



Effects of prophylactic drug therapies and anti-calcitonin peptide-related monoclonal antibodies on subjective sleep quality: An Italian multicenter study

Giovanna Viticchi^{a,*}, Vincenzo Di Stefano^b, Claudia Altamura^c, Lorenzo Falsetti^d, Angelo Torrente^b, Nicoletta Brunelli^c, Sergio Salvemini^a, Paolo Alonge^b, Marco Bartolini^a, Chiara Di Felice^a, Maria Stella Adragna^b, Gianluca Moroncini^d, Fabrizio Vernieri^c, Filippo Brighina^b, Mauro Silvestrini^a

^a Neurological Clinic, Experimental and Clinical Medicine Department, Marche Polytechnic University, Via Conca 1, 60020, Ancona, Italy

^b Department of Biomedicine, Neuroscience and Advanced Diagnostics (BiND), University of Palermo, Via del Vespro 129, 90127, Palermo, Italy

^c Unit of Headache and Neurosonology, Department of Medicine and Surgery, Fondazione Policlinico Universitario Campus Bio-Medico, Via Alvaro del Portillo 200, 00128, Roma, Italy

^d Clinica Medica, Department of Clinical and Molecular Sciences, Marche Polytechnic University, Via Conca 1, 60100, Ancona, Italy

ARTICLE INFO

Keywords:
Sleep quality
Migraine
Prophylaxis
Pittsburgh sleep quality index

ABSTRACT

Objective/background: sleep alterations strongly influence migraine severity. Prophylactic therapies have a major impact on migraine frequency and associated symptoms. The study purpose was to compare the impact of oral drug therapies or gene-related anti-calcitonin monoclonal antibodies (anti-CGRP mAbs) on sleep alterations. We also evaluated which drug therapies are more effective on sleep quality and the different impact on migraine frequency and life quality.

Patients/methods: this is a multicenter, prospective study conducted in three specialized headache centers (Marche Polytechnic University, Ancona; University of Palermo, Palermo; Fondazione Policlinico Campus Bio-Medico, Rome). At baseline, we assigned migraine patients to preventive therapy with first-line drugs or anti-CGRP mAbs. The Pittsburgh Sleep Quality Index (PSQI) and Migraine Disability Assessment (MIDAS) scales were administered. After three months, we re-evaluated the patients with the same scales.

Results: 214 patients were enrolled. Any prophylaxis was significantly associated with a reduction in PSQI score (mean difference 1.841; 95%CI:1.413–2.269; $p < 0.0001$), most significantly in the anti-CGRP mAb group (mean difference 1.49; 95%CI:2.617–0.366; $p = 0.010$). Anti-CGRP mAbs resulted in significant improvement in migraine severity and MIDAS scores. Among oral therapies, calcium antagonists and antidepressants were the most effective in reducing PSQI score between T0 and T1 ($p = 0.042$; $p = 0.049$; $p < 0.0001$, respectively).

Conclusions: anti-CGRP mAbs revitalized the management of migraine with stable and well-documented efficacy. Our data also suggest that anti-CGRP mAbs result in a positive effect on sleep quality, with a significant improvement in PSQI scores. Knowing the relevant impact of sleep disruption on migraine severity, these data could help for the management of migraine patients.

1. Introduction

Sleep alterations are common in migraine patients and contribute greatly to impaired quality of life [1]. The relationship between sleep alterations and migraine severity is close, but not completely established. For example, in the most prevalent sleep disorder, obstructive

sleep apnea (OSA), the prevalence of all headache types was 33%, while the prevalence of migraine was 16% [2]. OSA did not significantly increase the risk of headache onset [2].

Several studies have reported a close relationship between increased number of migraine attacks and altered or deprived sleep. According to some investigations, migraine patients have reduced REM sleep compared to controls, which also correlates with the occurrence of

* Corresponding author. Neurological Clinic, Marche Polytechnic University, Via Conca 1, 60020, Ancona, Italy.

E-mail address: g.viticchi@staff.univpm.it (G. Viticchi).

<https://doi.org/10.1016/j.sleep.2024.03.026>

Received 11 January 2024; Received in revised form 28 February 2024; Accepted 16 March 2024

Available online 17 March 2024

1389-9457/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Abbreviations

Anti-CGRP mAbs	Anti-calcitonin gene-related peptide monoclonal antibodies
PSQI	Pittsburgh Sleep Quality Index; MIDAS: Migraine Disability Assessment
OSA	obstructive sleep apnea
ICHD-3	third edition of the International Classification of Headache Disorders
CERM	Ethics Committee of the Marche Region
MMDs	monthly migraine days
NSAIDs	non-steroidal anti-inflammatory drugs
SD	standard deviation
IQR	interquartile range
DH31	diuretic hormone 31

cutaneous allodynia [1,3,4]. It has been hypothesized that migraine and sleep may have a common driver corresponding to the hypothalamus. Functional alterations in hypothalamus-brain connectivity could both influence sleep alterations and trigger migraine attacks [5,6].

According to international guidelines, prophylactic therapies aim to reduce the number and intensity of migraine attacks when they reach a severity that significantly reduces quality of life [7]. However, some medications may have a positive or negative impact on sleep maintenance or consolidation. For example, tricyclic antidepressant drugs may induce sleep, while other antidepressants may promote early awakening. The intake of different substances may have an unclear impact on headache: for example, studies on the relationship between alcohol intake and headache have shown conflicting data, from a protective role of alcohol consumption for migraine to complete avoidance of alcohol in migraine patients [8].

Anti-calcitonin gene-related monoclonal antibodies (Anti-CGRP mAbs) are one of the newest therapeutic approaches for migraine in both chronic and episodic forms. Recent studies are also demonstrating the possibility of switching from one type of anti-CGRP mAbs to another to increase benefits [9]. Their effectiveness on migraine severity is well established, but little evidence is available on their possible effects on sleep quality [10]. In addition, there are no well-established data on the effectiveness of different prophylactic therapies on sleep quality and characteristics. To our knowledge, no study has directly investigated the impact of different prophylactic therapies on sleep quality, despite the relevant role of sleep alterations on migraine and treatment compliance.

This study aims to compare the influence of different oral preventive drugs and anti-CGRP mAbs on sleep quality in a population of migraine patients. In addition, we compared each individual drug class to understand which type could result in a better effect on sleep alterations. Finally, we completed our evaluation by comparing the different impact of oral therapies and anti-CGRP mAbs on migraine frequency and quality of life in our patients. Our hypothesis was that different therapeutic approaches might have a different impact on sleep quality, just as with migraine severity.

2. Material and Methods

2.1. Study design

We designed a multicenter prospective study conducted in three Specialist Headache Centers (Clinica Neurologica, Università Politecnica delle Marche; Department of Biomedicine, Neuroscience and Advanced Diagnostics (BiND), University of Palermo; Headache and Neurosonology Unit, Fondazione Policlinico Campus Bio-Medico, Rome). Consecutive patients attending outpatient headache services who had a diagnosis of migraine with or without aura according to the

third edition of the International Classification of Headache Disorders (ICHD-3) [7] were evaluated at each center during a one-year period (January 1, 2022 to December 31, 2022).

We subjected each patient to a comprehensive general and neurological examination with collection of medical history and instrumental tests performed. According to international guidelines, when the frequency of migraine attacks led to a debilitating headache for more than four days per month and the quality of life (assessed by specific scores, such as the Migraine Disability Assessment-MIDAS score) was significantly impaired, we prescribed prophylactic drug therapy choosing from specific drug classes (beta-blockers, calcium antagonists, antiepileptics, antidepressants). If the subject had already undergone more than three courses of prophylactic therapy with different drug classes without significant improvement in migraine frequency, we proposed treatment with one of the anti-CGRP mAbs available in Italy at the time of the study (galcanezumab, erenumab, fremanezumab).

In order to directly compare conventional pharmacological prophylaxis with anti-CGRP mAbs, patients treated with onabotulinum toxin A were excluded. At the time of prophylaxis prescription (T0), we asked all patients to complete self-administered questionnaires to assess sleep quality and migraine burden. Specifically, we recorded the frequency of migraine attacks per month, calculated the MIDAS questionnaire [11] and submitted each patient to the Pittsburgh Sleep Quality Index (PSQI). The latter scale is a self-administered sleep quality questionnaire consisting of 19 items [12]. After three months (T1), we reassessed all enrolled patients and subjected them to the same questions and scales.

We excluded from the study all patients who had not been taking treatments regularly, including those showing side effects, or subjects unavailable for follow-up visit.

Inclusion criteria were: a) diagnosis of migraine with or without aura; b) compliance with assigned prophylaxis therapy; c) age >18 years;

Exclusion criteria were: a) not regularly taking prophylaxis therapy; b) active treatment with onabotulinum toxin A.

2.2. Compliance with ethical standards

The Ethics Committee of the Marche Region (CERM), Italy, approved the study (protocol number 2023 342, 11/16/2023). All participants gave their informed written consent to participate and were treated according to the Declaration of Helsinki. All procedures were performed in compliance with relevant laws and institutional guidelines.

2.3. Power and sample size analysis

We predetermined the sample size considering an error α of 0.05 and a power (1- β) of 0.95. Based on these parameters, for a repeated-measures MANOVA (F-test) considering an effect size f of 0.30, 5 groups and two measures, the optimal sample size was estimated to be between 160 (for between-factor effects) and 212 subjects (between-factor interaction). The sample size was estimated with G*Power 3.1.9.3 for MacOS systems.

2.4. Statistical analysis

For each patient, at the time of enrollment, the following were collected: age, sex, monthly migraine days (MMDs_{T0}), MIDAS score (MIDAS_{T0}), PSQI score (PSQI_{T0}), years of illness (YD), type of acute attack treatment (ATTACK_THERAPY) and type of prophylaxis used (PROPHYLAXIS_TYPE). After three months, subjects were re-evaluated with MIDAS score (MIDAS_{T1}), PSQI score (PSQI_{T1}) and MMDs_{T1}. The PSQI score at T0 and T1 was also recoded into dichotomous variables, considering a ≥ 5 cutoff to differentiate mild from moderate-severe forms of sleep disturbance.

We collected the following variables as continuous: age, MMDs_{T0}, MIDAS_{T0}, PSQI_{T0}, YD, MIDAS_{T1}, PSQI_{T1}, MMDs_{T1}. Sex was

collected as a dichotomous variable. Treatments taken by the patient (ATTACHMENT_THERAPY and PROFILASSI_TIPO) were coded into categorical variables: for ATTACHMENT_THERAPY, nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, acetaminophen, ASA and indomethacin were considered, while for PROFILASSI_TIPO, beta-blockers, antiepileptics, calcium antagonists, antidepressants and anti-CGRP mAb were considered. The latter variable was further recoded into a binary variable considering drug prophylaxis versus anti-CGRP mAbs (PROPHYLAXIS_BINARY).

Continuous variables were tested for normality with the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean and standard deviation (SD) and compared with a *t*-test (two-level variables) or ANOVA (multiple levels). Non-normally distributed variables were presented as the median and interquartile range (IQR) and compared with the Mann-Whitney *U* test (two-level variables) or the Kruskal-Wallis *H* test (multiple levels). Categorical and dichotomous variables were presented as absolute numbers and percent and compared with the chi-squared test.

In order to assess the differences of continuous measures between T0 and T1 according to the type of prophylaxis used, we prepared different GLM/Multivariate models for repeated measures considering: the dependent, repeated variables (MMDs_T0 – MMDs_T1; MIDAS_T0 – MIDAS_T1; PSQI_T0 – PSQI_T1), PROPHYLAXIS_BINARY as the independent variable, and YD, AGE, SEX, and ATTACK_THERAPY as covariates. Covariate selection was performed on a clinical basis.

The variable containing the drug type was further recoded into a variable containing the classes of drugs, namely beta-blockers, antiepileptics, calcium antagonists, antidepressants, and Anti-CGRP mAbs. We last performed a full-factorial, non-corrected for covariates, GLM/Multivariate analysis for repeated measures considering the PSQI scale at T0 and T1 as the main dependent variable and the class of drug introduced for pharmacological prophylaxis as the independent variable.

We considered significant all the differences at a level of $p < 0,05$. Statistical analysis was performed with SPSS 13.0 for Windows Systems.

3. Results

Two hundred and sixty-three consecutive patients were enrolled. Forty-nine patients were excluded (35 due to reduced compliance with treatment and 14 due to the development of side effects). Finally, we obtained a sample of 214 patients (84 from the Polytechnic University of Marche, 100 from the University of Palermo and 30 from the Campus Bio-Medico University of Rome). The basal characteristics of the overall cohort are summarized in Table 1.

Patients treated with monoclonal antibodies had significantly longer disease duration, more attacks in the previous three months, more monthly attacks, higher MIDAS and PSQI scores at T0 than those treated with any other treatment, as shown in Table 1. The number of subjects with a moderate to severe form of sleep disturbance, summarized as $PSQI \geq 5$, decreased from T0 (163 subjects, 76.2%) to T1 (126 patients, 58.9%) and this reduction was confirmed both in patients treated with oral prophylaxis (from 70.6% to 52.4%) and in subjects treated with monoclonal antibodies (from 87.3% to 71.8%), with a significant difference in distribution ($p < 0,0001$, chi-square test).

The first multivariable model considered the PSQI score at T0 and T1 as the main dependent variable, the type of drug used as prophylaxis (other drugs versus Anti-CGRP mAbs) as the independent variable, age, sex, type of treatment for the acute attack as covariates. The PSQI score was significantly reduced between T0 and T1 (mean difference 1.841; 95% CI: 1.413–2.269; $p < 0.0001$) and the use of anti-CGRP mAb was associated with a more significant decrease in the PSQI score (difference mean 1.491; 95% CI: 2.617–0.366; $p = 0.010$). Multivariable testing showed that the type of drug used as prophylaxis was significantly associated with the outcome ($p = 0.017$) and gender played a significant role in the differences in outcome ($p = 0.042$). Considering this effect,

Table 1
Baseline characteristics of the sample.

Variable	Whole population (n = 214)	Oral preventive drugs (n = 143)	Anti-CGRP mAbs (n = 71)	P
Age (mean, \pm SD), years	43,07 \pm 12,43	39,70 \pm 12,19	49,86 \pm 9,95	0,0001
Female sex (n, %)	159 (74,3%)	109 (76%)	50 (70,4%)	0,360
Migraine with aura (n, %)	25 (11,7%)	23 (10,7%)	2 (0,9%)	0,004
Years of disease (mean, \pm SD), years	19,37 \pm 13,45	15,43 \pm 11,57	27,32 \pm 13,53	0,0001
MMDs (median, IQR), T0	10 [15]	10,31 \pm 8,59	19,73 \pm 7,62	0,0001
Attacks in the previous 3 months (median, IQR), T0	30 [45]	31,05 \pm 25,79	59,49 \pm 22,79	0,0001
MIDAS (median, IQR), T0	40 [69]	38 [44]	99 [65]	0,0001
PSQI (median, IQR), T0	7 [5]	6,73 \pm 3,68	9,13 \pm 4,34	0,0001
Pathological PSQI at T0 (n, %)	163 (76,2%)	101 (70,6%)	62 (87,3%)	0,007
Pathological PSQI at T1 (n, %)	126 (58,9%)	75 (52,4%)	51 (71,8%)	0,007
Attacks in the previous 3 months (median, IQR), T1	12 [22]	16 [19]	27 [18]	0,0001
Attacks per month (median, IQR), T1	5 [7]	8 [15]	9 [6]	0,406
MIDAS (median, IQR), T1	15 [38]	27 [45]	44 [48]	0,0001
PSQI (median, IQR), T1	5 [5]	5,50 \pm 3,65	6,66 \pm 3,73	0,0001
Type of prophylaxis:				
• Beta-blockers (n, %)	• 20 (9,3%)	• 38 (26,6%)	• 20 (28,3%)	0,294
• Antiepileptics (n, %)	• 37 (17,3%)	• 48 (33,6%)	• 43 (60,6%)	
• Ca-antagonists (n, %)	• 48 (22,4%)	• 71 (49,6%)	• 2 (2,8%)	
• Antidepressants (n, %)	• 71 (33,2%)	• 45 (31,5%)	• 12 (16,9%)	
• Monoclonal Antibodies (n, %)	• 65 (30,4%)	• 81 (56,6%)	• 43 (60,6%)	
Treatment of acute attack:				
• NSAIDs (n, %)	• 124 (57,9%)	• 12 (8,4%)	• 43 (60,6%)	
• Triptans (n, %)	• 14 (6,5%)	• 2 (1,4%)	• 2 (2,8%)	
• Paracetamol (n, %)	• 5 (2,3%)	• 3 (2,1%)	• 3 (4,2%)	
• ASA (n, %)	• 6 (2,8%)		• 3 (4,2%)	
• Indomethacin (n, %)				

Legend: SD = standard deviation; MMDs = monthly migraine days; MIDAS = Migraine Disability Assessment; PSQI = Pittsburgh Sleep Quality Index; IQR = interquartile range; NSAIDs = Nonsteroidal anti-inflammatory drugs.

we observed a significant difference in the PSQI score at T0 between anti-CGRP mAb users and non-anti-CGRP mAb users ($p < 0.0001$), while at T1 this difference was significantly reduced ($p = 0.113$) because anti-CGRP mAbs resulted in a significant reduction in PSQI scores, as shown in Fig. 1.

The second multivariable model considered the number of monthly migraine attacks at T0 and T1 as the main dependent variable, the type of drug used as prophylaxis (other drugs versus anti-CGRP mAb) as the independent variable, age, sex, type of treatment for the acute attack as covariates. The number of attacks in one month was significantly reduced between T0 and T1 (mean difference T1-T0: 6.980; 95% CI: 4.987–8.972; $p < 0.0001$) and the use of anti-CGRP mAbs was associated to a greater decrease (mean difference of anti-CGRP mAbs-other drugs: 4.405; 95% CI: 1.718–7.092; $p < 0.0001$). The multivariable test demonstrated that the type of drug used as prophylaxis was significantly associated with the outcome ($p < 0.0001$). Considering this effect, we observed a significant difference in the number of attacks in one month

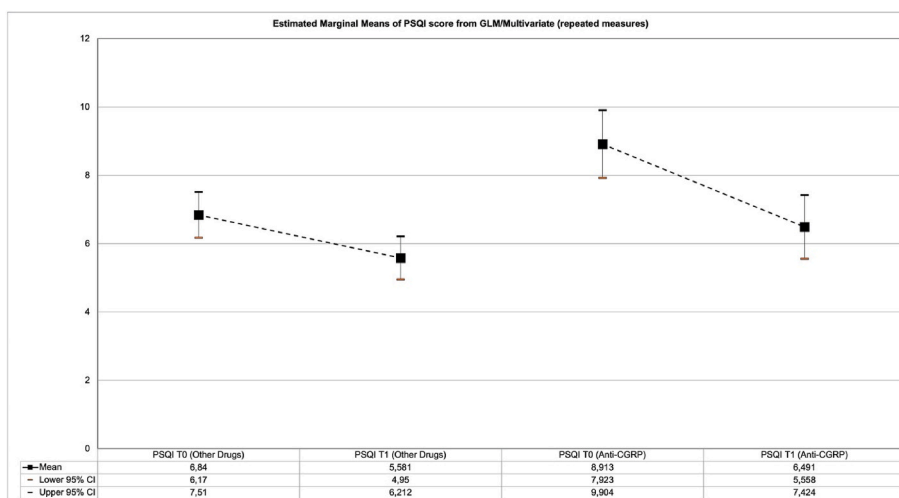


Fig. 1. Estimated Marginal Means of PSQI score from GLM/Multivariate (repeated measures). The difference between subjects treated with oral preventive drugs and those treated with Anti-CGRP mAbs is significant ($p < 0.0001$) at T0 and nonsignificant at T1 ($p = 0.113$).

at T0 between anti-CGRP mAbs users and non-*anti*-CGRP mAbs users ($p < 0.0001$), with a difference that remained significant also at T1 ($p < 0.0001$), as shown in Fig. 2.

The third multivariable model considered the number of migraine attacks in 3 months (T0 and T1) as the main dependent variable, the type of drug used as prophylaxis (other drugs versus anti-CGRP mAb) as the independent variable, age, sex, type of treatment for the acute attack as covariates. The number of attacks in three months was significantly reduced between T0 and T1 (mean difference: 23.241; 95% CI: 19.722–26.759; $p < 0.0001$) and mAb use was associated with greater concession (difference mean: 18.589; 95% CI: 12.674–24.504; $p < 0.0001$). The multivariable test demonstrated that the type of drug used as prophylaxis was significantly associated with the outcome ($p < 0.0001$). Considering this effect, we observed a significant difference in the number of attacks in three months at T0 between anti-CGRP mAbs users and non-*anti*-CGRP mAbs users ($p < 0.0001$), with a difference that remained significant also at T1 ($p < 0.0001$), as shown in Fig. 3.

The last multivariable model considered the MIDAS score at T0 and T1 as the main dependent variable, the type of drug used as prophylaxis (other drugs versus monoclonal antibodies) as the independent variable, age, sex, type of treatment for the acute attack as covariates. The MIDAS score was significantly reduced between T0 and T1 (mean difference:

33.111; 95%CI:27.764–38.457; $p < 0.0001$) and the use of monoclonal antibodies was associated with a greater decrease in the MIDAS score (mean difference: 34.106; 95 %CI:19.279–48.934; $p < 0.0001$). The multivariate test showed that the type of drug used as prophylaxis was significantly associated with the outcome, defined as mean change in PSQI between T0 and T1 ($p < 0.0001$). Considering this effect, we observed a significant difference in MIDAS score at T0 between mAbs users and non-mAbs users ($p < 0.0001$), with a difference becoming non-significant at T1 ($p = 0.094$), as shown in Fig. 4.

Pharmacological prophylaxis was significantly associated with both intra- and between-subject effects in the model ($p = 0.018$). We observed that any category of drugs used in prophylaxis was significantly associated with a significant reduction in the PSQI scale at T1 (mean difference: 1.412; 95%CI:1.845-0.979; $p = 0.0001$). The difference between T0 and T1 for each drug class is shown in Fig. 5, highlighting that calcium channel blockers, antidepressants and anti-CGRP mAbs were the most involved in modifying the mean PSQI score difference between T0 and T1.

4. Discussion

Our data show that prophylactic therapies are significantly

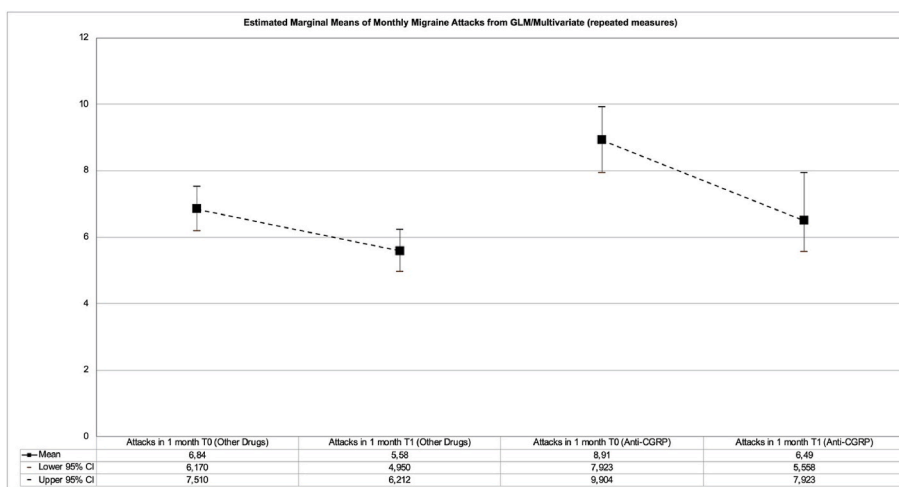


Fig. 2. Estimated marginal means of the number of monthly attacks from GLM/Multivariate (repeated measures). The difference between subjects treated with oral preventive drugs and those treated with Anti-CGRP mAbs is significant ($p < 0.0001$) at T0 and nonsignificant at T1 ($p = 0.123$).

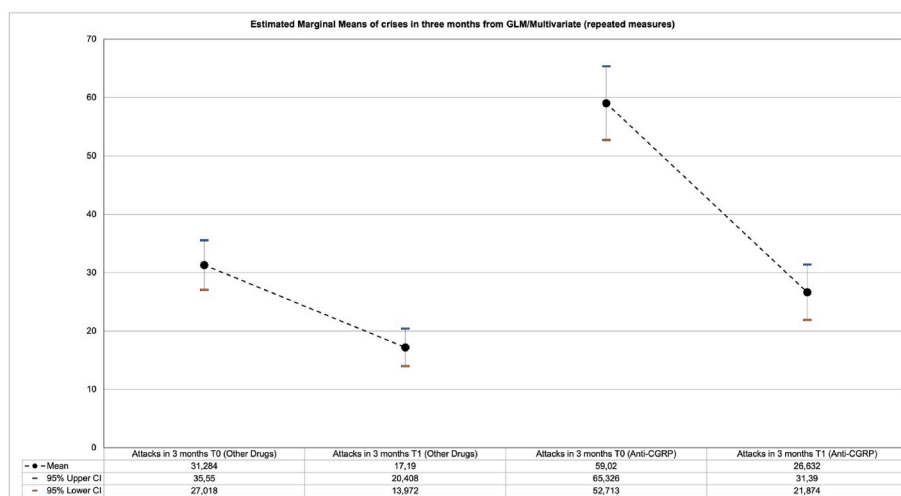


Fig. 3. Estimated Marginal Means of the number of attacks in three months from GLM/Multivariate (repeated measures). The difference between subjects treated with oral preventive drugs and those treated with Anti-CGRP mAbs is significant at T0 ($p < 0.0001$) and at T1 ($p < 0.0001$).

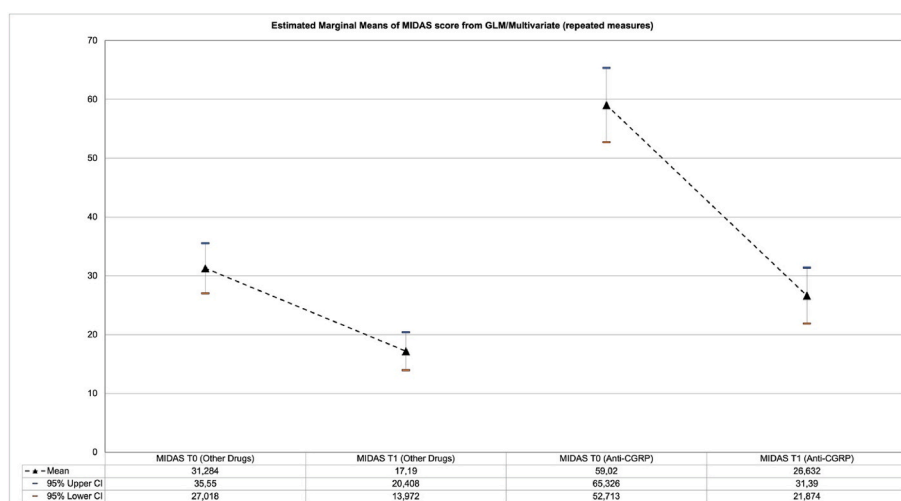


Fig. 4. Estimated Marginal Means of MIDAS score from GLM/Multivariate (repeated measures). The difference between subjects treated with oral preventive drugs and those treated with Anti-CGRP mAbs is significant at T0 ($p < 0.0001$) and nonsignificant at T1 ($p = 0.094$).

associated with improved sleep quality as assessed by the PSQI questionnaire. The use of anti-CGRP mAbs produced a more substantial effect, with an average reduction in PSQI score from 8.913 to 6.491, as shown in Fig. 1. Of note, patients who received anti-CGRP mAbs had significantly longer disease duration, significantly more attacks, and higher MIDAS and PSQI scores. Interestingly, patients with a frankly pathological PSQI score at T0 showed a better improvement in sleep quality, from 76.2% to 58.9% of the total sample. Subjects with a more impaired baseline condition showed better results in each assessment domain.

We decided to use the MIDAS and PSQI scales for our assessment because they are widely validated assessment tools in clinical practice. In addition, they are very easy to apply and self-administered by patients. Finally, they are commonly used for scientific purposes in migraine literature.

Sleep is a relevant aspect in the assessment of quality of life. Several studies have shown a close relationship between sleep quality and migraine severity [2,13]. Patients with impaired sleep quality or repeated awakenings during the night tend to have more migraine attacks and more medication use than patients with good sleep quality [14,15]. In addition, impaired sleep-wake balance could increase the

severity of migraine [6].

The use of anti-CGRP mAbs appears to have a positive effect on sleep quality, although data from the literature are conflicting. Some studies have shown that people treated with erenumab showed improvement in both sleep quality scales [10,16] and polysomnographic recordings [16]. Iannone et al. showed that anti-CGRP mAbs were associated with an improvement in sleep quality in 38.8% of patients but observed a worsening in 5.0% of them [17]. Pilati et al., on the other hand, reported no particular change in sleep quality in chronic migraine patients treated with erenumab, although a slight beneficial effect on insomnia was observed [18].

In our study, the better effect of anti-CGRP mAbs on sleep quality compared with drug therapies is probably mainly due to the reduction of migraine attacks. There is a significant association between the number of migraine attacks and sleep quality, and several studies have correlated a higher frequency of migraine attacks with more impaired sleep [19].

In addition, some authors have hypothesized a possible indirect role of CGRP in sleep modulation.

CGRP exerts a pro-nociceptive effect within the meningeal trigeminal afferents with trigeminovascular sensitization and excitatory input

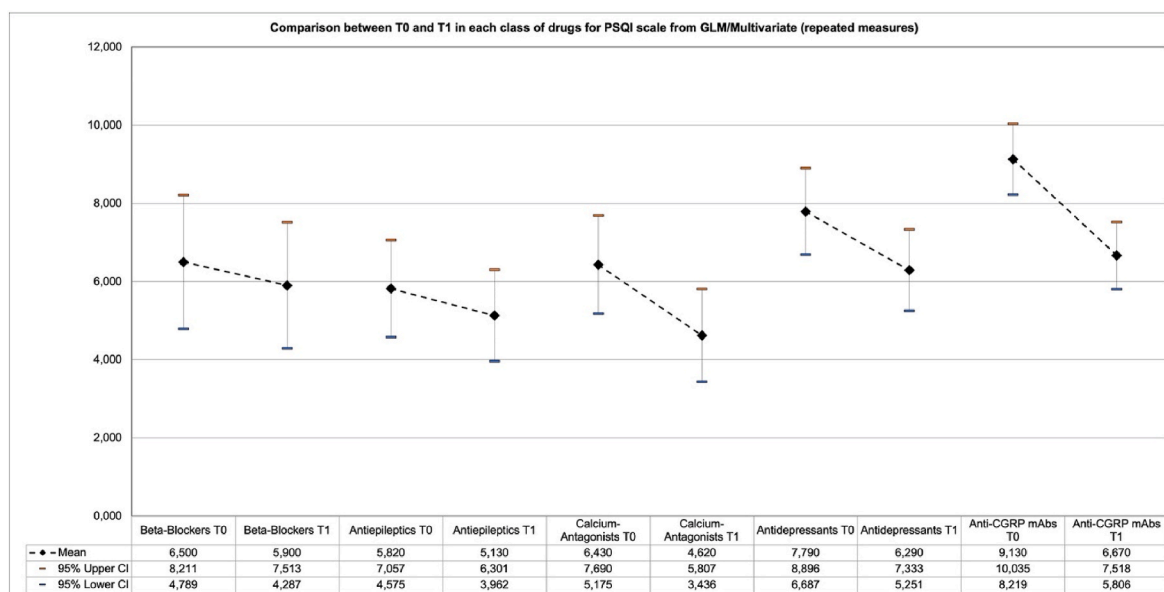


Fig. 5. Comparison between T0 and T1 in each class of drugs for PSQI scores from GLM/Multivariate (repeated measures). The difference at T0 and T1 resulted significant for calcium-antagonists ($p = 0.042$), antidepressant ($p = 0.049$) and Anti-CGRP mAbs ($p < 0.0001$).

to the migraine matrix of chronic migraine patients. This effect may explain the increase in migraine attacks and accompanying symptoms, such as sleep alterations or eating disorders [17]. The effect of mAbs on CGRP could reduce all these aspects, improving sleep quality. Experimental studies in animal models (based mainly on *Drosophila Melanogaster*) have investigated an analog of CGRP called diuretic hormone 31 (DH31). This hormone produces a circadian wakefulness-promoting signal that can wake the fly in anticipation of dawn. DH31 is produced by dorsal circadian neurons involved in circadian rhythm regulation, which can suppress late-night sleep [20]. Experimental flies with loss of DH31 function exhibit higher sleep consolidation with fewer and longer sleep episodes and increased nighttime sleep with reduced pre-dawn awakening [20]. Other studies have shown that in mice, CGRP has a role in maintaining a persistent state of fear and responding to feeding-related stimuli. Because CGRP transmits potentially life-threatening signals, its inhibition could contribute to adaptive behaviors [21,22]. With these pathophysiological premises, the human analogue of DH31, CGRP, could have similar capabilities and its inhibition could improve sleep quality.

In addition, CGRP promotes anxiety-like behaviors in response to stress and more persistent pain states [23]. Anxiety, mood alterations, and stress are well-documented risk factors for migraine chronification and sleep alterations. Some authors have hypothesized a possible common source for anxiety and migraine, represented by the hypothalamus and the ventral tegmentum of the midbrain. Activation of these structures could promote both neuronal hyperexcitability and, consecutively, cortical spreading depression and recruitment of the trigeminal nucleus with sensitization of central pathways and pain production [24–26].

Recent studies in mice have shown that CGRP induces an increase in anxiety indices and potentiates anxious behaviors, especially in females [27,28]. In addition, high levels of CGRP cause dysfunction of the descending inhibitory pathway, which has the role of modulating the ascending spino-parabrachioamygdaloid tract [28,29]. The final effect obtained is a prolonged pain state and reduced neuronal homeostasis in the spinal cord [23].

Based on these data, it is possible to speculate that CGRP might play a significant role both as a major protein in the cascade mechanisms of migraine and in sleep modulation. This hypothesis may strengthen the evidence that anti-CGRP mAbs may exert a relevant effect on sleep quality, based on their CGRP-inhibiting action. In addition, anti-CGRP

mAbs have shown a positive effect on anxiety behaviors and pain catastrophizing [17,30].

In our opinion, anti-CGRP mAbs could have a good effect on sleep quality either directly, by acting on CGRP as a sleep modulator, or indirectly, by reducing sleep-disrupting factors such as anxiety. On the other hand, anti-CGRP mAbs cannot cross the blood-brain barrier and cannot act directly on central sleep pathways. In contrast, drugs usually used for migraine prophylaxis, such as amitriptyline, can have a central action. Several drugs act directly on sleep architecture, modulate the sleep-wake cycle, or have drowsiness as a side effect.

In the second part of our study, we examined the effect on the PSQI score of the different classes of drugs taken for migraine prophylaxis and found that antidepressants and calcium channel blockers gave the best results. This result is not surprising, since both classes affect sleep. Among antidepressants, amitriptyline has the strongest evidence of efficacy: recent studies have confirmed that low doses of this drug improve sleep onset and maintenance, with significant reduction in daytime fatigue [31]. Calcium antagonists could also stimulate an increase in total sleep time and shorten sleep latency [32]. The most significant problem in the use of these drugs is the occurrence of significant side effects causing low compliance with a high rate of self-interruption by patients [31,33].

Our data show that migraine preventive therapy is associated with a reduction in attack frequency and disability as expressed by MMD and MIDAS score. We extended our analysis on the number of migraine days up to three months of medication intake to obtain more realistic data over a longer period instead of just one month. Notably, anti-CGRP mAbs were associated with a more significant reduction in migraine attacks in the first three months of therapy than oral treatments.

These results confirm data from several trials and real-world studies reporting a reduction in migraine attacks as early as the first week of intake [34,35]. Anti-CGRP mAbs improve tolerance with significantly fewer adverse events than the classical pharmacological approach: they are more specific, better tolerated, and show a positive effect on ancillary aspects of migraine, such as sleep quality. Considering all these aspects, it can be expected that their use will continue to increase.

5. Limitations

This study has some limitations. Among these, we would like to point

out the absence of an assessment of the possible presence of psychiatric co-morbidities, such as anxiety and depression. These could be relevant because their impact on sleep quality is well known. In addition, the follow-up of our patients lasted only three months, so it would be desirable to extend our evaluation for longer periods in a future study. In addition, the assessment of sleep quality was based only on patients' reports, without instrumental confirmation of sleep assessment. We hope to improve the value of the study by adding instrumental assessment of sleep quality, such as video polysomnography. Finally, we did not include a control group in the study plan to test for sleep alteration in untreated migraine subjects, and we hope to better evaluate this possibility in the future.

6. Conclusion

Our data suggest a positive effect on sleep quality for all types of prophylactic therapeutic approach. Anti-CGRP mAbs show better results than conventional drugs, resulting in improved tolerance and greater patient compliance. More in-depth studies are needed to better understand the real impact of these therapies on such a relevant aspect of migraine patients' quality of life and to make the results of this study more generalizable.

Funding source

This work has been partially supported by "Fondazione Giorgini".

CRediT authorship contribution statement

Giovanna Viticchi: Writing – original draft, Conceptualization. **Vincenzo Di Stefano:** Data curation, Conceptualization. **Claudia Altamura:** Data curation, Conceptualization. **Lorenzo Falsetti:** Methodology, Conceptualization. **Angelo Torrente:** Methodology. **Nicoletta Brunelli:** Investigation. **Sergio Salvemini:** Investigation. **Paolo Alonge:** Investigation. **Marco Bartolini:** Data curation. **Chiara Di Felice:** Investigation. **Maria Stella Adragna:** Investigation. **Gianluca Moroncini:** Supervision. **Fabrizio Vernieri:** Supervision. **Filippo Brighina:** Supervision. **Mauro Silvestrini:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Mauro Silvestrini reports financial support was provided by Giorgini Foundation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The study was partially supported by a grant of Fondazione Giorgini.

References

- Stanyer EC, Creeny H, Nesbitt AD, et al. Subjective sleep quality and sleep architecture in patients with migraine: a meta-analysis. *Neurology* 2021;97(16):e1620–31. <https://doi.org/10.1212/WNL.00000000000012701>.
- Błaszczak B, Martynowicz H, Więckiewicz M, et al. Prevalence of headaches and their relationship with obstructive sleep apnea (OSA) - systematic review and meta-analysis. *Sleep Med Rev* 2024;73:101889. <https://doi.org/10.1016/j.smrv.2023.101889>.
- Dexter JD. The relationship between stage III + IV + REM sleep and arousals with migraine. *Headache* 1979;19:364–9. <https://doi.org/10.1111/j.1526-4610.1979.hed1907364.x>.
- Kim SH, Park JY, Shin HE, et al. The influence of rapid eye movement sleep deprivation on nociceptive transmission and the duration of facial allodynia in rats: a behavioral and Fos immunohistochemical study. *J Headache Pain* 2019;20:21. <https://doi.org/10.1186/s10194-019-0977-0>.
- Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain* 2016;139:1987–93. <https://doi.org/10.1093/brain/aww097>.
- Viticchi G, Falsetti L, Paolucci M, et al. Influence of chronotype on migraine characteristics. *Neuro Sci* 2019;40:1841–8. <https://doi.org/10.1007/s10072-019-03886-4>.
- Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders. *Cephalalgia* 2018;38:1–211. <https://doi.org/10.1177/0333102417738202>. 3rd edition.
- Błaszczak B, Straburzyński M, Więckiewicz M, et al. Relationship between alcohol and primary headaches: a systematic review and meta-analysis. *J Headache Pain* 2023;24:116. <https://doi.org/10.1186/s10194-023-01653-7>.
- Waliszewska-Proszó M, Martelletti P. Real-world effectiveness of fremanezumab in patients with migraine switching from another mAb targeting the CGRP pathway. *Dent Med Probl* 2024;61:9–11. <https://doi.org/10.17219/dmp/174706>.
- Russo A, Silvestro M, Scotto di Clemente F, et al. Multidimensional assessment of the effects of erenumab in chronic migraine patients with previous unsuccessful preventive treatments: a comprehensive real-world experience. *J Headache Pain* 2020;21:69. <https://doi.org/10.1186/s10194-020-01143-0>.
- D'Amico D, Mosconi P, Genco S, et al. The Migraine Disability Assessment (MIDAS) questionnaire: translation and reliability of the Italian version. *Cephalalgia* 2001;21:947–52. <https://doi.org/10.1046/j.0333-1024.2001.00277.x>.
- Buysse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatr Res* 1989;28:193–213. [https://doi.org/10.1016/0165-1781\(89\)90047-4](https://doi.org/10.1016/0165-1781(89)90047-4).
- Bierhals IO, de Oliveira GSP, Santos IS, et al. Relationship between sleep problems and headaches among adolescents: pelotas 2004 Birth cohort. *Sleep Med X* 2023;6:100079. <https://doi.org/10.1016/j.sleepx.2023.100079>.
- Viticchi G, Altamura C, Falsetti L, et al. Poor sleep quality in patients affected by migraine: a population study. *Neuro Sci* 2020;41:495–6. <https://doi.org/10.1007/s10072-020-04673-2>.
- Vgontzas A, Pavlović JM. Sleep disorders and migraine: re-view of literature and potential pathophysiology mechanisms. *Headache* 2018;58:1030–9. <https://doi.org/10.1111/head.13358>.
- Pellitteri G, Pez S, Nilo A, et al. Erenumab impact on sleep assessed with questionnaires and home-polysomnography in patients with migraine: the ERESON study. *Front Neurol* 2022;13:869677. <https://doi.org/10.3389/fneur.2022.869677>.
- Iannone LF, De Cesaris F, Ferrari A, et al. Effectiveness of anti-CGRP monoclonal antibodies on central symptoms of migraine. *Cephalalgia* 2022;42:1323–30. <https://doi.org/10.1177/0333102422111526>.
- Pilati L, Torrente A, Di Marco S, et al. Erenumab and possible CGRP effect on chronotype in chronic migraine: a real-life study of 12 Months treatment. *J Clin Med* 2023;12:3585. <https://doi.org/10.3390/jcm12103585>.
- Ødegård SS, Engstrøm M, Sand T, et al. Associations between sleep disturbance and primary headaches: the third Nord-Trøndelag Health Study. *J Headache Pain* 2010;11:197–206. <https://doi.org/10.1007/s10194-010-0201-8>.
- Kunst M, Hughes ME, Raccuglia D, et al. Calcitonin gene-related peptide neurons mediate sleep-specific circadian output in *Drosophila*. *Cell Biol* 2014;4:24:2652–64. <https://doi.org/10.1016/j.cub.2014.09.077>.
- Campos CA, Bowen AJ, Roman CW, et al. Encoding of danger by parabrachial CGRP neuro. *Nature* 2018;555:617–22. <https://doi.org/10.1038/nature25511>.
- Padilla SL, Qiu J, Soden ME, et al. Agouti-related peptide neural circuits mediate adaptive behaviors in the starved state. *Nat Neurosci* 2016;19:734–41. <https://doi.org/10.1038/nn.4274>.
- Durham PL. Diverse physiological roles of calcitonin gene-related peptide in migraine pathology: modulation of neuronal-glia-immune cells to promote peripheral and central sensitization. *Curr Pain Headache Rep* 2016;20:48. <https://doi.org/10.1007/s11916-016-0578-4>.
- Kumar R, Asif S, Bali A, et al. The development and impact of anxiety with migraines: a narrative review. *Cureus* 2022;14(6):e26419. <https://doi.org/10.7759/cureus.26419>.
- Dodick DW. Migraine. *Lancet* 2018;391:1315–30. [https://doi.org/10.1016/S0140-6736\(18\)30478-1](https://doi.org/10.1016/S0140-6736(18)30478-1).
- Giacobbe P, Flint A. Diagnosis and management of anxiety disorders. *Continuum* 2018;24:893–919. <https://doi.org/10.1212/CON.0000000000000607>.
- Rahman SM, Jafferany M, Barkauskaite R. Both systemic Calcitonin Gene Related Peptide (CGRP) and a vestibular challenge promote anxiety-related behaviors and dynamic imbalance in mice. *Clin Exp Dermatol* 2023. <https://doi.org/10.1093/ced/llad247>. llad247.
- Gungor NZ, Pare D. CGRP inhibits neurons of the bed nucleus of the stria terminalis: implications for the regulation of fear and anxiety. *J Neurosci* 2014;34:60–5. <https://doi.org/10.1523/JNEUROSCI.3473-13.2014>.
- Todd AJ. Neuronal circuitry for pain processing in the dorsal horn. *Nat Rev Neurosci* 2010;11:823–36. <https://doi.org/10.1038/nrn2947>.
- Silvestro M, Tessoro A, Orologio I, et al. Galcanezumab effect on "whole pain burden" and multidimensional outcomes in migraine patients with previous unsuccessful treatments: a real-world experience. *J Headache Pain* 2022;23:69. <https://doi.org/10.1186/s10194-022-01436-6>.
- Bakker MH, Hugtenburg JG, Smits MG, et al. Off-label low dose amitriptyline for insomnia disorder: patient-reported outcomes. *Pharmacopeidemiol Drug Saf* 2023;32:435–45. <https://doi.org/10.1002/pds.5561>.
- Puca F, Prudenzianno MP, Savarese M, et al. Headache and sleep: clinical and therapeutic aspects. *J Headache Pain* 2004;5:S123–7. <https://doi.org/10.1007/s10194-004-0126-1>.

- [33] Hepp Z, Dodick DW, Varon SF, et al. Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia* 2015;35:478–88. <https://doi.org/10.1177/0333102414547138>.
- [34] Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine. *Neurology®* 2020;94:e1365–77. <https://doi.org/10.1212/WNL.0000000000009169>.
- [35] Vernieri F, Brunelli N, Marcosano M, et al. Maintenance of response and predictive factors of 1-year Galcanezumab treatment in real-life migraine patients in Italy: the multicenter prospective cohort GARLIT study. *Eur J Neurol* 2023;30:224–34. <https://doi.org/10.1111/ene.15563>.