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ORIGINAL RESEARCH ARTICLE

Effect of Atogepant on Sleep Quality and Sleep-Related Adverse Events in Adult Patients with Migraine: A Prospective Observational 12-Week Study

Luigi Francesco Iannone[1,2] · Alberto Boccalini[1] · Flavia Lo Castro[1] · Daria Brovia[1] · Marina Romozzi[3,4] · Fabrizio Vernieri[5,6] · Claudia Altamura[5,6] · Simona Guérzoni[1]

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Abstract

Background Migraine is often associated with impaired sleep quality, including insomnia, fragmented sleep, and circadian rhythm disturbances. These factors can exacerbate migraine severity and chronification. Calcitonin gene-related peptide (CGRP), a key player in migraine pathophysiology, also influences sleep regulation. While CGRP monoclonal antibodies have shown mixed effects on sleep, no study to date has evaluated the impact of gepants on sleep quality. This study assessed whether atogepant, recently approved for migraine prevention, affects sleep quality and sleep-related adverse events in real-world settings.

Methods We conducted a prospective, observational, open-label, single-center study. All received atogepant 60 mg/day up to 12 weeks. Adults (≥ 18 years) with migraine (with/without aura or chronic migraine) experiencing ≥ 4 monthly migraine days were enrolled. Inclusion required ≥ 1 month of headache diaries and stable preventive or sleep treatments for ≥ 3 months. Patients were accepted regardless of prior preventive failures. Exclusion criteria were unstable treatments, recent sleep-impacting disease, and pregnancy. Sleep quality was assessed using five validated questionnaires (Pittsburgh Sleep Quality Index [PSQI], Athens Insomnia Scale [AIS], Bergen, Epworth Sleepiness Scale [ESS], Insomnia Severity Index [ISI]) at baseline and at follow-up. Migraine frequency, disability (Migraine Disability Assessment [MIDAS], Headache Impact Test [HIT-6]), allodynia (Allodynia Symptom Checklist [ASC-12]), acute medication use, and adverse events (AEs) were also recorded. Pre–post differences were assessed with Wilcoxon and McNemar's tests, while linear mixed-effects models were applied to evaluate the impact of clinical factors (response status, psychiatric comorbidities, prior anti-CGRP failures) on PSQI outcomes, with model fit estimated via REML and pseudo-R^2.

Results The study population included 43 participants (93.0% female, mean age of 51.6 [IQR 48.4–54.8] years, mean age at disease onset of 18.9 [16.0–21.7] years); 30 (69.8%) participants had chronic migraine, and among them, 23 (76.7%) had a concomitant diagnosis of medication overuse headache. Atogepant significantly improved sleep quality with PSQI scores decreased from 9.6 to 8.2 ($p = 0.002$) and improvements in AIS ($p = 0.014$) and Bergen scores ($p = 0.046$). Sleep duration was the only PSQI subdomain with a statistically significant change. No differences were found in ESS or ISI scores. Notably, no patients reported sleep-related AEs such as somnolence, nightmares, or vivid dreams. Psychiatric comorbidities were associated with poorer baseline sleep but did not influence the magnitude of improvement. Prior anti-CGRP failure predicted a lesser sleep benefit. Finally, migraine burden improved across all evaluated migraine-related variables. Only two patients discontinued treatment.

Conclusions Atogepant improved subjective sleep quality without causing sleep-related adverse events, supporting its role in comprehensive migraine management, particularly in patients with disrupted sleep.

Luigi Francesco Iannone and Alberto Boccalini have Contributed equally.

Extended author information available on the last page of the article

Key Points

Atogepant 60 mg daily for 12 weeks significantly improved subjective sleep quality, mainly through longer sleep duration, without causing sleep-related adverse events.

Migraine outcomes improved in parallel, with two-thirds of patients achieving ≥ 50% response and decreased disability scores.

Psychiatric comorbidities predicted poorer baseline sleep, and prior anti-calcitonin gene-related peptide (CGRP) monoclonal antibody failures predicted reduced sleep benefit, but with optimal overall tolerability.

1 Introduction

Migraine is a highly prevalent and disabling neurological disorder, affecting approximately 1 billion people worldwide [1]. It ranks among the leading causes of disability and is often associated with various comorbidities [2]. Among these, sleep disturbances, including insomnia, obstructive sleep apnea (OSA), restless legs syndrome (RLS), and circadian rhythm dysfunctions, are more common in individuals with migraine [3].

Sleep deprivation is a well-established trigger for migraine, and sleeping is also one of the most effective non-pharmacological treatments for acute migraine attacks [4]. Fragmented sleep, poor sleep quality, and circadian misalignment appeared to be more significant factors in migraine onset than total sleep duration [5].

Neuroimaging and sleep studies have demonstrated that patients with migraine often experience altered sleep architecture, including increased sleep onset latency, reduced slow-wave sleep (SWS), and fragmented REM sleep. The hypothalamus, which both regulates sleep–wake cycles and plays a central role in migraine pathogenesis, has been identified as a crucial link between these two conditions [6].

Calcitonin gene-related peptide (CGRP), a neuropeptide strongly involved in migraine pathophysiology, plays an important role in sleep regulation, particularly in the brain's arousal response to hypoxia [7–9]. It has been suggested that CGRP in patients with migraine may contribute to an increased risk of chronic insomnia and a heightened arousal threshold, although the underlying mechanisms remain unclear. CGRP may modulate sleep architecture, possibly through its effects on hypothalamic and brainstem circuits involved in arousal and circadian regulation, including the parabrachial nucleus that largely expresses CGRP [9]. Furthermore, in experimental models, the Drosophila homolog of CGRP functions as a negative regulator of sleep maintenance, promoting arousal in anticipation of dawn [8].

Anti-CGRP (or CGRP receptor) monoclonal antibodies (mAbs), namely erenumab, fremanezumab, galcanezumab, and eptinezumab, have substantially transformed migraine prevention [10, 11]. Only a few observational studies evaluated the effects of anti-CGRP mAbs, specifically the first available subcutaneous mAbs, on sleep quality and patterns. While findings have been inconsistent, they generally indicate a positive impact on sleep quality [12, 13]. CGRP-antagonism may influence sleep through modulation of hypothalamic circuits, particularly the suprachiasmatic nucleus and sleep-wake regulatory pathways [7, 14]. In addition, CGRP blockade may reduce brainstem activity within arousal-promoting regions, reducing hyperexcitability that disrupts normal sleep architecture [7, 14]. Altogether, these observations suggest that CGRP inhibition may play a direct or indirect role in sleep regulation.

Gepants, a novel class of selective CGRP-targeted therapies, act by antagonizing the CGRP receptor and are approved for acute treatment (rimegepant, ubrogepant, zavegepant) and preventive treatment (rimegepant and atogepant), with rimegepant being approved for both acute and preventive use [15–19]. However, no studies have been conducted to evaluate the impact of any gepant on sleep quality and disturbances as well as adverse events (AEs) on sleep related to their use.

Atogepant (10 mg or 60 mg) was recently approved in Europe for the preventive treatment of episodic (EM) and chronic migraine (CM) [17, 20]. Randomized clinical trials (RCTs) have extensively demonstrated its efficacy and tolerability, with the majority of AEs affecting the gastrointestinal system (primarily nausea and constipation) [17, 20]. Interestingly, some patients reported somnolence and fatigue, and a recent study collecting data from the US Food and Drug Administration Adverse Event Reporting System (FAERS) database identified a few signals of abnormal dreams and nightmares as unusual and unexpected AEs, findings that did not emerge during RCTs [21]. Whether these effects are treatment related, and by what mechanism, remains unknown.

Herein, we evaluated the impact of treatment (12 weeks) with atogepant 60 mg in clinical practice, aiming to assess sleep quality and disturbances in migraine patients, alongside migraine treatment effectiveness, using a panel of five standardized questionnaires.

2 Methods

2.1 Study Design

We performed a real-world, prospective, single-center, investigator-initiated, and independent study (Anápausis study), considering all consecutive outpatients treated with atogepant 60 mg orally for EM and CM at the Headache Center of Modena General Hospital, Modena, Italy.

In this study, we included all patients with a potential 12-week follow-up period, taking atogepant 60 mg tablet regardless of discontinuation for any reason from June to December 2024. Thus, patients who discontinued treatment but fulfilled the questionnaires at 12 weeks were included in the analysis.

The questionnaires to assess sleep quality and disturbance (see paragraph below) have been administered by a clinician expert in sleep management (AB) at baseline (before starting atogepant, T0) and after 3 months (T3), regardless of discontinuation of treatment.

The open online database Research Electronic Data Capture (REDCap) was used for data collection. During the study, atogepant was not subsidized by the Italian National Health Service. Therefore, patients received the drug under an agreement among the Italian Medicines Regulatory Agency (AIFA), regional healthcare systems, and the manufacturing company that provided the drug at no cost.

The local ethics committee approved the study as part of the *Registro Italiano Cefalee* (RICe) study (Studio RICe, 14591_oss CEAVC Studio RICe, 14591_oss and subsequent amendments). All patients signed a written informed consent before starting treatment with atogepant.

2.2 Patient Features

Participants were enrolled regardless of the number of preventive treatments interrupted for ineffectiveness or tolerability. Ineffectiveness was defined as no meaningful improvement in migraine-related variables after the administration of drugs for $\geq$ 6 weeks at the appropriate dose according to the European Headache Federation (EHF) criteria [22].

2.3 Inclusion/Exclusion Criteria

Inclusion criteria were: (i) patients aged 18 years or older; (ii) diagnosis of migraine without aura, with aura, or CM according to ICHD-3 [23]; (ii) at least 4 monthly migraine days (MMDs) in the 3 months before enrollment; (iii) availability of headache diaries over at least 1 month before enrollment; (v) clinical indication for prescription of atogepant 60 mg; and (vi) stable treatment with other preventive treatments for migraine or sleep 3 months prior and during the study.

Exclusion criteria were: (i) patients with any contraindications to atogepant according to the summary of product characteristics; (ii) no stable treatment for at least 3 months of any migraine drugs and during the study for sleep-inducing medications (including amitriptyline for migraine) and/or with a recent onset of a disease that significantly impacts sleep; and (iii) pregnancy and breastfeeding.

2.4 Collected Variables

Clinicians diagnosed migraine and collected clinical and demographic features through a face-to-face interview and a semi-structured questionnaire: concomitant and previous preventive treatments, monthly headache days (MHDs), number of monthly acute medications (AMNs), and days with at least one use of acute medications (AMDs) before atogepant first intake (i.e., baseline). We defined patients with medication overuse headache (MOH) as those patients with CM only with overuse of acute or symptomatic headache medication (on 10 or more days/month for triptans and combination analgesics or 15 or more days/month for non-opioid analgesics) for more than 3 months and a related secondary headache, according to ICHD3 definition [23]. Timing of administration, subdivided into morning (06:01–18:00) and evening (18:01–06:00) or irregular (i.e., random hours during the day), was reported. Other clinical variables, including comorbidities, were reported according to patients' charts and outpatient interviews during clinical practice. In particular, psychiatric comorbidities defined as patient-reported or clinically recognized symptoms of anxiety and/or depression were not classified as major psychiatric disorders per DSM-5, but were considered comorbid affective symptoms, as often associated with migraine burden. For each patient, the interview included targeted questions to assess both anxiety and depressive symptoms; these covered emotional and somatic dimensions and the presence of somatic complaints. No standardized tools were used to assess these symptoms.

The presence of stable co-treatments (for migraine or any other treatment) was also reported according to patients' charts and outpatient interviews. Finally, a panel of questionnaires for migraine disability was administered at baseline and after 12 weeks of therapy (T3): the Headache Impact Test (HIT-6)[24], the Migraine Disability Assessment (MIDAS) questionnaire [25], the 12-item Allodynia Symptom Checklist (ASC-12) [26], and the Migraine Interictal Burden Scale (MIBS-4) [27]. The Patient's Global Impression of Change (PGIC) was administered at T3 [28].

To evaluate the overall burden of migraine, we evaluated MHDs as headache days, defined as any day on which a patient recorded any type of headache.

Any AEs were collected, with particular attention to sleep-related AEs, including diurnal somnolence, vivid dreams, nightmares, and insomnia, using open-ended questions and examples, according to clinical practice in outpatient visits. Patients were instructed to report all events occurring during the 12-week period and they were allowed to contact the headache center for any concerns about adverse events.

2.5 Questionnaires for sleep assessment

We administered five questionnaires to assess sleep quality and disturbance at baseline (T0) and after 12 weeks of treatment (T3):

1. Pittsburgh Sleep Quality Index (PSQI) [29]: assessing overall sleep quality and disturbances over the past month. It consists of 19 self-reported items in 7 key domains of sleep quality: (1) subjective sleep quality; (2) sleep latency; (3) sleep duration; (4) habitual sleep efficiency; (5) sleep disturbances; (6) use of sleep medication; and (7) daytime dysfunction. These domains are compiled into a global score, where a cutoff score of > 5 differentiates poor sleepers from good sleepers. The minimum PSQI score is 0 (indicative of no sleep disturbances), while the maximum score is 21 (severe sleep impairment).
2. Athens Insomnia Scale (eight items, AIS-8) [30]: screening and assessing the severity of insomnia. It includes eight items measuring sleep onset, nighttime and early morning awakenings, sleep quality, and the impact of insomnia on daily functioning. The total score for the AIS-8 ranges from 0 to 24 and evaluates insomnia severity, with lower scores indicating better sleep quality. The cutoff from good sleep to mild to moderate insomnia was assessed as ≥ 6 on the total score.
3. Bergen Insomnia Scale [31]: a six-item questionnaire (each scored on a scale from 0 to 7) evaluating sleep difficulties and their frequency over the past month. It assesses sleep onset latency, nighttime awakenings, early morning awakenings, sleep dissatisfaction, and the impact of insomnia on daily life. The total score ranges from 0 to 42, with higher scores indicating greater insomnia severity. To be classified as positive scores at least one of the first four questions (A criteria) must be ≥ 3 (i.e., symptoms present at least 3 days per week) and at least one of the last two questions (B criteria) must be ≥ 3.
4. Epworth Sleepiness Scale (ESS) [32]: a widely used tool in sleep medicine for measuring excessive daytime sleepiness using 8 items (scoring 0–3 points). It consists of eight scenarios in which respondents rate their likelihood of sleeping, providing an indication of overall sleepiness levels. The total ESS score ranges from 0 to 24, with higher scores indicating greater daytime sleepiness. The cutoff score was assessed as ≥ 10 (normal to mild excessive daytime sleepiness).
5. Insomnia Severity Index (ISI) [33]: a brief, seven-item questionnaire assessing the severity of insomnia symptoms, sleep dissatisfaction, daytime impact, and distress. It is commonly used for screening and evaluating treatment outcomes. Each item is rated on a 0–4 scale, and the total score ranges from 0 to 28. A higher score suggests more severe insomnia. The cutoff used was ≥ 8 (from no clinically significant insomnia to subthreshold insomnia).

2.6 Outcomes

The co-primary outcomes were: (i) changes in sleep quality/disturbance after 12 weeks of treatment compared with baseline in the PSQI, AIS, Bergen, ESS, and ISI questionnaires total score; and (ii) the occurrence of sleep-related treatment-emergent adverse events (TEAEs) to evaluate the safety of the drug in a real-world population.

Secondary outcomes included from baseline to T3:

i. changes in the PSQI, AIS, Bergen, ESS, and ISI questionnaires clinical cutoffs (as defined above);
ii. changes in the PSQI seven subitems;
iii. changes in MHDs;
iv. percentage of responders (namely patients who presented a reduction of MHDs ≥ 50% [RR50%] compared with baseline) after 12 weeks of treatment;
v. changes in acute medication use (both AMNs and AMDs);
vi. percentage of patients with MOH reverted during treatment;
vii. changes in ASC-12 questionnaire scores (0–24 scale);
viii. changes in HIT-6 questionnaire scores (36–78 scale);
ix. changes in MIDAS questionnaire (0–270 scale);
x. descriptive evaluation of the patient satisfaction measured with the PGIC questionnaire.

2.7 Statistical Analysis

Due to the lack of data on the overall effects of gepants in real-world settings, particularly on sleep, we did not perform a structured sample size calculation and based the analysis on a convenient sample. The normality test by means of the Shapiro–Wilk test proved the non-normality of several variables. Thus, statistical analysis was conducted with non-parametric tests. We reported mean [95% confidence interval or interquartile range (IQR) or mean plus standard deviation (SD) as appropriate] for continuous variables and number

(percentage) for categorical data. No imputation was made for missing data, which are reported in tables and in the text. Pre–post treatment differences within groups for quantitative variables were compared using the Wilcoxon signed-rank test, while the exact McNemar's test was applied for proportions in paired samples. A Mann–Whitney *U* test was conducted to assess differences between two independent groups for continuous variables.

To evaluate whether some clinical relevant variables could impact sleep improvement, we performed both repeated measures generalized linear models (GLMs) and linear mixed-effects models (LMMs). Considering the baseline variability of variables included, we reported only the LMMs models in the manuscript. The variables were selected on the basis of clinical relevance, and the number of predictors included in the model was limited to ensure the appropriate model fit given the small sample size.

A first LMM was conducted to evaluate the effect of time (baseline versus 12 weeks), 50% response rate in MMDs (RR50%), and psychiatric comorbidity on sleep quality, as measured by the PSQI (dependent variable). The dataset was structured with each participant contributing two observations (one at baseline and one at follow-up). Time was modeled as a within-subject factor, while RR50% response and psychiatric comorbidity (categorical) were treated as between-subject categorical fixed effects. Interactions between time and each of the two between-subject variables were included to explore differential change from baseline to 12 weeks.

Estimated marginal means (EMMs), i.e., least-squares means, were computed to explore the effects of the fixed factors and their interactions on PSQI scores.

To account for the interindividual variability in baseline PSQI scores, a random intercept for subject (ID) was included in the model. A random slope for time was initially tested but was removed due to convergence issues. The repeated measures structure was modeled using a compound symmetry (CS) covariance matrix, appropriate for two equally spaced timepoints. The model was estimated using restricted maximum likelihood (REML). Model fit was evaluated using Pseudo $R^2 = [1 - (\text{residual variance full model / residual variance null model})]$ and residual variability (σ^2).

A second LLM was conducted to examine the main effect of time (baseline versus 12 weeks), prior anti-CGRP mAbs failures, and psychiatric comorbidity on sleep quality, as measured by PSQI. The same interactions and model characteristics were applied.

A two-tailed p-value < 0.05 was considered significant for all variables, with a Bonferroni's correction where appropriate. All data were analyzed using SPSS software version 29.0 (IBM Corp. SPSS Statistics, Armonk, NY, USA), and graphs were designed using GraphPad Prism version 10.00 (La Jolla, USA).

3 Results

The final study population included 43 participants (93.0% female, mean age of 51.6 [IQR 48.4–54.8] years, mean age at disease onset of 18.9 [IQR 16.0–21.7] years); 30 (69.8%) participants had CM, and among them, 23 (76.7%) had a concomitant diagnosis of MOH. Figure 1 reported the study flowchart, with only two patients discontinuing treatment for adverse events (see below).

At baseline, participants presented a mean of 20.5 [IQR 17.9–23.0] MHDs, and a mean of 18.3 [IQR 15.9–20.8] days of AMDs and 24.0 [19.1–28.9] doses of acute AMNs. A mean 5.4 [IQR 4.0–6.8] score at ASC-12 was reported. Clinical and demographic features, as well as disability (MIDAS and HIT-6) questionnaire scores, are fully detailed in Table 1.

The average number of previously failed preventive classes was 2.7 [IQR 2.3–3.2]. In total, 27 patients (62.8%) were previously in treatment with other CGRP-targeting therapies and 23 (53.5%) with onabotulinumtoxinA. Previous preventive treatments are detailed in Table S1 in the supplementary material (Fig. 2).

A total of 19 participants (44.2%) were under other preventive treatment at baseline, and 23 (53.5%) had at least one comorbidity (Table 1), and among them 9 (20.3%) had a psychiatric comorbidity (as defined above). The included patients did not report any known sleep disorders.

Atogepant was prescribed for one or more of the following reasons: lack of effectiveness of previous preventive

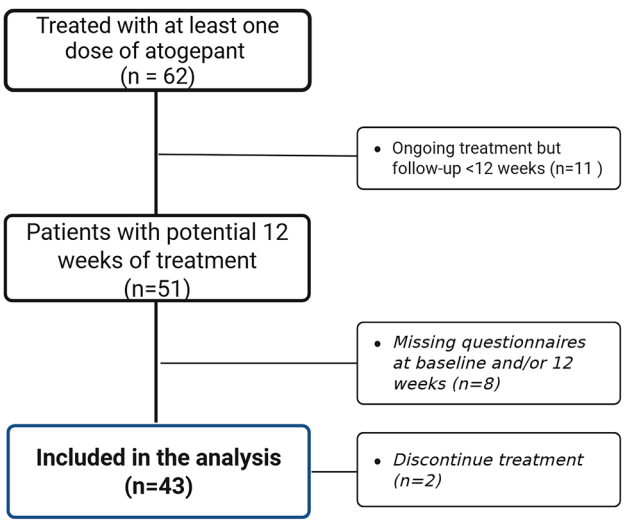

Figure 1 Flow chart of patients

Table 1 Clinical and demographic features of the overall population

	Cohort ($n = 43$)
Age years; mean (SD)	51.67 (10.3)
Female sex, % (n)	93.0 (40)
Onset age years; mean (SD)	18.9 (8.8)
CM, % (n)	69.8 (30)
MOH, % (n)[a]	76.7 (23)
Age of chronicization, mean (SD)[a]	35.3 (9.2)
BMI kg/m^2; mean (SD)	23.29 (4.22)
Weight kg; mean (SD)	62.1 (12.8)
Pain intensity (NRS), mean (SD)	7.7 (0.9)
Clinically relevant comorbidities, % (n)	53.5 (23)
Vascular	25.6 (11)
Psychiatric	20.9 (9)
Gastroenterological	14.0 (6)
Neurological	4.7 (2)
Immunological	14.0 (6)
Endocrinological	20.9 (9)
Migraine related variables, mean (SD)	
MHDs	20.51 (8.2)
AMNs	24.0 (15.9)
AMDs	18.3 (7.9)
MIDAS	77.67(65.2)
HIT-6 [n]	67.24 (5.0) [41]
ASC-12 [n]	5.4 (4.2) [42]

Percentages are calculated on column total

CM, chronic migraine; *MOH*, medication overuse headache; *BMI*, body mass index; *MHDs*, monthly headache days; *AMNs*, number analgesics per month; *AMD*; days with at least one analgesics use per month; *HIT-6*, headache impact test; *MOH*, medication overuse headache; *MIDAS*, Migraine Disability Assessment questionnaire; SD, standard deviation

[a]Calculated in patients with CM

treatments (97.7%), partial effectiveness (4.7%), or adverse events/lack of tolerability (2.3%).

Regarding the timing of atogepant administration, 76.7% of patients (33/43) took it in the morning, 20.9% (9/43) in the evening, and 2.3% (1/43) at random times during the day. Overall, 74.4% of patients took atogepant with food. Only two subjects (4.6%) dropped out of the treatment with atogepant due to adverse events (i.e., nausea) and poor tolerability (Fig. 3).

3.1 Quality of Sleep and Insomnia Questionnaires

From baseline to T3, the total PSQI score was significantly reduced from a mean of 9.6 (95% CI 8.3,10.8) to 8.2 (95% CI 6.9, 9.4), $p = 0.002$ (Table 2). Regarding PSQI seven subdomains, although all domains were reduced (and therefore positive for sleep pattern), only sleep duration (third domain, indicating longer sleep duration) significantly differed after 12 weeks of treatment, from 1.3 (95% CI 1.1, 1.5) to 0.8 (95% CI 0.6, 1.1) score ($p = 0.003$); other domains were not statistically significantly different (Table 3).

The AIS and the Bergen questionnaires total scores were significantly reduced from 8.0 (95% CI 6.6, 9.4) to 7.1 (95% CI 5.7, 8.5), $p = 0.014$, and from 16.8 (95% CI 14.1, 19.6) to 15.1 (95% CI 12.2, 18.0), $p = 0.046$, respectively, after 12 weeks of treatment. No significant changes were reported for the ESS and ISI total score questionnaires ($p = 0.49$ and $p = 0.25$, respectively). All results are detailed in Table 2.

Categorizing specific cutoffs that underline clinical significance (*e*.g., presence of insomnia or diurnal somnolence) for different questionnaires (reported above and in Table 4), no significant changes above the cutoff were reported in the patients before and after 12 weeks of treatment. Notably, there was no difference in total

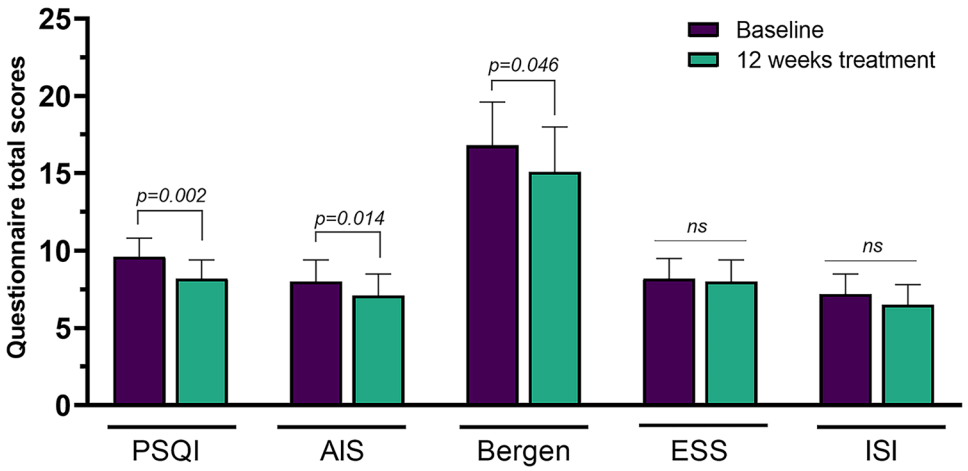

Figure 2 Sleep questionnaires total score at baseline and after 12 weeks with atogepant. *AIS*, Athens Insomnia Scale; *Bergen*, Bergen Insomnia Scale; *ESS*, Epworth Sleepiness Scale; *ISI*, Insomnia Severity Index; *Ns*, not significant; *PSQI*, Pittsburgh Sleep Quality Index

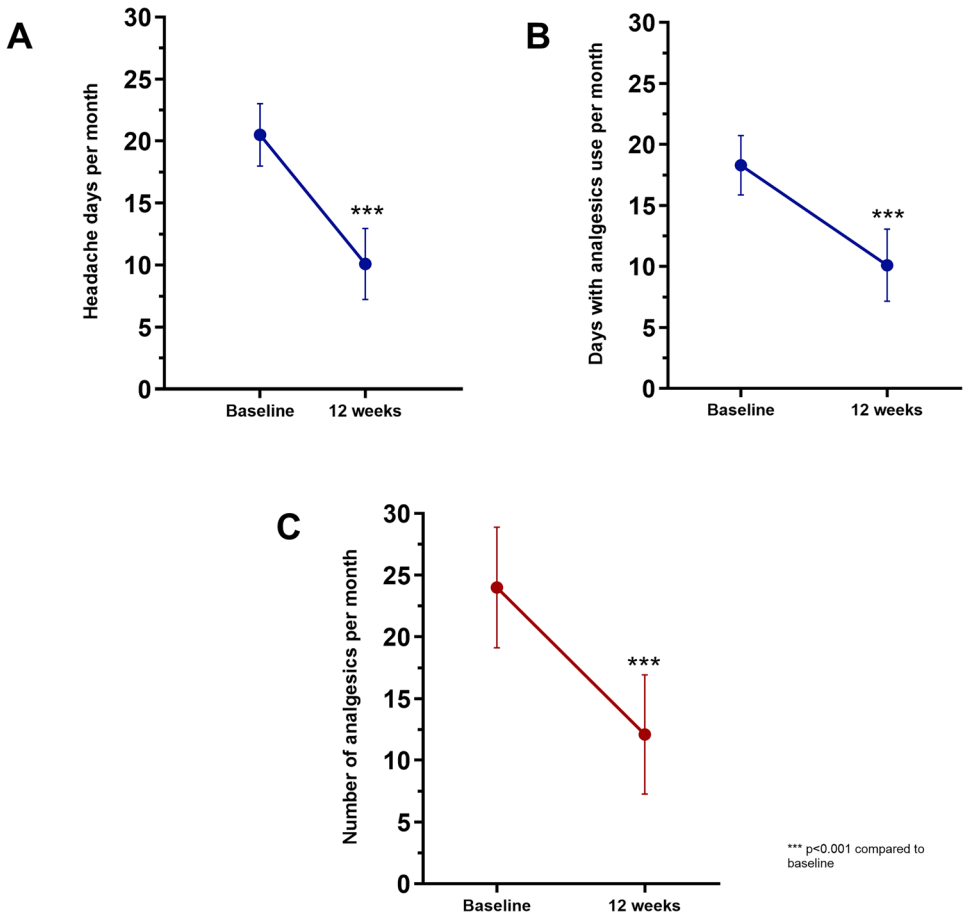

Figure 3 Migraine-related variables (MHD, AMDs, and AMNs) at baseline and after 12 weeks with atogepant. *AMD*; days with at least one analgesic use per month; *AMNs*, number analgesics per month; *MHDs*, monthly headache days

Table 2 Sleep quality and insomnia questionnaires at baseline and after 12-week therapy with atogepant

Total score	T0	T3	Change (mean, 95% CI)	*p-Value*
PSQI	9.6 (8.3, 10.8)	8.2 (6.9, 9.4)	−1.3 (−2.3, −0.4)	**0.002**
AIS	8.0 (6.6, 9.4)	7.1 (5.7, 8.5)	−0.9 (−1.6, −0.1)	**0.014**
Bergen	16.8 (14.1, 19.6)	15.1 (12.2, 18.0)	−1.6 (−3.8, 0.4)	**0.046**
ESS	8.2 (7.0,9.5)	8.0 (6.7, 9.4)	−0.3 (−1.3, 0.9)	0.497
ISI	7.2 (5.8, 8.5)	6.5 (5.2, 7.8)	−0.6 (−1.7, 0.3)	0.251

Values in bold are statistically significant. All values are reported as mean (95% CI)

PSQI, Pittsburgh Sleep Quality Index; *AIS*, Athens Insomnia Scale; Bergen Insomnia Scale; *ESS*, Epworth Sleepiness Scale; *ISI*, Insomnia Severity Index

questionnaire scores and patients reaching the clinically significant cutoff in patients with atogepant administration in the morning or in the evening, although the small sample size limits any further consideration (Fig. 4).

Regarding the other co-primary outcome on sleep-related TEAEs, no specific TEAEs or AEs (including somnolence, vivid dreams, and nightmares) were reported.

3.2 Influence of Response Status, Prior anti-CGRP Failure, and Psychiatric Comorbidities on Sleep Improvement

The first model, including RR50% and psychiatric comorbidities, demonstrated a significant main effect of time

Table 3 Pittsburgh Sleep Quality Index (PSQI) seven subdomains at baseline and after 12-week therapy with atogepant

Total score	T0	T3	Change (mean, 95% CI)	*p-Value*
Subjective sleep quality	1.4 (1.2, 1.7)	1.3 (1.0, 1.5)	−0.1 (−0.3, 0.05)	0.166
Sleep latency	1.1 (0.8, 1.4)	1.1 (0.8, 1.3)	−0.06 (−0.3, −0.1)	0.467
Sleep duration	1.3 (1.1, 1.5)	0.8 (0.6, 1.1)	−0.4 (−0.7, −0.1)	**0.003**
Habitual sleep efficiency	1.5 (1.1, 1.8)	1.3 (0.9, 1.6)	−0.2 (−0.5, 0.1)	0.327
Sleep disturbances	1.7 (1.5, 1.9)	1.6 (1.4, 1.8)	−0.07 (−0.2, 0.1)	0.405
Use of sleep medication	1.0 (0.6, 1.5)	0.8 (0.4, 1.2)	−0.2 (−0.5, 0.1)	0.196
Daytime dysfunction	1.4 (1.1, 1.7)	1.1 (0.8, 1.4)	−0.3 (−0.6, 0.05)	0.068

Values in bold are statistically significant. All values are reported as mean (95% CI)

PSQI, Pittsburgh Sleep Quality Index

Table 4 Sleep quality and insomnia questionnaires clinical cutoffs at baseline and after 12-week therapy with atogepant

	T0	T3	Change	*p-Value*
PSQI (> 5 score)	36 (83.7)	31 (72.1)	−5 (−11.6)	0.125
AIS (≥ 6 score)	31 (72.1)	25 (58.1)	−6 (−14.0)	0.070
Bergen (criteria-based cut off[a])	27 (62.8)	26 (60.5)	−1 (−2.3)	1.00
ESS (≥ 10 score)	13 (30.2)	16 (37.2)	3 (7.0)	0.607
ISI (≥ 8 score)	18 (41.9)	17 (39.5)	−1 (−2.3)	1.00

[a]Score of ≥ 3 on at least one of the first four items AND score ≥ 3 on at least one of the last two items. Data are expressed as *n* (%). *PSQI*, Pittsburgh Sleep Quality Index; *AIS*, Athens Insomnia Scale; Bergen Insomnia Scale; *ESS*, Epworth Sleepiness Scale; *ISI*, Insomnia Severity Index

($F(1,40) = 9.615$, $p = 0.004$), indicating that PSQI scores significantly improved during treatment, regardless of other factors. There was also a significant main effect of psychiatric comorbidity ($F(1,40) = 6.175$, $p = 0.017$), with patients reporting psychiatric conditions having significantly worse sleep quality overall.

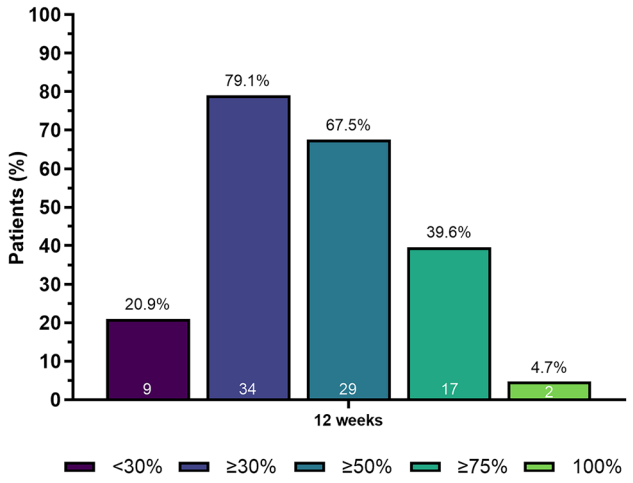

Figure 4 Response rate (RR%) after 12 weeks of treatment. Note: Number in the columns (in white) report the absolute number of patients. Patients can be included in more categories

The main effect of RR50% was not statistically significant ($F(1,40) = 1.695$, $p = 0.200$), indicating no overall difference in PSQI scores between responders and non-responders across timepoints. However, time (pre–post treatment) × RR50% interaction approached significance ($F(1,40) = 3.383$, $p = 0.073$), suggesting a possible trend toward greater sleep improvement over time in responders, though this did not reach statistical significance. The time (pre–post treatment) × psychiatric comorbidity interaction was not significant ($p = 0.936$), indicating that psychiatric status did not influence the rate of change in PSQI scores over time.

Estimated marginal means showed that patients without psychiatric comorbidity improved from a mean PSQI of 9.33 (standard error [SE] 0.70) at baseline to 7.64 (SE 0.70) at 12 weeks, while those with comorbidity improved from 12.64 (SE 1.24) to 10.86 (SE 1.24), indicating overall higher PSQI scores but a parallel improvement trend. Regarding treatment response, nonresponders improved from 12.19 (SE 1.01) to 9.53 (SE 1.01), whereas responders had better PSQI at baseline (9.79, SE 0.86) and showed a smaller improvement to 8.96 (SE 0.86).

Variance components revealed moderate residual variability ($\sigma^2 = 4.374$) and moderate correlation between repeated measurements (CS covariance = 9.341). The comparison with a null model ($\sigma^2 = 5.419$) indicated that the fixed effects explained approximately 19.3% of the variance in PSQI scores (pseudo R^2).

In the second model, including prior anti-CGRP mAbs failure and psychiatric comorbidities, there was a confirmed significant main effect of time ($F(1,40) = 7.006$, $p = 0.012$), indicating improved PSQI scores after 12 weeks. Psychiatric comorbidity was also a significant predictor ($F(1,40) = 7.313$, $p = 0.010$), with poorer sleep quality observed among patients with psychiatric disorders. The interaction between time (pre–post treatment) and psychiatric comorbidity was

not significant (F (1,40) = 0.953, $p = 0.335$), suggesting that the rate of PSQI improvement did not differ on the basis of psychiatric status. To note, anti-CGRP mAbs failure did not show a significant main effect (F (1,40) = 0.251, $p = 0.619$); however, the time (pre–post treatment) × anti-CGRP prior failure interaction was significant (F (1,40) = 4.551, p = 0.039), indicating that the degree of improvement in sleep quality over time differed depending on anti-CGRP treatment history, with less improvement in patients that failed prior anti-CGRP mAbs.

Estimated marginal means showed that patients with psychiatric comorbidity had higher PSQI scores at both baseline (12.80, SE 1.25) and 12-week follow-up (10.80, SE 1.25), compared with those without comorbidity (baseline 8.69 and follow-up 7.78, SE 0.68). Therefore, although both groups improved, patients with psychiatric symptoms maintained higher PSQI scores. Regarding treatment response, patients without prior anti-CGRP failure showed a modest improvement (from 10.52 to 10.07, SE 0.97), while those with prior failure improved more noticeably (from 10.97 to 8.51, SE 0.88), suggesting that patients with prior treatment failure may benefit more in terms of sleep quality.

Variance components revealed moderate residual variability ($\sigma^2 = 4.259$) and moderate correlation between repeated measurements (CS covariance = 9.812). The comparison with a null model ($\sigma^2 = 5.419$) indicated that the fixed effects explained approximately 21.4% of the variance in PSQI scores (pseudo R^2).

Thus, neither response status (RR50%) nor psychiatric comorbidity significantly modified the rate of improvement. On the contrary, PSQI improvement over time differs on the basis of CGRP failure history. As confirmed in both models, psychiatric comorbidities were associated with persistently worse sleep quality overall, and there was a trend suggesting that patients who responded to migraine treatment may have experienced better sleep quality.

3.3 Migraine-Related Variables

A significant reduction was observed across all the migraine-related variables evaluated. MHDs changed a mean of −10.3 (95% CI −12.8, −7.8) ($p < 0.001$) after 12 weeks of treatment. A response rate ≥ 50% (RR50% in MHDs) was achieved by 67.4% (29/43) of patients, with 39.6% (17/43) achieving a response ≥ 75%. Two patients (4.7%) achieved migraine freedom (i.e., no more migraine attacks) at 12 weeks. A significant reduction in the use of analgesics was also reported, with AMNs decreasing by 11.8 (95% CI −16.0, −7.6; $p < 0.001$) and AMDs declining by 8.3 (−10.5, −5.9; $p < 0.001$). Patients with MOH also significantly decreased from 23 (76.7%) to 17 (39.5%); $p < 0.001$.

Disability and headache-related burdens were also significantly improved. The MIDAS score decreased by 44.9 (95% CI −63.7, −26.1) at 12 weeks ($p < 0.001$), while HIT-6 scores dropped by 15.3 points (95% CI −19.0, −11.6; $p < 0.001$). Patient-reported allodynia severity, measured through the ASC-12, showed a mean reduction of 3.2 points (95% CI −4.6, −1.7; $p < 0.001$). The PGIC score after 12 weeks of treatment has a mean of 5.42 (SD 1.72). All data, including reduction from T0 to T3, are reported in Table 5.

3.4 Overall Tolerability and Adverse Events Analysis

At least one adverse event was reported in 51.2% of cases (22/43). Only five subjects reported more than one AE. Most (90.0%) adverse events were mild and self-limiting. Two AEs were severe or intermediate (both nausea) as intensity and led to treatment discontinuation. The most common adverse events were constipation (37.2%, $n = 16$), lack of appetite (18.6%, $n = 8$), and nausea (9.3%, $n = 4$) (Table 6).

4 Discussion

In the present study, we demonstrated an improvement in sleep quality with atogepant during the first 12 weeks of treatment in a population of individuals with migraine and a high disease burden, in a real-world setting. Furthermore, no patients reported sleep-specific AEs (e.g., nightmares, vivid dreams, or insomnia), and no overall impairments in sleep quality emerged when assessed using multiple specific questionnaires.

Our findings can be summarized as follows: (i) 12-week treatment with atogepant significantly improved the PSQI

Table 5 Patient reported outcomes and migraine-related variables at baseline and after 12-week therapy with atogepant

	T0	T3	Change (mean, 95% CI)	*p-Value*
MHDs	20.5 (8.2)	10.1 (9.3)	−10.3 (−12.8, −7.8)	**< 0.001**
AMNs	24.0 (15.9)	12.2 (15.7)	−11.8 (−16.0, −7.6)	**< 0.001**
AMDs	18.3 (7.9)	10.1 (9.6)	−8.3 (−10.5, −5.9)	**< 0.001**
MIDAS	69.1 (51.8)	32.7 (39.0)	−44.9 (−63.7, −26.1)	**< 0.001**
HIT-6 ($n = 41$)	64.8 (8.3)	51.9 (11.7)	−15.3 (−19.0, −11.6)	**< 0.001**
ASC-12 ($n = 42$)	6.2 (4.9)	2.1 (2.7)	−3.2 (−4.6, −1.7)	**< 0.001**

Table 6. Treatment-emergent adverse events, intensity, and drop-out rates after 12 weeks of treatment with atogepant

	Total cohort ($n = 43$)
Patients with at least one treatment-emergent adverse events, *n* (%)	22 (51.2)
Number of adverse events ($n = 22$), *n* (%)	
Constipation	16 (37.2)
Lack of appetite	8 (18.6)
Nausea	4 (9.3)
Fatigue	2 (4.7)
AEs intensity, *n* (%)[a]	
Mild	18/20 (90.0)
Intermediate	1/20 (5.0)
Severe	1/20 (5.0)
Dropout rate, *n* (%)	2 (4.6)

[a]Calculated on 20 adverse events. Percentages are calculated on column total if not otherwise specified.

total score (assessing overall sleep quality and disturbances) from 9.6 (8.3–10.8) to 8.2 (6.9–9.4), with a significant improvement in the sleep duration subdomain; (ii) an overall improvement in PSQI scores was observed regardless of psychiatric comorbidities or response status (RR50%) but influenced by prior anti-CGRP treatment failures; (iii) psychiatric comorbidities contributed to poorer sleep quality overall; and (iv) no sleep-related AEs, diurnal somnolence, or overall sleep disturbances were reported in our cohort.

These findings contribute to the growing body of evidence suggesting that CGRP antagonists may influence sleep-related parameters. Previous studies have demonstrated that gepants effectively reduce migraine frequency and severity, but their impact on sleep has largely been overlooked [34]. However, a meta-analysis of clinical trials on atogepant identified somnolence and fatigue as frequently reported emergent adverse events associated with its use [35]. Additionally, the FAERs database reported a small proportion of patients experiencing nightmares and vivid dreams following atogepant treatment [21].

No cases of self-reported somnolence were observed. This finding was further supported by results from the ESS, which indicated a very low percentage of patients experiencing daily somnolence at baseline and after 12 weeks of treatment, with no significant difference. Notably, no significant differences in sleep outcomes (as assessed by five different questionnaires) were observed on the basis of whether atogepant was administered in the morning or the evening. However, the small sample size of this study limits its power to detect less common adverse events, and further confirmation is needed in larger studies with a more defined timeframe for administration.

Few studies have specifically examined the effects of anti-CGRP mAbs on sleep quality. One observational study explored the impact of galcanezumab, erenumab, and fremanezumab on sleep disturbances and patterns in migraine patients using the PSQI questionnaire. The study reported a significant improvement in PSQI scores after 3 months of treatment, together with their effectiveness in reducing migraine-related symptoms [12].

Another study evaluating a 12-month treatment with erenumab suggested a potential influence of CGRP modulation on sleep patterns (assessed using PSQI, the Sleep Condition Indicator [SCI], and the ESS), as well as on chronotype (assessed with the Morningness–Eveningness Questionnaire [MEQ-SA]). An initial slight reduction in insomnia was observed with an improvement in SCI scores and a reduction in perceived sleepiness; however, these effects were not confirmed in later follow-ups. Statistical significance was only reached for SCI score variations [13]. Interestingly, patients who initially had a morning chronotype (MEQ score) exhibited a shift toward an intermediate chronotype during erenumab therapy. However, this change was not statistically significant in subsequent follow-ups.

A study using two sleep questionnaires (ESS and PSQI) and home polysomnography (PSG) evaluated the effect of erenumab after 3 and 12 months of treatment, demonstrating an improvement in both subjective and objective sleep quality in patients with migraine [36].

On the contrary, another study evaluating galcanezumab on "whole pain burden "assessed the quality of sleep by the Medical Outcomes Study (MOS) Sleep Scale, a self-reported scale able to evaluate six different disturbances (i.e., difficulty falling asleep and maintaining sleep, daytime sleepiness, respiratory disorders, presence of ronchopathy, amount of sleep), showing no change in quality of sleep assessed by the MOS sleep scale from baseline after the third and sixth administration [37].

Finally, in a previous study conducted by our group, which assessed the effectiveness of anti-CGRP mAbs in 80 patients with migraine, 38.8% of participants reported improved sleep quality, while 5.0% reported worsening. However, it should be noted that this study did not use standardized sleep questionnaires, and sleep quality was only a secondary topic of investigation [38].

It is important to note that atogepant may differ in its impact on sleep due to pharmacological and pharmacokinetic properties from anti-CGRP mAbs. Atogepant is a small-molecule receptor antagonist with oral administration, rapid absorption, a relatively short half-life (~ 11 h), and once-daily dosing [39, 40], whereas mAbs require parenteral administration and maintain prolonged systemic exposure over several weeks [41]. These distinctions may influence both the onset and variability of sleep-related effects. Moreover, the possibility of adjusting oral dosing and timing provides a unique interaction with circadian regulation and sleep-wake cycles, a feature not applicable to long-acting

anti-CGRP mAbs. A comparative study on the effect of sleep among anti-CGRP drugs could be highly informative.

Overall, these findings suggest that CGRP inhibition may contribute, directly or indirectly, to better sleep regulation, aligning with our results. Whether these effects stem from direct CGRP modulation in the hypothalamus (or other brain regions) or are secondary to reductions in migraine frequency and severity remains an open question [6]. However, since gepants, and to an even lesser extent mAbs, cross the blood–brain barrier minimally, a direct effect on sleep appears unlikely and requires further investigation [42, 43]. However, this does not preclude gepants from exerting limited central effects in areas with reduced barrier function, such as the trigeminal *nucleus caudalis*, area postrema, and circumventricular organs. Interestingly, ubrogepant was shown in a randomized controlled trial to be effective even during the prodrome phase (including symptoms such as cognitive dysfunction) [44].

Of note, our study showed a trend suggesting that patients who achieved response status (RR50%) may have experienced better overall sleep quality (according to PSQI score), though this was not statistically confirmed. We can speculate on the possibility that, similarly to improvement in migraine-related variables, longer periods are needed to maximize the effect on sleep and demonstrate a correlation with response rates. As expected, psychiatric comorbidities contributed to poorer sleep quality overall, but interestingly, this does not impact the rate of improvement over time. On the contrary, prior anti-CGRP mAb failure has a significant role in sleep improvement, with patients who were anti-CGRP naïve reporting higher sleep quality after 12 weeks of treatment. This finding is in line with results on switching, showing less improvement in migraine-related outcomes (including response rate) compared with naïve patients. Further studies are needed to confirm these findings and explore the potential mechanisms.

Sleep is a crucial factor in assessing quality of life. Several studies have demonstrated a strong relationship between sleep quality and migraine severity [45]. Patients with impaired sleep quality or frequent nighttime awakenings tend to experience more migraine attacks and increased medication use compared with those with good sleep quality [3, 45]. Furthermore, a disrupted sleep–wake balance may exacerbate migraine severity. Given the well-established association between sleep disturbances and migraine chronification, our findings emphasize the importance of incorporating sleep assessments into migraine studies [46]. Future research should explore objective sleep measures such as polysomnography and actigraphy to determine whether atogepant modifies sleep architecture, including REM latency, slow-wave sleep, and sleep efficiency. Interestingly, a recent case-control study [47] investigated sleep bruxism, obstructive sleep apnea, and migraine in patients with temporomandibular disorders using polysomnography. A total of 30 patients with migraine were compared with 89 controls without migraine. Patients with migraine and TMD showed more frequent mixed bruxism and longer SB episodes, but no overall link between migraine and SB or OSA was found. Migraine without aura was associated with a higher risk of OSA. These results suggest possible shared mechanisms but no strong direct association [47].

Additionally, we assessed the effectiveness and overall tolerability of atogepant, confirming and expanding upon findings from RCTs. Our results highlight its effectiveness after 12 weeks of treatment, not only in significantly reducing migraine frequency, but also in alleviating disability and key symptoms such as allodynia (as assessed by the ASC-12 questionnaire). Safety assessments and patient-reported outcomes supported good tolerability and high patient satisfaction, likely driven by the combination of optimal tolerability and effectiveness. Notably, allodynia severity decreased consistently, with a mean ASC-12 score reduction of 3.2 points (95% CI −4.6, −1.7; $p < 0.001$). This suggests that a reduction in migraine frequency was rapidly associated with improved central sensitization, which in turn may have contributed to improved sleep quality. Indeed, a study suggests that exposure to chronic insufficient sleep may increase vulnerability to chronic pain by altering processes of pain habituation and sensitization [48].

This is the first study to report the impact of atogepant on sleep quality and sleep-related adverse events. The strengths of our study include its prospective design, which reflects common clinical practice in tertiary headache centers, and the inclusion of a migraine patient population often excluded from RCTs (e.g., those with prior anti-CGRP treatment failures). Another strength is the use of five standardized sleep assessment questionnaires, including the PSQI. Furthermore, we adjusted our analysis with different mixed effect models for psychiatric comorbidities, prior anti-CGRP therapies, and response status.

However, our study has several limitations, including the absence of a predefined sample size, the lack of a placebo control group, and unmeasured confounders such as impact of co-medications, work or lifestyle factors, or undiagnosed sleep disorders. Furthermore, the reliance on self-reported data for effectiveness (via paper diaries) and sleep quality (via validated but subjective questionnaires, which may be subject to recall bias) may also have influenced outcomes. Indeed, self-reported, sleep-related questionnaires differ from prospective sleep diaries, actigraphy, and polysomnography; the latter is the only objective method of assessing sleep disorders. Additionally, the study duration was limited to 12 weeks, and longer follow-ups are needed to assess the sustained impact on sleep quality. However, we have already observed an improvement within this timeframe. Finally, the generalizability of

our results is limited by the single-center design and predominantly CM cohort. Studies including treatment-naïve patients, a large cohort of EM, and multicenter recruitment are needed to broaden applicability.

Overall, our findings reinforce the importance of integrating sleep assessments into migraine management strategies, above all in pharmacological resistant migraine, not just for CGRP drugs, but also for developing drugs [49].

5 Conclusions

This study provides evidence that atogepant not only reduces migraine burden, but also significantly improves sleep quality, as reflected by different specific questionnaires. These findings align with previous studies on anti-CGRP mAbs to support the idea that CGRP inhibition may play a role in sleep regulation, although further research is needed to clarify the mechanisms underlying these effects and potential differences among anti-CGRP drugs. Considering that somnolence and fatigue have been identified as emergent adverse effects of atogepant, it is necessary to distinguish between sleep improvements as a therapeutic benefit versus potential adverse events.

Future multicenter, randomized, placebo-controlled trials with longer follow-up and objective assessments (e.g., polysomnography, actigraphy) are warranted to confirm and extend these findings.

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Author Contributions L.F.I. and A.B. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; they also designed the study, performed statistical analysis, and drafted the 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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Declarations

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Availability of Data and Material Data supporting the findings in the present study are reported in the article and in the supplementary materials. The data collected and analyzed for the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Conflicts of Interest L.F.I. received financial support, consulting fees for the participation in advisory boards and support for attending meetings from: Teva, Eli Lilly, Lundbeck, Pfizer, and AbbVie; he is associate editor for *Frontiers in Neurology Headache and Neurogenic Pain* section. F.V. has received financial support from Allergan-AbbVie, Angelini, and Lundbeck for investigator-initiated trials; consulting fees for the participation in advisory boards from AbbVie, Angelini, Eli Lilly, Lundbeck, Organon, Novartis, Pfizer, and Teva; honoraria for scientific lectures and presentations from AbbVie, Eli Lilly, Lundbeck, Novartis, Organon, Pfizer, and Teva; support for attending meetings from Abbvie, Amgen, Eli Lilly, Lundbeck, Pfizer, and Teva; he has been principal investigator in clinical trials sponsored by AbbVie, Eli Lilly, Lundbeck, Pfizer, and Teva; he is co-specialty editor for *Frontiers in Neurology Headache and Neurogenic Pain* section. S.G. has received fees and honoraria for advisory boards, speaker panels, or clinical investigation studies from Novartis, Teva, Eli Lilly, Pfizer, Lundbeck, Angelini, and AbbVie. C.A. 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. Other authors have no relevant financial or non-financial interests to disclose.

Ethics Approval The local Ethics committee approved the study as part of the Registro Italiano Cefalee (RICe) study (Studio RICe, 14591_oss CEAVC Studio RICe, 14591_oss and subsequent amendments).

Consent to Participate All patients written an informed consent before the enrollment in the study.

Consent to Publish Not applicable.

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Authors and Affiliations

Luigi Francesco Iannone[1,2] · Alberto Boccalini[1] · Flavia Lo Castro[1] · Daria Brovia[1] · Marina Romozzi[3,4] · Fabrizio Vernieri[5,6] · Claudia Altamura[5,6] · Simona Guérzoni[1]

✉ Luigi Francesco Iannone
luigifrancesco.iannone@unimore.it

[1] Digital and Predictive Medicine, Pharmacology and Clinical Metabolic Toxicology-Headache Center and Drug Abuse-Laboratory of Clinical Pharmacology and Pharmacogenomics, University of Modena and Reggio Emilia, AOU Policlinico di Modena, Modena, Italy

[2] Department of Biomedical, Metabolic, and Neural Science, University of Modena and Reggio Emilia, Modena, Italy

[3] Dipartimento Universitario di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy

[4] Neurologia, Dipartimento di neuroscienze, Organi di Senso e Torace, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

[5] Headache Unit, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy

[6] Università Campus Bio-Medico di Roma, Rome, Italy