP), central to migraine pathophysiology, also contributes to sleep regulation through hypothalamic and brainstem circuits that control arousal and circadian rhythms. This overlap raises the question of whether pharmacological inhibition of CGRP with monoclonal antibodies (mAbs) or gepants could affect sleep.

This scoping review summarizes evidence on anti-CGRP therapies and their impact on sleep quality, efficacy, and tolerability. Although results are inconsistent across instruments, emerging data suggest that anti-CGRP mAbs and gepants, particularly erenumab, galcanezumab, and atogepant, can improve subjective sleep quality and objective measures such as sleep efficiency in some cases. Evidence for fremanezumab and eptinezumab remains scarce, whereas large-scale pharmacovigilance datasets indicate low rates of insomnia, somnolence, or abnormal dreams.

Overall, current findings suggest that CGRP inhibition impacts the sleep system, but the mechanisms of this interaction remain partly understood, representing a promising area for mechanistic exploration and clinical application. Future studies with standardized sleep endpoints are needed to distinguish direct neuropharmacological effects from indirect benefits mediated by improvement in migraine burden.

1. Background

Migraine and sleep are closely related, with a well-established bidirectional correlation [1–3]. Migraine is among the most prevalent neurological disorders, affecting approximately 15% of the global population [4]. Sleep disturbances, particularly insomnia and poor sleep quality, are also highly prevalent in this population [2,5]. In large cohorts, patients with migraine consistently report reduced sleep quality compared to controls. For example, about 40-45% of individuals with migraine have clinically relevant poor sleep quality based on the Pittsburgh Sleep Quality Index (PSQI) questionnaire [3,6], with disturbed sleep or changes in sleep timing that often precede a migraine episode. In fact, sleep disturbance may represent not only a trigger but also a manifestation of the premonitory phase of migraine, preceding pain onset by hours and reflecting early hypothalamic and brainstem dysregulation [7]. Recent evidence from a case-control and Mendelian randomization study revealed that insomnia is also significantly and causally associated with an increased risk of migraine [8]. Several mechanisms have been proposed for these links [9]. Neural circuits

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Glossary

AE	Adverse event
AIS	Athens Insomnia Scale
AMD	Acute medication days
AMN	Acute medication number
BBB	Blood–brain barrier
CGRP	Calcitonin gene-related peptide
CM	Chronic migraine
CI	Confidence interval
CNS	Central nervous system
EM	Episodic migraine
ESS	Epworth Sleepiness Scale
FAERS	FDA Adverse Event Reporting System
ISI	Insomnia Severity Index
mAb	Monoclonal antibody
MIDAS	Migraine Disability Assessment Questionnaire
MOH	Medication overuse headache
mAbs	Monoclonal antibodies (plural)
NREM	Non-rapid eye movement sleep
OX1R/OX2R	Orexin-1 and Orexin-2 receptors
PSQI	Pittsburgh Sleep Quality Index
PSG	Polysomnography
REM	Rapid eye movement sleep
ROR	Reporting odds ratio
RR50%	≥50% responder rate
RCT	Randomized controlled trial
SCN	Suprachiasmatic nucleus
SD	Standard deviation
WASO	Wake after sleep onset
HIT-6	Headache Impact Test-6
ASC-12	Allodynia Symptom Checklist-12

within the brainstem, hypothalamus, and thalamus are implicated both in migraine pathophysiology and in the regulation of sleep-wake and circadian rhythms. Dysregulation of neurotransmitter systems, including serotonin, orexin, melatonin, and adenosine, likely contributes to both phenomena [10,11]. Sleep deprivation itself increases cortical excitability and lowers the threshold for cortical spreading depolarization, a mechanism central to migraine aura [11].

Circadian misalignment, such as irregular bedtimes or shift work, disrupts hormonal rhythms, including melatonin and cortisol, further influencing susceptibility to migraine episodes. Clinically, this close association highlights the importance of assessing and managing sleep disturbances in patients with migraine [12]. Poor sleep contributes not only to increased migraine frequency and intensity, but also to higher risks of disability and chronification [8].

Calcitonin gene-related peptide (CGRP), a neuropeptide central to migraine pathophysiology [13,14], is also implicated in sleep regulation, particularly in mediating arousal responses to hypoxia [15]. In migraine, CGRP has been hypothesized to contribute to an increased risk of chronic insomnia and altered arousal thresholds, although the precise mechanisms remain uncertain [12]. Experimental data in pain suggest that CGRP can influence sleep architecture through its actions on hypothalamic and brainstem circuits governing arousal and circadian rhythms [16].

The monoclonal antibodies (mAbs) targeting CGRP or its receptor (erenumab, fremanezumab, galcanezumab, and eptinezumab) have markedly advanced migraine prevention but only a limited number of observational studies have investigated their effects on sleep quality and patterns. Although not entirely consistent, some results indicate an overall improvement in subjective sleep quality, suggesting that CGRP inhibition may influence sleep regulation. Whether this effect is indirectly driven by the reduction of migraine burden or represents a direct neuromodulatory effect on sleep-wake circuits is unknown.

Gepants represent a newer class of selective CGRP receptor antagonists [17]. Rimegepant, ubrogepant, and zavegepant are approved for acute treatment, while rimegepant (along with the acute use) and atogepant are indicated for prevention [18]. To date, no dedicated studies have assessed the effects of gepants on sleep quality, disturbances, or sleep-related adverse events. Nevertheless, some patients reported somnolence and fatigue, and pharmacovigilance data from the FDA Adverse Event Reporting System (FAERS) have also identified abnormal dreams and nightmares as rare and unexpected adverse events, which were not observed in clinical trials [19,20]. Whether these findings represent treatment-related effects, and through which mechanisms they might occur, remains to be clarified.

In this scoping review, we summarize current evidence on the impact of anti-CGRP therapies on sleep quality and patterns, addressing both efficacy and tolerability, and outline future research directions. Firstly, we summarize the current evidence on the complex relationship between sleep, CGRP and migraine.

1.1. Relationship between sleep and migraine

Recent reviews summarize the role of sleep in migraine [2,15,21]. Briefly, epidemiological studies consistently show that individuals with migraine have a higher prevalence of insomnia, difficulty initiating or maintaining sleep, poor subjective sleep quality, and excessive daytime sleepiness compared with the general population. Migraine pain itself often disrupts sleep continuity, leading to nocturnal awakenings [22] or compels patients to seek sleep as a coping mechanism [23]. Conversely, patients commonly identify insufficient sleep, excessive sleep, irregular sleep habits and fragmented sleep as triggers for migraine episodes. Interestingly, the best natural treatment for a migraine episode is often sleep, which is the ultimate reduction in sensory input [24]. The association between sleep disturbance and migraine is particularly marked in chronic migraine (CM) [5,25], where patients report shorter sleep duration, greater fatigue severity, and higher rates of insomnia symptoms relative to those with episodic migraine (EM). Sleep disruption has also been linked with an increased risk of migraine chronification, suggesting that poor sleep not only worsens migraine frequency but may influence long-term disease course.

In a large study of over 11,000 individuals using a digital diary, both increased sleep interruptions and deviations from usual sleep duration predicted migraine episodes the following day, while episodes themselves were associated with longer subsequent sleep duration. Insomnia symptoms are strongly linked with higher headache frequency, greater disability, and an increased risk of migraine chronification [26]. Importantly, evidence suggests that sleep fragmentation and deviations from an individual's habitual sleep pattern may be more predictive of a migraine episode than total sleep duration alone. A recent systematic review explored the circadian features of migraine and cluster headache (CH) [27] (*see below*). Interestingly, a study involving the use of both an electronic diary and wrist-worn actigraphy showed no associations between nightly diary-reported short sleep duration, high sleep fragmentation, or low sleep quality. However, nightly lower sleep efficiency was associated with subsequent headache onset in patients with episodic migraine not on the day immediately following sleep (day 0), but on day 1 (the following day) [28].

Actigraphy evidence of sleep quality has shown that good multidimensional sleep health, rather than a majority of singular dimensions of sleep, may account for 3-4 fewer headache days per month [29].

Polysomnography (PSG) is the gold standard for the objective assessment of sleep architecture and sleep-related disorders. Some

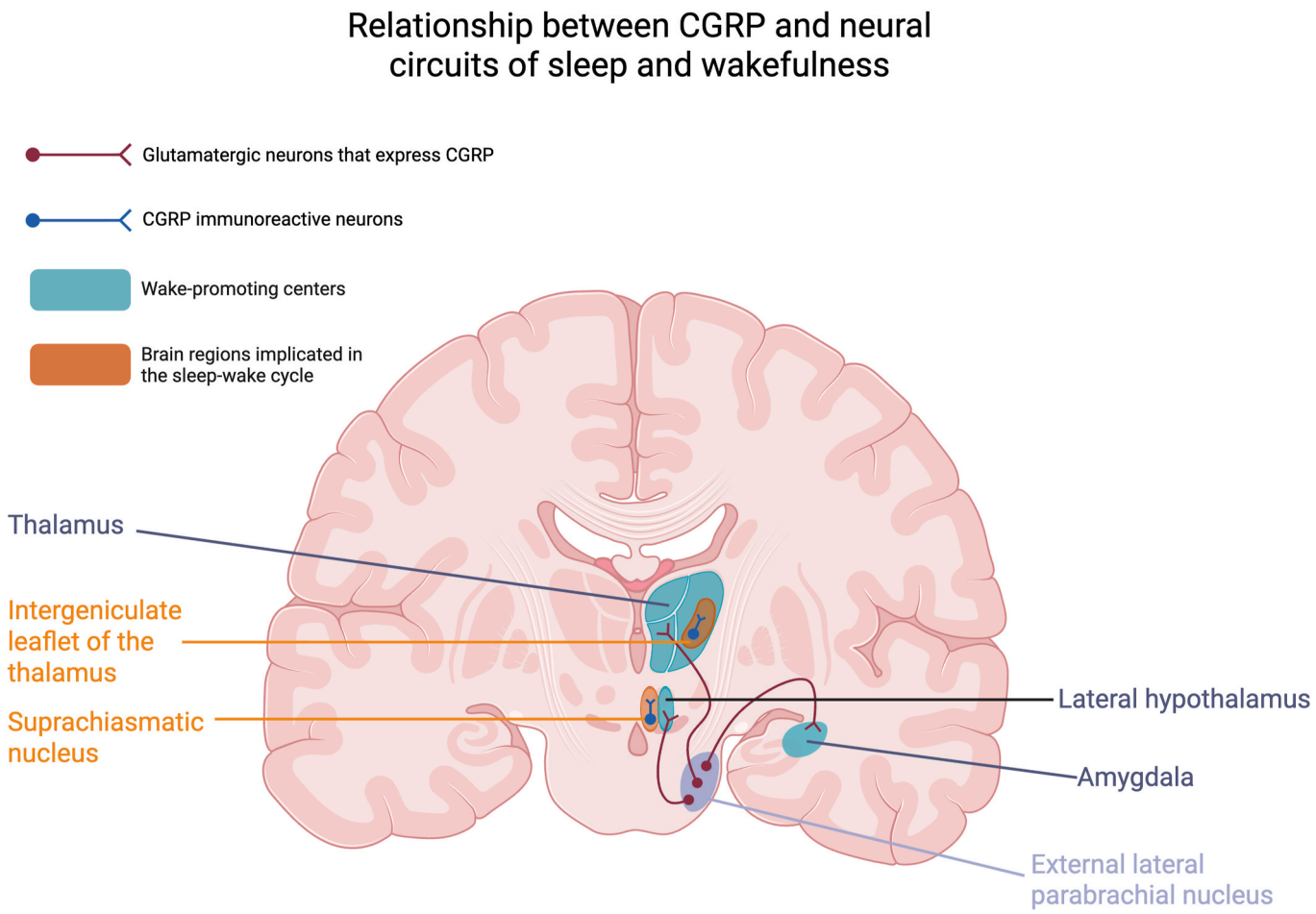

Fig. 1. Relationship between CGRP and neural circuits regulating sleep and wakefulness.
Schematic representation of key brain regions and neuronal populations involved in the interaction between calcitonin gene-related peptide (CGRP) signaling and sleep-wake regulation. CGRP-expressing glutamatergic neurons located in the external lateral parabrachial nucleus project to wake-promoting centers, including the basal forebrain, lateral hypothalamus, thalamus, and amygdala. Within the hypothalamus, CGRP-immunoreactive neurons interact with orexinergic and circadian nuclei, such as the suprachiasmatic nucleus (SCN) and the intergeniculate leaflet of the thalamus, both crucial for circadian timing. These networks integrate nociceptive and homeostatic inputs to regulate arousal and the transition between sleep and wake states. Overactivation of CGRP pathways may enhance arousal and contribute to sleep fragmentation, whereas CGRP inhibition could reduce hyperexcitability within these circuits, favoring more stable and restorative sleep. Created in BioRender. Sebastianelli, G. (2025) https://BioRender.com/v4htr2u.

studies using this technique supported the presence of sleep architecture alterations in migraine. In a video-polysomnography study including 110 patients, CM was associated with a significant reduction in REM sleep percentage, and REM was independently associated with CM [30]. Additionally, a separate polysomnographic study of patients with temporomandibular disorders demonstrated associations among sleep bruxism, obstructive sleep apnea, and migraine using full-night video-PSG, further supporting the relevance of objective sleep assessment in this population [31].

Mechanistic explanations for this interaction highlight overlapping neural substrates Hypothalamic and brainstem circuits that regulate circadian rhythms and arousal are also implicated in migraine pathophysiology [32]. Dysregulation of neurotransmitters such as serotonin, orexin, adenosine, and melatonin provides a further biological basis for the association between impaired sleep and migraine susceptibility. Orexinergic signaling has emerged as a key regulator not only of vigilance but also of pain processing [33]. Experimental models demonstrate that activation of orexin-1 receptors (OX1R) may attenuate trigeminal nociceptive transmission and dural vasodilation, whereas orexin-B and orexin-2 receptor (OX2R) pathways can exert pronociceptive effects. Dysregulation of the orexin system has been implicated in narcolepsy and may represent a shared mechanism linking sleep disorders and migraine pathophysiology [33]. Autonomic fluctuations across sleep stages further modulate migraine vulnerability (Fig. 1). Transitions between slow-wave sleep and REM are characterized by sympathetic-parasympathetic shifts that may influence trigeminovascular excitability [34]. Sleep itself may act as a homeostatic reset, reducing cortical hyperexcitability and trigeminovascular activation, thereby explaining the clinical observation that sleep often terminates migraine episodes. Conversely, sleep deprivation has been shown to influence cortical GABAergic inhibition, increasing cortical excitability and predisposing to an attack [24,35,36].

Clinically, patients frequently report that seeking sleep during migraine episodes alleviates pain, suggesting an endogenous protective mechanism. However, hypnotic medications do not consistently reproduce this effect (indeed, they are not recommended for migraine treatment, either acute or preventive) [37], highlighting that the benefit of sleep may be mediated by processes other than sedation alone. In addition, glymphatic dysfunction, most effective during slow-wave sleep, may contribute to migraine by impairing the clearance of pro-inflammatory mediators and CGRP, reinforcing neuroinflammatory cascades [38]. These pathophysiological insights reinforce the rationale for targeting CGRP pathways, which intersect both trigeminovascular activation and hypothalamic regulation, in exploring the impact of anti-CGRP therapies on sleep.

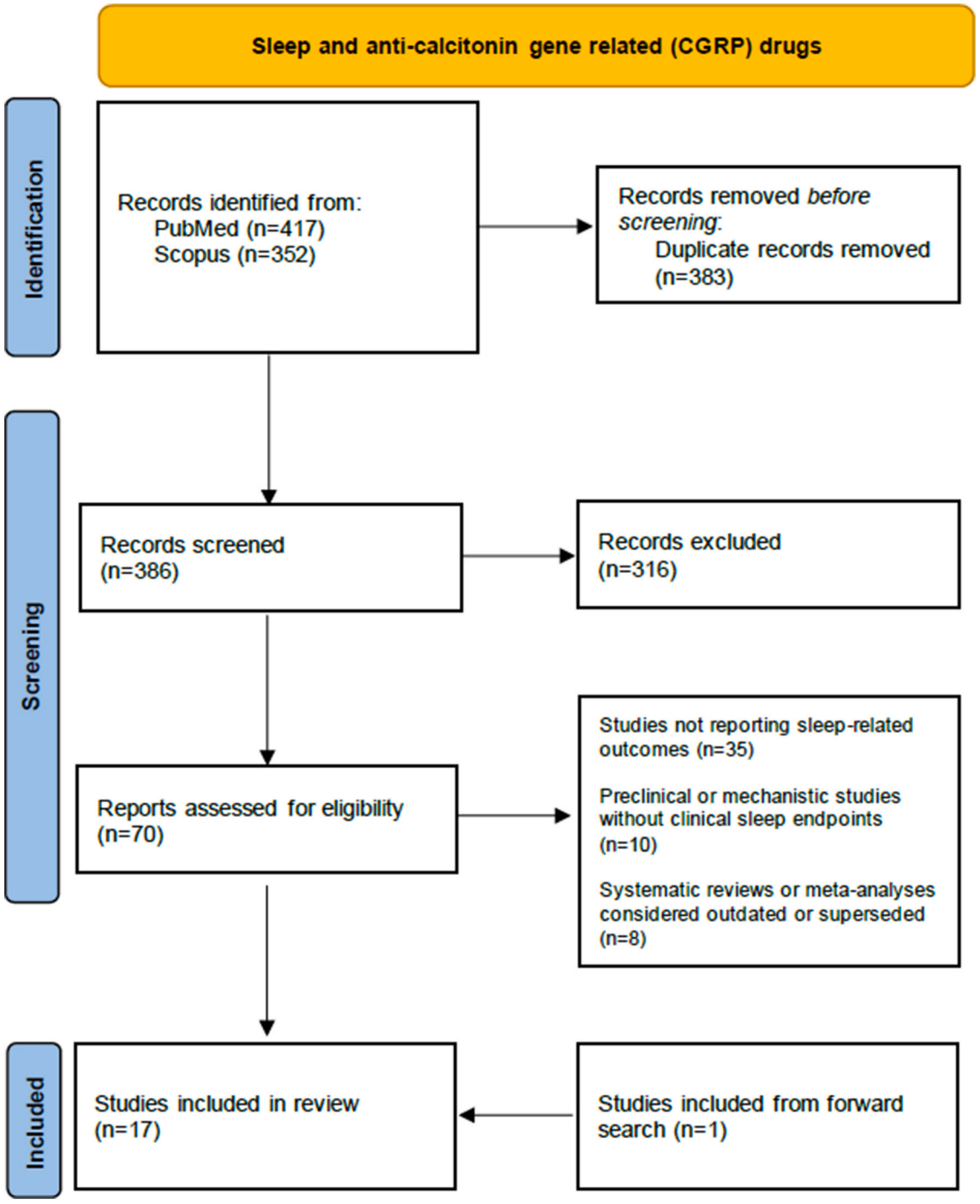

Fig. 2. Flowchart of studies' search.

1.2. CGRP in sleep regulation

CGRP is widely expressed in the central and peripheral nervous system. In particular, its release from peripheral terminals of peptidergic primary sensory neurons (mostly C-fiber nociceptors) elicits locally arteriolar vasodilation and, also via Schwann cell and neuronal activation, hypersensitivity [13,39,40]. However, CGRP, in addition to producing pain signals, appears to play diverse roles across pathophysiological contexts, including neural circuits of sleep and wakefulness [41]. CGRP-immunoreactive neurons have been found in the suprachiasmatic nucleus (SCN) of the hypothalamus and in the intergeniculate leaflet of the thalamus [42], suggesting that CGRP is involved in circadian signaling and in the control of the sleep-wake cycle. The *Drosophila* CGRP ortholog, the neuropeptide DH31, is released by a subset of clock neurons and acts as a wake-promoting circadian output signal that suppresses sleep toward the end of the night [43]. Flies lacking this CGRP-like signal fail to appropriately wake in anticipation of dawn, whereas excess DH31 causes early awakening [43]. Similarly, CGRP in mammals may help to coordinate the timing of arousal with the circadian cycle.

Beyond its role as a circadian pacemaker regulator, CGRP may be involved in the brain's arousal pathways. The external lateral parabrachial nucleus (PBel) of the brainstem contains a population of glutamatergic neurons that express CGRP and project to wake-promoting

Table 1
Sleep-related study results with anti-CGRP therapies.

Study (Year)	Drug	Design	Sample size	Main sleep findings
Pellitteri 2022 (ERESON)	Erenumab	Prospective, PSG and PSQI, 3–12 months	n = 29 (3 months); n = 15 (12 months)	Increase sleep efficiency (88.1 → 91.0%, p = 0.006); reduced WASO and awakenings; PSQI improved.
Ilgaz Aydinlar 2024	Galcanezumab	Prospective, PSQI, 3 months	n = 54	PSQI ≥5 prevalence reduced (72.7% → 56.2%); PSQI sleep disturbance domain improved (p = 0.016); better in baseline insomnia patients.
Viticchi 2024	Anti-CGRP mAbs vs oral preventives	Prospective, PSQI, 3 months	n = 214	PSQI improved by mean −1.84 overall; greater reduction with mAbs (8.9-6.5, p = 0.01).
Silvestro 2022	Galcanezumab	Prospective, MOS Sleep Scale, 3–6 months	n = 43	No significant changes in MOS Sleep Scale domains after 3–6 months.
Pilati 2023	Erenumab	Prospective, PSQI, SCI, ESS, MEQ-SA, 12 months	n = 88 (34 for sleep sub-study)	SCI improved at 3 months (p = 0.014) but not sustained; PSQI unchanged; transient chronotype shift (from morning to intermediate).
Iannone 2022	Erenumab, Fremanezumab, Galcanezumab	Prospective, exploratory, ad hoc questionnaire-based, 7 months mean	n = 80	Sleep changes in 51.2%: 38.8% improved, 5% worsened (self-reported).
Melo-Carrillo 2025	Fremanezumab	Case series, ISI , 3 months	n = 6	4/6 pts improved in sleep parallel to migraine; one improved sleep without migraine improvement; one no change.
Iannone 2025	Atogepant	Prospective, PSQI, (AIS), Bergen Insomnia Scale, ESS, and ISI, 3 months	n = 43	Significant reduction in the PSQI total score from 9.6 to 8.2 (p = 0.002), in the AIS (p = 0.014) and the in Bergen Insomnia Scale (p = 0.046).

AIS, Athens Insomnia Scale; CGRP, Calcitonin Gene Related Peptide; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; mAb, Monoclonal Antibody; MEQ-SA, Morningness–Eveningness Questionnaire–Self-Assessment; MOS, Medical Outcomes Study; PSG, Polysomnography; PSQI, Pittsburgh Sleep Quality Index; SC, Sleep Condition Indicator; WASO, Wake After Sleep Onset.

centers, including the basal forebrain, lateral hypothalamus (which contains orexinergic neurons), thalamus, and amygdala [44]. These CGRP-positive brainstem neurons function as relays for visceral and nociceptive afferent signals. Experiments in rodents have shown that activating PBel CGRP-positive neurons abruptly awakens the animal from sleep, whereas inhibiting these neurons prevents arousal in situations that would normally wake the brain. For instance, elevated CO2 (hypercapnia) during sleep, as occurs in sleep apnea, triggers arousal via this PBel CGRP circuit [43,45]. Optogenetic silencing of CGRP neurons (or their terminals in the forebrain) allows mice to sleep through conditions that would normally prompt awakening, such as high CO2 levels or certain pain stimuli. Thus, CGRP neurons function as a central alarm system, rapidly switching the brain from sleep to wakefulness in response to internal stressors. This is adaptive in short bursts (e.g., waking to restore breathing in apnea), but if overactive it can fragment sleep [16]. Notably, CGRP itself is a potent excitatory modulator and when applied in certain brain areas it can increase neuronal firing and promote wake-like EEG patterns. Consistent with this, administering CGRP or analogs to animals tends to increase locomotor activity and alertness [46]. Conversely, blocking CGRP action might reduce such arousing signals, for example, studies have found that ablating PBel CGRP neurons can attenuate the degree of sleep fragmentation in chronic pain models [16].

2. Methods

This scoping review aimed to analyze the existing evidence on the impact of anti-CGRP therapies, both mAbs and gepants, on sleep quality, sleep disorders, and sleep-related adverse events in patients with migraine. A comprehensive literature search was conducted in PubMed/MEDLINE and Scopus from inception to August 2025. Search terms included combinations of: *("erenumab" OR "fremanezumab" OR "galcanezumab" OR "eptinezumab" OR "rimegepant" OR "ubrogepant" OR "atogepant" OR "zavegepant" OR "vazegepant" OR "gepant*" OR "monoclonal antibody" OR "mAb" OR "CGRP receptor antagonist") AND ("sleep" OR "sleep quality" OR "sleep disorder*" OR "insomnia" OR "sleep disturbance*" OR "circadian" OR "REM" OR "non-REM" OR "sleep architecture" OR "sleep efficiency" OR "sleep apnea")*. On Scopus, to avoid overgeneralization, we eliminated *"monoclonal antibody" and "mAb"*.

To evaluate the effect and safety of anti-CGRP drugs on sleep, studies were selected according to a standardized PICOT framework as the following: Population: individuals with migraine regardless of age; Intervention: any treatment with anti-CGRP drugs (both gepants and mAbs); Comparison: any if available (including both placebo or active substances); Outcome: any effectiveness/efficacy sleep quality outcomes and any reported sleep-related adverse events; Type of study: randomized controlled trials (RCTs), observational studies, case series, case reports. Thus, we considered original studies (randomized controlled trials, observational studies, case series, case reports) and systematic/narrative reviews that reported data on sleep-related outcomes in patients treated with anti-CGRP drugs. Both efficacy (e.g., sleep quality, sleep architecture, sleep-related questionnaires, polysomnography) and safety outcomes (sleep-related adverse events) were evaluated. Conference abstracts, editorials, and non-English publications were excluded. The reference lists of included articles and relevant reviews were screened for additional eligible studies. Mechanistic studies were selected and included separately and are not part of the PICOT framework.

Two reviewers (AB and LFI) independently screened the titles and abstracts of papers for relevance. In the event of disagreement, a third reviewer (MR) was consulted. Full texts of potentially eligible articles were retrieved and screened by the same authors, who then assessed them against the inclusion criteria above. Data extraction was performed using a predefined spreadsheet capturing study design, population characteristics, type and dose of anti-CGRP therapy, sleep-related efficacy outcomes, and sleep-related adverse events. All extracted data were systematically recorded in an Excel spreadsheet.

Given the heterogeneity of study designs and outcomes, no quantitative synthesis was performed. Results were summarized narratively and organized by drug class (and molecule) and pathophysiology.

This scoping review is reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist.

3. Results

A total of 17 articles met the inclusion criteria after screening 769 records identified through PubMed, and Scopus, up to August 2025, following PRISMA-ScR guidelines. One study (1) was included by Authors after the search (Fig. 2). Evidence was grouped by drug molecule and analyzed narratively according to reported sleep-related efficacy or adverse events outcomes. The effects of anti-CGRP therapies on sleep quality and sleep architecture have been investigated exclusively in observational studies (n = 8), with the most evidence derived from anti-CGRP mAbs (n = 7). Among these, erenumab was evaluated in three studies (n = 3), galcanezumab in two (n = 2), fremanezumab in one case series (n = 1), and one multicenter study assessed anti-CGRP mAbs as a pooled group (n = 1). Only one prospective study investigated a gepant,

specifically atogepant (n = 1). No clinical studies assessing sleep outcomes were identified for eptinezumab or for other gepants (rimegepant, ubrogepant, zavegepant). Furthermore, no RCTs have specifically evaluated sleep-related endpoints with anti-CGRP therapies.

Only one of the included studies explicitly reported the involvement of a sleep-certified specialist in the assessment of sleep disturbances [47], whereas the remaining studies did not specify whether evaluations were conducted by personnel with formal training in sleep medicine. Furthermore, information on pharmacological confounders (i.e., concomitant drugs that could affect sleep) was inconsistently reported. This incomplete reporting may introduce methodological variability and potential bias in the interpretation of sleep-related outcomes. Table 1 reports the details of the included studies with sleep-related results.

Regarding sleep-related adverse events, these effects were also reported in RCTs (and related systematic reviews with meta-analysis) as well as pharmacovigilance studies.RCTs have generally reported a favorable safety profile for both mAbs and gepants, with sleep-related adverse events (insomnia, abnormal dreams and somnolence) uncommon and inconsistently described [48]. In the most recent network meta-analysis [48] of 19 phase 3 trials comprising over 14,000 participants (and including all RCTs retrieved by our literature search), insomnia was reported at low frequencies across all anti-CGRP mAbs without a statistically significant increase compared to placebo [48]. Similarly, results were reported in real-world studies and in FAER analyses [20,49]. Regarding gepants, insomnia was not consistently reported across the gepants trials. Importantly, serious adverse events did not differ from placebo for either anti-CGRP mAbs or gepants, and the overall tolerability profile was dominated by injection-site and gastrointestinal complaints [48]. The studies are detailed in the paragraphs below.

4. Effects of anti-CGRP drugs on sleep

4.1. Erenumab

In a 12-month study of erenumab [50], Pilati and Colleagues explored the effects of erenumab on chronotype and sleep in 88 patients with CM, most with medication overuse and multiple prior preventive treatment failures, treated with monthly doses of erenumab 140 mg. Sleep and circadian features were assessed in a subgroup of 34 patients using validated questionnaires, including the Pittsburgh Sleep Quality Index (PSQI), the Sleep Condition Indicator (SCI), the Epworth Sleepiness Scale (ESS), and the Morningness-Eveningness Questionnaire (MEQ-SA). At baseline, nearly two-thirds reported poor sleep quality, and 44% exhibited a morning chronotype. After three months, a significant shift toward an intermediate chronotype was observed, although this was not maintained at later assessments. Sleep quality, measured by the PSQI, remained unchanged, while the SCI improved transiently at three months before returning to baseline levels. Daytime sleepiness showed a slight but non-significant decline [50]. Interestingly, some responders experienced reduced sleep efficiency over time, and a small proportion of patients reported insomnia, particularly in the days immediately following injection. These findings suggest that erenumab may exert subtle influences on circadian preference and insomnia in addition to its established migraine-preventive efficacy [50].

More objective evidence comes from the ERESON study, which combined sleep questionnaires (ESS and PSQI) with home polysomnography (PSG) [23] and demonstrated both subjective and objective improvements in sleep quality at 3 and 12 months of erenumab therapy. In detail, after three months of erenumab, sleep efficiency improved significantly, rising from 88.1% to 91.0%, whereas wake after sleep onset and nocturnal awakenings were reduced. Importantly, the distribution of sleep stages, including REM and NREM proportions, total sleep time, and sleep latency, remained unchanged, indicating that erenumab improves continuity and stability of sleep without altering its physiological architecture. Subjective measures parallel these findings, with PSQI scores decreasing from 7 to 5 and ESS scores declining at 12 months, suggesting better sleep quality and reduced daytime sleepiness [23].

4.2. Galcanezumab

In a real-world cohort of 54 Turkish patients with EM and CM [51], galcanezumab was evaluated over three months with specific attention to sleep quality assessed by the PSQI. At baseline, nearly three-quarters of patients reported poor sleep quality (PSQI $\geq$5). This proportion decreased to 57.5% at one month and 56.2% at two months, suggesting an early improvement. By the third month, a significant reduction was observed in the PSQI sleep disturbances domain for the overall cohort ($p = 0.016$). Importantly, patients with comorbid sleep disorders at baseline showed marked benefits, with significant improvements in total PSQI scores ($p = 0.027$), as well as in subjective sleep quality ($p = 0.034$) and daytime dysfunction ($p = 0.013$) [51]. Improvements in sleep parameters were also evident in patients without baseline depression or anxiety, where sleep disturbance scores declined significantly. Conversely, no major changes were observed in other PSQI domains, such as sleep latency, sleep duration, or habitual efficiency. Overall, these findings highlight a domain-specific and comorbidity-dependent effect of galcanezumab on sleep, with the most pronounced benefits in patients who had pre-existing sleep disturbances or lower psychiatric burden at baseline [51].

In contrast, another study assessing galcanezumab did not show significant changes in the Medical Outcomes Study (MOS) Sleep Scale over six months of treatment [52]. In detail, the study included 43 patients with high-frequency episodic and CM, who were assessed for multiple patient-reported outcomes during treatment. Sleep quality was evaluated using the MOS Sleep Scale, which explores six domains, including difficulties falling asleep, sleep maintenance, daytime somnolence, respiratory problems, snoring, and sleep quantity. At baseline, a high prevalence of sleep problems was observed, in line with prior evidence that sleep disturbances are frequent in migraine. However, after three and six months of treatment, no significant change was detected in the overall sleep problem index, suggesting that galcanezumab did not exert a measurable effect on subjective sleep quality within the study timeframe [52]. The Authors speculated that longer follow-up may be required to observe meaningful effects on sleep-wake rhythm abnormalities, or that improvements in migraine parameters may not directly translate into measurable sleep benefits when using this scale [52].

4.3. Fremanezumab

In a case series [53], Melo-Carrillo et al. examined the effects of fremanezumab on sleep in six patients with CM or high-frequency episodic migraine. Sleep quality was tracked prospectively with daily electronic diaries and the Insomnia Severity Index (ISI) for one month before and three months during treatment. Four patients showed parallel improvements in both migraine outcomes and sleep parameters, suggesting that headache reduction was the main driver of sleep benefits. One patient improved in sleep without migraine reduction, raising the possibility of a direct, though unproven, effect of fremanezumab on hypothalamic sleep-promoting neurons. Conversely, another patient experienced no changes in either domain. Overall, the findings support that fremanezumab primarily enhances sleep by alleviating migraine frequency and severity and no patient reported sleep-related adverse events [53].

4.4. Merged anti-CGRP mAbs

In a large, prospective, multicenter study including 214 patients with migraine [54], Viticchi et al. directly compared the impact of oral

Table 2
Sleep-related adverse events with anti-CGRP drugs.

	Randomized clinical trials	FDA Adverse Event Reporting System (FAERS) or VigiAccess		
	Insomnia	Insomnia	Somnolence	Abnormal dreams
Erenumab	-	386/38,515 (2.40%), ROR 1.19; Cohort: 5/88 (5.7%)	-	52/38,515 (0.32%), ROR 2.32
Eptinezumab	-	No clear signal	-	-
Fremanezumab	OR 3.06 (0.61–15.27) Dose 225 mg	93/5332 (1.58%), ROR 1.52	-	10/5332 (0.17%), ROR 2.37
Galcanezumab	OR 0.09 (0–1.60) Dose 120 mg	203/19,485 (1.21%), ROR 1.34	-	29/19,485 (0.17%), ROR 2.77
Atogepant	-	VigiAccess: 51/3058 (0.79%)	VigiAccess: 75/3058 (1.17%)	13 cases, ROR 7.74 (95% CI > 4.49)
Rimegepant	-	VigiAccess: 69/6949 (0.54%)	VigiAccess: 159/6949 (1.26%)	-
Ubrogepant	-	VigiAccess: 26/1759 (0.75%)	a = 58, ROR 5.97 (95% CI > 4.6)	4 cases, ROR 4.84 (95% CI 1.82)

Empty cells indicate not estimated/not reported adverse events. FAERS, FDA Adverse Event Reporting System; OR, odds ratio.

preventive drugs and anti-CGRP mAbs on subjective sleep quality. Sleep was assessed with the PSQI at baseline and after three months of treatment. Overall, prophylactic therapy of any type was associated with significant improvement in PSQI scores, with a mean reduction of 1.84 points ($p < 0.0001$). The benefit was most pronounced among patients receiving anti-CGRP mAbs, with mean PSQI scores decreasing from 8.9 at baseline to 6.5 at follow-up ($p = 0.010$). The proportion of patients with pathological PSQI scores (≥5 cut-off) decreased from 76% to 59% overall, with reductions observed in both the oral drug group (70.6% to 52.4%) and the mAb group (87.3% to 71.8%). Interestingly, patients with more severe baseline sleep impairment derived the greatest benefit. The study thus provides strong real-world evidence that anti-CGRP mAbs not only reduce migraine frequency and disability but also exert a measurable positive effect on subjective sleep quality [54].

Finally, in an exploratory prospective study of 80 patients with CM treated with erenumab, fremanezumab, or galcanezumab, the Authors investigated potential central migraine symptoms, including sleep changes [55]. More than half of the cohort (51.2%) reported sleep alterations during treatment. Among them, 38.8% experienced an improvement in sleep quality or duration, while 5% reported worsening. Importantly, the study did not use standardized sleep questionnaires relying instead on self-reported changes [55].

4.5. Atogepant

A recent monocentric, prospective study, including 43 patients with migraine treated with atogepant, evaluated the effect pre-post treatment (at 12 weeks) on sleep and sleep-related adverse events using a panel of standardized questionnaires [47]. These include the PSQI, the Athens Insomnia Scale (AIS), the Bergen Insomnia Scale, the Epworth Sleepiness Scale (ESS), and the ISI. After twelve weeks of treatment, patients experienced an improvement in subjective sleep quality, as reported by a significant reduction in the PSQI total score from 9.6 to 8.2 ($p = 0.002$). Among the PSQI components, only the sleep duration domain was statistically significant ($p = 0.003$), indicating that the primary benefit was longer total sleep time. Parallel improvements were also observed in the AIS ($p = 0.014$) and the Bergen Insomnia Scale ($p = 0.046$), confirming a consistent enhancement in perceived sleep continuity and restfulness. Measures of daytime sleepiness and insomnia severity, assessed through the ESS and the ISI, respectively, remained stable, suggesting that atogepant did not induce either somnolence or residual insomnia after at least 12 weeks of treatment. Psychiatric comorbidities, present in about one-fifth of the sample, were linked to worse baseline sleep quality but did not significantly influence the extent of improvement during therapy. Statistical modeling confirmed a time-dependent effect on sleep quality ($p = 0.004$) independent of clinical response, whereas prior failure with anti-CGRP mAbs predicted a smaller improvement in PSQI (interaction $p = 0.039$). Overall, the results suggest that atogepant improves sleep in patients with migraine without exerting sedative or disruptive effects. However, the open-label design, small sample size, and reliance on self-reported questionnaires limit causal inference and external validity, and other studies are needed to assess the effectiveness of atogepant (and other gepants) on sleep [47].

5. Sleep-related adverse events with anti-CGRP drugs

In the network meta-analysis mentioned above [48], which included 19 phase 3 trials with over 14,000 participants, insomnia was reported at low frequency across all studies and was not statistically significant compared with placebo. Fremanezumab and galcanezumab showed odds ratios above and below unity, respectively, but all with very wide confidence intervals, reflecting the rarity of events [48]. To note, the relationship between these adverse events and the drug is also controversial, considering that they are commonly reported by patients with migraine even without treatments, and pharmacologically, anti-CGRP drugs have a low to very low permeability of the blood-brain barrier (BBB) and penetration in the CNS [18,56].

Regarding anti-CGRP mAbs, in the most recent FAERS disproportionality study covering years from 2018 to 2023 (65,792 total reports: erenumab 38,515; galcanezumab 19,485; fremanezumab 5332; eptinezumab 2460) [49], sleep-related terms emerged but at low frequencies and with modest signals overall. Insomnia was among the top events for subcutaneous anti-CGRP mAbs, with counts and proportions of erenumab 386 (2.40%), galcanezumab 203 (1.21%), and fremanezumab 93 (1.58%), each showing disproportionate signals relative to all other FAERS drugs (ROR 1.19, 1.34, and 1.52, respectively). Eptinezumab did not show an insomnia signal, likely due to fewer total reports. Abnormal dreams also generated signals for the three subcutaneous mAbs [erenumab: 52 (0.32%), ROR 2.32; galcanezumab 29 (0.17%), ROR 2.77; fremanezumab 10 (0.17%), ROR 2.37], suggesting a rare but recurrent phenotype across class [49]. To note, interpretation is constrained by spontaneous-reporting biases, under-reporting, confounding by indication, and non-estimable incidence. Nevertheless, FAERS supports that sleep-related AEs are uncommon overall, with small number of insomnia signals for subcutaneous mAbs and rare abnormal dreams.

Post-marketing pharmacovigilance data provide complementary insights into sleep-related adverse events also with gepants (zavegepant had minimal VigiAccess entries and no FAERS mining at that cutoff) [20]. Analysis of more than 10,000 reports from the most recent study, which assessed both VigiAccess and FAERS through March 2024, identified insomnia, somnolence, and abnormal dreams as the most relevant sleep-related adverse events, although all occurred infrequently. Insomnia was reported in less than 1% of cases for rimegepant, atogepant, and ubrogepant, with no consistent disproportionality signal across databases. Somnolence appeared more frequently, affecting approximately 1% of reports for rimegepant and atogepant in VigiAccess, and generated a strong, disproportionate reporting signal for ubrogepant in FAERS (ROR 5.97; lower 95% CI 4.60). Abnormal dreams and nightmares were particularly noted with atogepant, with FAERS analyses showing a robust signal (ROR 7.74; lower 95% CI 4.49), and to a lesser extent with ubrogepant (ROR 4.84; lower 95% CI 1.82), whereas they were rarely reported with rimegepant [20]. Overall, these findings

suggest that sleep-related adverse events with gepants are uncommon in routine clinical use, but may manifest as occasional insomnia, daytime somnolence, or vivid dreams, with some differences across individual gepants, probably also related to their acute or preventive use. As with all spontaneous reporting data, these signals do not establish causality or incidence rates. Table 2 reports the details of the included studies with sleep-related adverse events.

6. Implications and perspectives

Current findings suggest that anti-CGRP mAbs and gepants do not fundamentally alter sleep architecture but may improve sleep continuity and subjective quality. From a pharmacological perspective, this is a clear distinction between prior standard-of-care preventive agents (such as tricyclic antidepressants, antiseizure medications, beta-blockers), and anti-CGRP drugs. While the former act through broad neuromodulation and often exert sedative or sleep-disruptive effects, anti-CGRP drugs offer migraine-specific efficacy without major interference in sleep-wake physiology. This selective mechanism of action supports their use in patients where poor sleep quality and fatigue are already major comorbid issues. Furthermore, sleep-related adverse events emerging from pharmacovigilance studies and RCTs are uncommon or rare [20,48,49].

Pharmacologically, both anti-CGRP mAbs and gepants exhibit limited central nervous system penetration, making direct modulation of sleep-wake regulatory circuits less likely [18,56]. Monoclonal antibodies are large molecules that remain confined to the periphery [18,56], preventing access to hypothalamic or brainstem sites in available quantities where CGRP neurons influence arousal and circadian rhythms. Gepants, despite being small molecules, also exhibit relatively poor BBB permeability, with cerebrospinal fluid-to-plasma ratios typically <2%, suggesting only very limited central availability, although higher than that of anti-CGRP mAbs [18,56]. As such, the improvements in sleep quality consistently observed in clinical studies are more plausibly indirect, reflecting reduced migraine frequency and decreased pain-related nocturnal awakenings, rather than direct. It is noteworthy that sleep disturbances are increasingly recognized not only as a trigger for migraine attacks but also as part of the prodromal or premonitory symptom complex. Recent studies have shown that both preventive and acute CGRP-targeted therapies can reduce premonitory symptoms. For instance, a recent study demonstrated that galcanezumab decreases the frequency and severity of prodromal symptoms [57], while Goadsby et al. reported that ubrogepant administered during the early premonitory phase can abort attacks and attenuate associated symptoms [58]. From this perspective, the apparent improvement in sleep quality observed during treatment with anti-CGRP drugs might, at least in part, reflect the suppression of sleep-related premonitory phenomena rather than a direct effect on sleep regulation itself. In other words, by preventing the onset of migraine or reducing attack frequency, these therapies may also eliminate one of its early features, such as sleep disturbance. Further studies specifically designed to capture premonitory and interictal sleep changes could help clarify whether sleep improvement represents a true pharmacological effect of CGRP inhibition or simply the downstream consequence of aborting migraine pathophysiology at its earliest stages.

Finally, the sporadic reports of insomnia, somnolence, or abnormal dreams in real-world pharmacovigilance may represent idiosyncratic central effects in sensitive individuals or downstream consequences of altering peripheral nociceptive pathways, rather than evidence of robust direct neuromodulation. However, considering that the absence of evidence is not evidence of absence, the potential direct neuromodulation, above all with gepants, needs to be specifically investigated.

In preclinical studies, CGRP blockade may serve as a unique model for investigating the neurochemical crosstalk among the pain, arousal, and circadian systems [59,60]. CGRP-expressing neurons in the parabrachial nucleus and suprachiasmatic nucleus are ideally positioned to integrate nociceptive and circadian inputs. In clinical studies, stratification by pharmacological class (ligand-binding vs receptor-targeting mAbs, gepants vs anti-CGRP mAbs) may uncover differential sleep profiles. Comparative studies using polysomnography and actigraphy are required to determine whether these differences translate into clinically relevant improvements or risks. Given that poor sleep quality increases the risk of migraine chronification, and that effective migraine prevention may in turn normalize sleep patterns, anti-CGRP therapies could theoretically exert effects not only through pain control but also via sleep stabilization (indifferently if directly or indirectly). Conversely, the sporadic occurrence of insomnia or abnormal dreams highlights the need for clinicians to monitor sleep complaints during treatment and differentiate between drug-related phenomena and migraine-related sleep disruption.

To date, a key limitation is the heterogeneity of the included clinical studies in terms of design and outcome measures, together with the predominant reliance on validated self-reported sleep questionnaires rather than objective assessments such as polysomnography, which may limit measurement accuracy and increase the risk of reporting bias. It is also important to address the safety of long-term anti-CGRP therapy, particularly in the context of potential cumulative adverse effects and the limited biological specificity of CGRP pathway inhibition [61]. Given the widespread physiological role of CGRP in vascular regulation, gastrointestinal function, and nervous system homeostasis, prolonged blockade may theoretically interfere with these non-nociceptive pathways. Future clinical trials should incorporate standardized sleep endpoints alongside headache outcomes, ideally combining subjective questionnaires (PSQI, ISI, ESS) with objective measures (PSG, actigraphy), and explore dose-response relationships across the drug classes when possible (for instance with eptinezumab 100 vs 300 mg or atogepant 30 vs 60 mg). Clinically, the implications for CGRP and sleep with migraine also need to use an ideal combination of subjective and objective assessment tools. Nocturnal sleep disruptions, a marker of sleep efficiency, and many other parameters may be underreported by self-reported diaries. While PSG is useful as an objective assessment, it could be burdensome, with confounders like first night effect, and cannot be used effectively in patients with episodic migraine. There is a need for a search for related and interconnected biomarkers that can be

Practice points

Anti-calcitonin gene-related peptide (CGRP) drugs may:

- Improve sleep continuity and subjective sleep quality in patients with migraine without altering sleep architecture.
- Offer migraine-specific prevention without the sedative or sleep-disruptive effects seen with tricyclic antidepressants, beta-blockers, or antiseizure medications.
- Be monitored for rare sleep-related adverse events (insomnia, somnolence, abnormal dreams) emerging in real-world use.

Research agenda

Further research should determine:

- Whether anti-calcitonin gene–related peptide therapies exert direct neuropharmacological effects on arousal and circadian circuits beyond reducing migraine burden.
- The relationship between improvements in migraine frequency and changes in objective sleep parameters such as sleep efficiency and fragmentation.
- Optimize methodological approaches combining polysomnography, actigraphy, and standardized questionnaires to assess sleep in migraine trials.
- Biomarkers linking sleep quality fluctuations and migraine onset to guide precision prescribing and monitoring of sleep-related adverse effects.

studied to evaluate sleep quality over many days and their fluctuations to migraine onset. Actigraphy or even the development of technology that can be installed in smart watches to assess sleep quality in a less obstructive fashion. Finally, the identification, if any, of sleep-related adverse effects could inform precision prescribing, guiding drug selection based on individual susceptibility to insomnia, fatigue, or parasomnia.

7. Conclusion

Anti-CGRP therapies offer a pharmacologically selective approach for migraine that minimizes the sedative and disruptive side effects of some standard of care, including sleep-related disorders. Their interaction with sleep systems remains incompletely understood but represents a promising area for mechanistic exploration and clinical application. Future pharmacological research should aim to separate indirect improvements mediated by the reduction of migraine burden from direct neuromodulatory effects on arousal circuits, ultimately clarifying whether CGRP-targeted therapies can contribute to both migraine prevention and sleep regulation.

Authors' contributions

AB and LFI supervised the review, conducted the screening of studies (including magnetic resonance studies), and wrote the initial manuscript. All Authors critically reviewed the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Conflict of interest

LFI received financial support, consulting fees for the participation in advisory boards and support for attending meetings from: Teva, Eli Lilly, Lundbeck, Pfizer, Organon and AbbVie; he is Associate Editor for Frontiers in Neurology and junior editor for Confinia Cephalagica, Cephalalgia and Cephalalgia report.

GS received honoraria from AbbVie; he is a member of the editorial board of Neurology Residents and Fellows sections, junior editorial board of The Journal of Headache and Pain, and junior editor of Confinia Cephalgica.

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P.G. has been in advisory boards and/or received fees for lectures from Novartis, Lundbeck, Amgen, TEVA, Pfizer and AbbVie, and is Editor in Chief of Confinia Cephalalgica.

CA is Associate Editor for Frontiers of Human Neuroscience and Frontiers in Neurology Headache and Neurogenic Pain section; she received travel grants and/or personal fees for advisory boards and speaker panels, from Novartis, Eli-Lilly, Lundbeck, Teva, Lusofarmaco, Laborest, Abbvie/Allergan, Almirall, and Pfizer.

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