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ORIGINAL ARTICLE

Changes in the rest-activity rhythm in migraine patients are associated with anxiety symptoms

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Objective: To characterize rest-activity rhythm in chronic migraine (CM) and to investigate the relationship between this rhythm and depressive and anxiety symptoms in patients with CM.
Methods: This was a study of adults aged 20 to 40 years. The rest-activity rhythm of patients with CM (n=23) and non-headache controls (NH, n=23) was assessed by actigraphy for 15 days, and they completed the following assessments: Visual Analogue Scale for pain intensity; Headache Diary; Headache Impact Test-6; Morningness-Eveningness Questionnaire; Pittsburgh Sleep Quality Index; Epworth Sleepiness Scale; Beck Depression Inventory; and State-Trait Anxiety Inventory.
Results: Patients with CM showed less activity over 24 hours and more fragmented sleep. Reduced interdaily stability of the rest-activity rhythm was observed, with less robustness of this rhythm in the CM group. Multiple linear regressions revealed a significant association between the rest-activity rhythm and trait anxiety variables in patients with CM, specifically regarding the relative amplitude of the cycle, activity throughout 24 hours and during sleep, and robustness of the rest-activity rhythm.
Conclusions: Our findings provide evidence that the robustness of the rest-activity rhythm, activity throughout 24 hours, and sleep fragmentation are associated with trait anxiety in patients with CM.
Clinical trial registration: Brazilian Clinical Trials Registry (registration number: RBR-4M5J4S).

Keywords: Chronic migraine; sleep; circadian rhythm; anxiety; depression

Introduction

Symptoms of depression and anxiety are prevalent among patients with chronic migraine (CM). The frequency of attacks and the severity of pain are positively associated with depression scores and levels of anxiety.[1] Despite these findings, there is no consensus about the causes of these emotional symptoms in patients with CM. CM is presumed to have a bidirectional association with anxiety and depression due to similarities in their pathological mechanisms[2] and in how they are incapacitating for work and social activities.[1]

Factors related to these mood alterations may be associated with changes in the sleep-wake cycle, since sleep deprivation can induce an increase in anxiety, for example.[3] Similarly, migraine is also related to changes in the sleep-wake cycle. According to a systematic review, the association between headache and insomnia is approximately 40-70% worldwide; and even higher in patients with high migraine frequency, severity, or presence of comorbidities.[4] In a study involving 357 patients, poor sleep quality was related to a higher frequency of migraine attacks.[5]

Although the gold standard for sleep assessment is polysomnography, simpler tools can be used in patients with CM. One example is actigraphy, which facilitates diagnostic analyses by considering the impact of the circadian rest-activity rhythm in the daily lives of individuals.[6] The activity and rest parameters measured by actigraphy provide objective and consistent sleep data, according to the American Academy of Sleep Medicine.[7] The rest-activity rhythm is a particularly important factor that can help elucidate the etiology of anxiety and depression related to sleep disorders in patients with CM.

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In women with CM, actigraphy showed that a higher frequency of attacks correlated with late sleep onset.[8] Another study showed that a lower sleep efficiency, longer sleep latency, and more fragmented sleep were all predictors of headache intensity.[9] Therefore, there is a need to study circadian rhythmicity, which also considers the wakefulness phase and analyzes the individual's behavior over several days. This approach would provide more robust information regarding the disruption of some aspects of the sleep-wake cycle in individuals with CM.

Impaired circadian rhythms are frequent in individuals with CM. Changes in sleep, diet, light exposure, and hormones can trigger migraine attacks[10]; migraine patients exhibit an abnormal phase of nocturnal melatonin secretion or a decrease in such secretion, for example. Furthermore, migraine attacks themselves occur in a circadian fashion, usually in the early morning. Therefore, migraines could be the result of a misalignment of circadian rhythms.[11,12]

Circadian rhythms also influence mood. For example, in major depressive disorder circadian rhythms are desynchronized, phase-shifted, or low in amplitude. This association between depressive symptoms and circadian rhythms is also strengthened by the existence of seasonal depression, which occurs due to the reduction in day length.[13] These mood disorders, which are often associated with circadian disorders,[14] can be treated with interventions which modulate light exposure, melatonin supplementation, or by maintaining sleep hygiene.[12,15,16]

Therefore, CM, impaired sleep, and anxiety and depression symptoms are related to sleep-wake cycle synchronization. We believe that desynchronization of the sleep-wake cycle could affect anxiety and depression symptoms in individuals with CM differently than healthy individuals due to the sum of the circadian rhythms' misalignment. However, to the best of the authors' knowledge, no study has looked beyond sleep-wake cycle parameters and assessed the chronobiological influence of the rest-activity rhythm on anxiety and depressive symptoms of individuals with CM. Our hypothesis is that changes in the rest-activity rhythm are associated with anxiety and depression symptoms in patients with CM. Thus, the aims of this study were to characterize rest-activity rhythm in chronic migraine (CM) and to investigate the relationship between this rhythm and anxiety and depression symptoms in patients with CM.

Materials and methods

Study design and participants

Patients diagnosed with CM according to the International Classification of Headache Disorders – Third edition,[17] aged between 20 and 40 years, who attended the Academic Headache Clinic of Universidade Estadual da Paraíba (UEPB) in Campina Grande, Paraíba, Brazil, were included in the study. For recruitment, all patients registered at the clinic and diagnosed with CM by a neurologist (with experience in headaches) were contacted and asked about their interest in participating in the study. Patients who reported being diagnosed with other neurological, psychological, or psychiatric conditions were excluded, as were night workers and pregnant women. Such criteria were also applied to the non-headache (NH) group, except for the inclusion of non-headache individuals according to self-report. The NH group was recruited through digital media (using search ads on social networks) and was enrolled in order of presentation once found to be compatible in age and gender with individuals in the CM group and meet all eligibility criteria for the NH group. A total of 114 individuals were recruited, of whom 46 individuals (23 in the NH group and 23 in the CM group) gave informed consent for experimentation and completed this study (Figure 1).

Procedure

Patients with CM completed a semi-structured questionnaire designed to collect the clinical characteristics of their migraines. These individuals were instructed to keep a headache diary for 30 days to assess the frequency of migraine attacks and wear actimeters for 15 days to obtain the rest-activity rhythm data.

After filling in the headache diary and using the actimeter, the CM group completed a sociodemographic and lifestyle assessment form, as well as a Visual Analog Scale (VAS) for pain intensity, the Headache Impact Test-6 (HIT-6), Horne & Ostberg Morningness-Eveningness Questionnaire (MEQ-HO), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAI). The NH group completed all of these instruments, except those related to headache.

Self-report measures

Sociodemographic and lifestyle habits

A sociodemographic and lifestyle habits assessment form, designed by our research group, was completed for each individual. It included basic information such as name, date of birth, gender, skin color, body weight, marital status, education, employment status, presence of comorbidities, consumption of alcoholic beverages, smoking, and use of other drugs.

Measurement of chronic migraine profile

Clinical evaluation form. The form was designed by our research group to collect data on the following aspects: time of onset of migraine attacks; characteristic, intensity, location, and progression of pain; associated symptoms; response to attacks; crisis duration; attack frequency and medication use per week; medications; and triggering factors.

VAS for pain intensity. The patients were asked to make a mark on a 10-cm horizontal line corresponding to the average intensity of their pain considering all headache/migraine days, with the left end of the scale (0 cm) representing the no pain condition, and the right end (10 cm) representing maximum pain. Likewise, patients were asked to score the discomfort level caused by CM, with

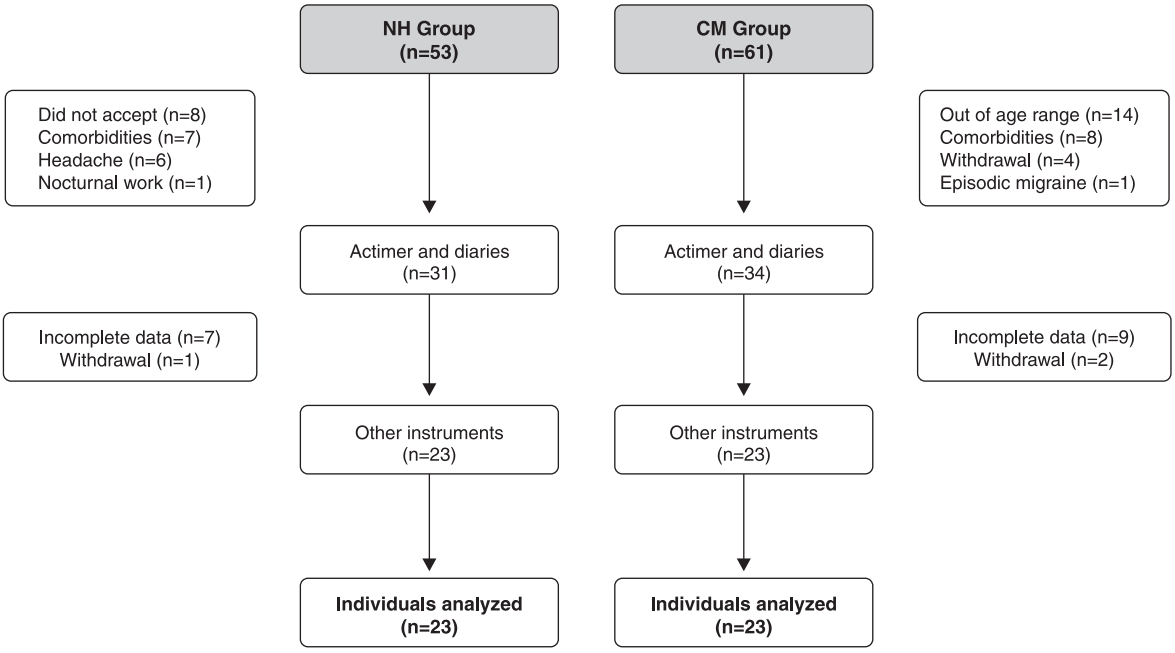

Figure 1 Study design. CM = chronic migraine; NH = non-headache.

the left end of the scale representing no discomfort and the right end corresponding to maximum discomfort. The score was expressed in centimeters for both variables.[18]

HIT-6. The HIT-6 assesses the severity of pain; impact of pain on work; domestic and social activities; general functionality; perceived vitality level; and cognitive and psychological aspects.[19] Each question has the following response options: never, rarely, sometimes, often, or always. The total number of points ranges from 36 to 78, with higher scores denoting a greater impact of migraine on the patient's daily life.

Headache diary. A headache diary (formulated by our research group) was given to patients for self-assessment of the frequency of migraine attacks over 30 days. Patients were asked to mark those days on which they had migraine.

Sleep habits

MEQ-HO. This questionnaire identifies the respondent's chronotype according to their biological predisposition to perform daily activities. Individuals may be classified as definitely evening (16-30 points), moderately evening (31-41 points), intermediate (42-58 points), moderately morning (59-69 points), or definitely morning (70-86 points).[20]

PSQI. Used to assess the subjective quality of sleep. This index measures seven domains: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, use of sleeping medication, and daytime dysfunction. The total result is the sum of the points; $>$ 5 points corresponds to poor sleep quality.[21]

ESS. This instrument assesses the risk of being drowsy during eight specific situations, such as reading while seated, watching television, as a passenger on a car trip, and sitting while talking to someone. The total score is calculated as the sum of the responses to the items; the higher the score, the greater the risk of becoming drowsy.[22]

Anxiety and depression symptoms

BDI. This was used to assess the presence and severity of depressive symptoms. Individuals were asked to choose the statement that best represented how they felt during the previous week. The final result was interpreted according to the following categorizations: minimal or no depression ($<$ 10 points), mild to moderate depression (10-18 points), moderate to severe depression (19-29 points), or severe depression (30-63 points).[23]

STAI. This was used to check for the presence and severity of anxiety symptoms on a self-report basis. The Inventory consists of 40 statements divided into two components: State Anxiety, which refers to the transient emotional state; and Trait Anxiety, which is more stable over time.[24] Each subscale can be scored as follows: 20 to 34 points correspond to mild anxiety; 35 to 49 points, moderate anxiety; 50 to 64 points, severe anxiety; and 65 to 80 points, very severe anxiety.

Actimeter-derived variables

Rest-activity rhythm

The rest-activity rhythm, which is considered an indirect marker of the sleep-wake cycle, was assessed by actigraphy. Actimeters (actigraphy devices) are miniature processors containing accelerometers for motion monitoring. The parameters are captured by sensors and then processed by integrated algorithms and translated into motion-related data. Both actimeter models used in the study were watch-type devices (ACT10 from Consultoria

Eletrônica and AT0503 from ActTrust/Condor Instruments). Both employ triaxial micro-electromechanical systems-based capacitive sensors, as do other state-of-art actigraphs available on the market. The devices were configured to record the activity data and process it with a Proportional Integral Mode algorithm with a 60-second epoch. The variables were controlled to avoid interference from possible differences in the records between the two brands of actimeters, and processed through the methods described below (additional detail in Table 1).

Cosinor method. The rhythmic variables evaluated using the cosinor method were the mean estimated statistic over rhythm (MESOR), amplitude (difference between the highest value and the MESOR), acrophase (highest phase point), and rhythmic percentage (%V, which refers to the degree of adjustment of the rest-activity rhythm to the cosine curve).[25]

Nonparametric method. This method is so termed because it does not try to fit the variables to the cosinor curve, in view of the particularities of the rest-activity rhythm. The following nonparametric variables were evaluated: L5 (average activity of the 5 continuous least active hours), M10 (average activity of the 10 continuous most active hours), relative amplitude (RA, the difference between M10 and L5 divided by the sum of M10 and L5), interdaily stability (IS, stability of the rhythm over days), and intradaily variability (IV, a proxy of rhythm fragmentation).[26]

Other variables. Other variables considered were: $AUC_{Activity}$ (area under the curve of the amount of activity over 24 hours); $\%AUC_{4h}$ (amount of activity 4 hours

Table 1 Description and interpretation of actimetric variables

Variables	Concept	Interpretation
Cosinor method[25]		
MESOR	Mean estimated statistic over rhythm.	Higher values indicate greater activity.
Amplitude	Difference between the highest value and the MESOR.	Higher values indicate greater activity.
Acrophase	Highest phase point.	The higher the value, the later the individual has his/her peak activity.
Rhythmic percentage (V%)	The degree of fit of the rest-activity rhythm to the cosine curve. In other words, it is the proportion of the overall variance accounted for by the fitted model.	The higher the value, the more rhythmic the individual.
Nonparametric method[26]		
L_5	Average activity of the 5 continuous least active hours.	Higher values indicate agitation during sleep.
M_{10}	Average activity of the 10 continuous most active hours.	The higher the value, the more active the individual during wakefulness.
RA	The difference between M10 and L5, divided by the sum of M10 and L5.	Higher values indicate a greater discrepancy in the intensity of activity between the periods of wakefulness and sleep, representing a more expressive rhythm.
IS	Stability of the rhythm over days.	The higher the values, the more stable the rhythm across the days.
IV	A proxy of fragmentation of the rhythm.	The higher the value, the more fragmented the rhythm.
Other variables[27-29]		
$AUC_{Activity}$	Area under the curve of the amount of activity over 24 hours.	Higher values indicate greater activity over 24 hours.
% AUC_{4h}	Amount of activity 4 hours before sleep onset. This parameter is associated to difficulties in sleep onset (i.e., increased sleep latency).	Higher values indicate greater agitation before sleep, that is, greater difficulty falling asleep.
% AUC_{Sleep}	The amount of activity between sleep onset and offset, i.e., the amount of activity during sleep.	Higher values indicate agitation during sleep.
CVAON	Variation in time to awakening.	Higher values indicate that individuals wake up at different times throughout the days.
CVAOF	Variation in time to fall asleep.	Higher values indicate that individuals fall asleep at different times throughout the days.
CFI	Overall measure to assess the robustness of the rest-activity rhythm. CFI incorporates three parameters: IV, IS and RA.	Higher values indicate a more robust rhythm, i.e., the higher, the better the rest-activity rhythm.
SRI	Regularity of sleeping and waking times throughout the days.	Higher values indicate that the individual sleeps and wakes up at the same times throughout the days.
fSoD	Fractional volume of epochs identified as sleep over daytime, using Cole-Kripke sleep-wake scoring algorithm.	Higher values indicate greater presence of sleep during the day.
Transition probability to awake once in sustained sleep (k_{RA})	Used to quantify the probability to transition from a rest state to an active state. This provides a quantification of the sleep fragmentation.	The higher the value, the greater the possibility of waking up from sleep (i.e., sleep fragmentation).

AUC = area under the curve; CFI = Circadian Function Index (a global measure to assess the robustness of the rest-activity rhythm); CVAON = coefficient of variation of activity onset (variation of wake-up time); CVAOF = coefficient of variation of activity offset (variation of sleep onset time); fSoD = fraction of sleep over daytime; IS = interdaily stability; IV = intradaily variability; L5 = average activity of the 5 continuous least active hours; M10 = average activity of the 10 continuous most active hours; MESOR = mean estimated statistic over rhythm; RA = relative amplitude; SRI = Sleep Regularity Index (regularity of sleeping and waking times over days).

before sleep onset); $\%AUC_{Sleep}$ (amount of activity during sleep); coefficient of variation of activity onset (CVAON, i.e., variation of wake-up time); coefficient of variation of activity offset (CVAOF, i.e., variation of sleep onset time); circadian function index (CFI, a global measure to assess the robustness of the rest-activity rhythm)[27]; sleep regularity index (SRI, regularity of sleeping and waking times over days)[28]; fraction of sleep over daytime (fSoD); and the transition probability to wake up once in sustained sleep (k_{RA}; probability to transition from a rest state to an active state, i.e., a quantitative marker of sleep fragmentation).[29]

The participants were instructed to wear the actimeter on their nondominant wrist, positioned firmly, but comfortably, 24 hours a day, taking it off only when there was a risk of wetting or damaging it and putting it back on immediately after the risk was removed. The participants also recorded their sleep habits in a diary, which was then used to adjust the actigraphy data, as in previous studies.[30,31]

Data analysis

Actigraphy data were analyzed using the El Temps software program. The cosinor method was used to investigate the presence of rhythmicity through the MESOR, amplitude, acrophase, and rhythmic percentage (%V) variables. The nparACT software package was used for nonparametric analysis (L5, M10, RA, IS, and IV). Other nonparametric variables ($AUC_{Activity}$, $\%AUC_{4h}$, $\%AUC_{Sleep}$, CVAON, CVAOF, CFI, SRI, fSoD, and k_{RA}) were processed using the pyActigraphy v1.0 package in Python 3.7.[32]

Data were expressed as absolute and relative frequencies, means and SD, and medians and ranges (minimum-maximum) as appropriate. Statistical analysis was performed using IBM® SPSS v. 20 and R v. 3.6.1; a 5% statistical significance level was considered. The Shapiro-Wilk test was used to investigate the normality of the data, and Student's *t*-test or the Mann-Whitney test were used to evaluate differences between the CM and NH groups.

A multiple linear regression model with interaction effect was applied. The actimetric variables were deemed independent, while depression and anxiety symptoms were deemed dependent variables. In addition, both groups were considered in the regression (NH and CM groups) in order to investigate whether the rest-activity rhythm is associated with anxiety and depression symptoms in patients with CM differently than in the NH group.

It is worth noting that the MESOR, amplitude, L5, and M10 variables were only available for individuals who wore the ACT10® (Consultoria Eletrônica) actimeter (n=17 each in the NH and CM groups), because the capture of these variables differed between the actimeter brands used. However, there was no interference with the results because individuals in the NH group received the same actimeter brand as their age- and gender-matched counterparts in the CM group. The other actimetric variables were not affected by use of either of the two actimeter brands; therefore, we analyzed the whole sample of 46 individuals (n=23 in each group) for these variables.

Ethics statement

This study was carried out in Brazil between December 2018 and October 2019, after approval by the ethics committee of Universidade Federal de Pernambuco (no. 92552318.6.0000.5208).

Results

Social and clinical characteristics of the individuals

The average age of individuals in the NH group was 27.4±6.3 years, versus 27.8±6.4 years in the CM group. The participants were predominantly female (96% of both groups), white in the NH group (61%) and brown in the CM group (70%), and had body weight within normal range (39% in the NH and 65% in the CM group). These and other demographic factors are presented in detail in Table S1, available as online-only supplementary material.

Regarding the migraine characteristics (Table 2), the VAS score was 70.6±12.2 for pain intensity and 76.1±15.1 for discomfort. HIT-6 revealed that the impact of headache on patients' lives corresponded to 65.1±4.0 points. Headache frequency was 17.4±7.8 days per month, and patients on medication reported taking medicines for attacks 3.2±2.1 days per week. Among patients on medications, 87% used drugs for acute treatment of crises and 8.7% used prophylactics. Simple analgesics (78.3%) and antispasmodics (52.2%) prevailed among the classes of drugs used. Other characteristics of migraine attacks are shown in Table S2.

Sleep quality characteristics and changes in the rest-activity rhythm

The participants predominantly had the intermediate chronotype (N_{NH} = 10; N_{CM} = 17), followed by morning characteristics (N_{NH} = 9; N_{CM} = 3) (Figure S1, available as online-only supplementary material). Patients with CM had worse sleep quality when compared to the NH group

Table 2 Migraine characteristics of individuals in the chronic migraine group (n=23)

Variables	Mean (SD)	Minimum	Median	Maximum
Pain intensity (VAS, cm)	7.1 (12.2)	4.0	7.0	9.0
Pain discomfort (VAS, cm)	7.6 (15.1)	4.0	7.0	9.0
HIT-6	65.1 (4.0)	54.0	65.0	76.0
Headache frequency (days per month)	17.4 (7.8)	8.0	16.0	30.0
Medicine frequency (days per week)	3.2 (2.1)	2.0	4.0	7.0

HIT-6 = Headache Impact Test-6; VAS = visual analogue scale.

Table 3 Rest-activity rhythm characteristics of individuals with and without chronic migraine

Variables	NH (n=23) (mean ± SD)	CM (n=23) (mean ± SD)	p-value
Pittsburgh Sleep Quality Index	5.17±2.31	8.74±2.60	< 0.001***
Epworth Sleepiness Scale	7.13±5.62	7.30±4.30	0.82
Actigraphic parameters			
MESOR†	86.69±9.42	72.11±18.94	0.01*
Amplitude†	47.35±9.52	34.40±17.50	0.02*
Acrophase (min)	918.76±73.87	967.84±180.86	0.04*
%V (%)	50.68±5.56	42.01±11.42	0.01*
L5†	23.17±5.28	19.91±5.70	0.03*
M10†	124.86±13.47	112.31±17.11	0.05
IS	0.50±0.11	0.38±0.14	< 0.01**
IV	0.63±0.08	0.67±0,11	0.63
RA	0.69±0.06	0.70±0.06	0.70
$AUC_{Activity}$	133193±21238	119000±28599	0.063
$\%AUC_{Sleep}$	9.35±2.35	13.29±4.18	< 0.001***
CVAON	0.17±0.07	0.28±0.12	< 0.001***
CVAOF	0.04±0.02	0.10±0.09	< 0.001***
CFI	0.58±0.05	0.51±0.08	< 0.001***
SRI	66.41±9.76	43.80±20.78	< 0.001***
fSoD	0.13±0.08	0.23±0.10	< 0.001***

Results expressed as mean and SD.
NH = non-headache; CM = chronic migraine; MESOR = mean estimated statistic over rhythm; Amplitude = difference between the highest value and the MESOR; acrophase = highest phase point; %V = rhythmic percentage (degree of fit of the rest-activity rhythm to the cosine curve); L5 = average activity of the 5 continuous least active hours; M10 = average of the 10 continuous most active hours; IS = interdaily stability (stability of the rhythm over days); IV = intradaily variability (a proxy of rhythm fragmentation); RA= relative amplitude (the difference between M10 and L5 divided by the sum of M10 and L5); $AUC_{Activity}$ = area under the curve of the amount of activity over 24 hours; $\%AUC_{Sleep}$ = amount of activity during sleep; CVAON = coefficient of variation of activity onset (variation of wake-up time); CVAOF = coefficient of variation of activity offset (variation of sleep onset time); CFI = Circadian Function Index (a global measure to assess the robustness of the rest-activity rhythm); SRI = Sleep Regularity Index (regularity of sleeping and waking times over days); fSoD = fraction of sleep over daytime.
† The variables represent the values of 34 individuals (n=17 each in the NH and CM groups). Shapiro-Wilk normality test; Student's *t*-test was used for the variables CFI, SRI, fSoD, $AUC_{Activity}$, and CVAON. For all other variables, the Mann-Whitney test was applied; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

($p < 0.001$, Table 3), with statistically significant differences observed for the following components: subjective sleep quality ($p < 0.001$), sleep latency ($p < 0.01$), and sleep duration ($p = 0.02$, Table S3 in the supplementary material). Despite the differences observed in terms of sleep quality, there was no significant difference regarding the level of daytime sleepiness ($p = 0.82$, Table 3).

Assessment of the rest-activity rhythm using actigraphy revealed that patients with CM showed less activity over 24 hours (MESOR: $p = 0.01$; amplitude: $p = 0.02$), including in the sleep phase (L5, $p = 0.03$). Patients with CM presented a delayed activity peak (acrophase, $p = 0.04$) when compared to individuals in NH group. Patients who experienced migraines presented more fragmented sleep ($\%AUC_{Sleep}$, $p < 0.001$) and greater fSoD ($p < 0.001$). Participants with CM showed greater variation in sleep onset (CVAOF, $p < 0.001$) and offset (CVAON, $p < 0.001$), as well as in the sleep regularity index (SRI, $p < 0.001$). A reduced IS of the rest-activity rhythm (%V, $p = 0.01$; IS, $p < 0.01$) was verified, with less robustness of this rhythm (CFI, $p < 0.001$).

Anxiety and depression symptoms

Regarding affective symptoms (Figure 2), individuals in both groups exhibited moderate symptoms for state (NH, 35.0±8.0; CM, 38.8±7.4) and trait (NH, 39.8±8.6; CM, 42.3±12.0) anxiety. While individuals in the NH group had minimal or no depressive symptoms (5.9±4.3), patients with CM presented mild to moderate depressive symptoms (12.0±7.3) ($p < 0.01$).

Interaction of rest-activity rhythm on depression and anxiety symptoms

Multiple linear regression models were used to analyze whether the rest-activity rhythm would interfere with anxiety and depression symptoms differently in patients with CM compared to the NH group. We found that fragmented sleep ($\%AUC_{Sleep}$) was associated with higher trait anxiety in CM ($p = 0.007$) (Table 4). This was also observed when subdividing the positive ($p = 0.001$) and negative ($p = 0.055$) items of the STAI-Trait. Higher activity (AUC_{24h}, $p = 0.023$) among patients with CM was associated with trait anxiety in the positive items of the test. Similarly, the most expressive and robust rhythms were associated with more severe trait anxiety (RA, $p = 0.027$; CFI, $p = 0.059$, respectively). However, no association was observed between the actigraphy variables and state anxiety or depressive symptoms ($p > 0.05$).

Discussion

The findings of the present study reveal that changes in the rest-activity rhythm – an excellent marker of the circadian timekeeping system and one of the indicators of the sleep-wake cycle – are more associated with trait anxiety in patients with CM. Specifically, the difference between peak activity and rest periods (RA), the amount of activity over 24 hours ($AUC_{Activity}$), sleep fragmentation ($\%AUC_{Sleep}$), and CFI, an indicator of the robustness of the rest-activity rhythm, increased the predictive power over trait anxiety when associated with CM. It was also

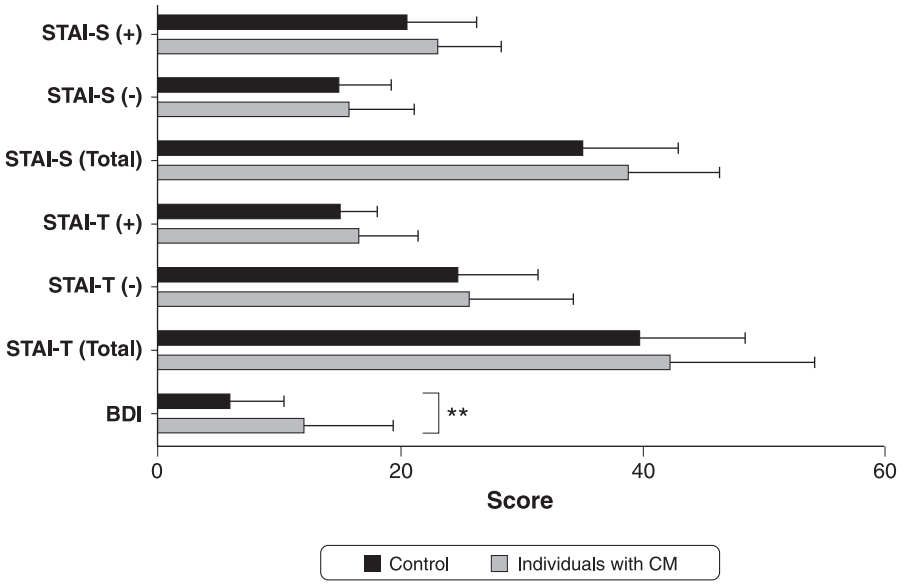

Figure 2 Profile of anxiety and depression symptoms in individuals with and without chronic migraine. BDI = Beck Depression Inventory; CM = chronic migraine; STAI = State-Trait Anxiety Inventory; S = State; (+) = Positive affirmations (the higher the scores on the positive components of the STAI, the greater the losses regarding them); (-) = Negative statements; T = Trait. Shapiro-Wilk test for normality; Mann-Whitney test, ** $p < 0.01$. Results expressed as mean and SD, considering the NH (n=23) and CM (n=23) groups.

Table 4 Linear regression analysis between actimetric variables and trait anxiety symptoms considering the interference of chronic migraine when compared to the non-headache group

	STAI-T (+)				STAI-T (-)				STAI-T (total)			
Activity/rest rhythm	EST	SE	R^2	p-value	EST	SE	R^2	p-value	EST	SE	R^2	p-value
RA	-26.57	11.61	0.15	0.02*	-18.50	23.11	0.03	0.42	-4.07	31.07	0.07	0.15
$AUC_{Activity}$	0.00	0.00	0.18	0.02*	0.00	0.00	0.04	0.74	0.00	0.00	0.08	0.27
$\%AUC_{Sleep}$	1.27	0.35	0.35	0.001**	1.48	0.75	0.15	0.05*	2.75	0.96	0.26	0.007**
CFI	-41.09	21.13	0.13	0.05*	-26.47	41.50	0.03	0.53	-67.55	56.04	0.06	0.23

STAI = State-Trait Anxiety Inventory; T = Trait; (+) = Positive statements; (-) = Negative statements; EST = estimate; SE = standard error; RA= relative amplitude (difference between M10 and L5 divided by the sum of M10 and L5); $AUC_{Activity}$ = area under the curve of the amount of activity over 24 hours; $\%AUC_{Sleep}$ = amount of activity during sleep; CFI = Circadian Function Index (a global measure to assess the robustness of the rest-activity rhythm); CM = chronic migraine; NH = non-headache.
In this analysis, we investigated the interference of CM on the interaction between the variables, compared to the NH group.
Results considering the NH (n=23) and CM (n=23) groups.
Multiple linear regression test, * $p < 0.05$, ** $p < 0.01$.

observed that patients with CM have decreased robustness of the rest-activity rhythm, worse subjective quality of sleep, and a tendency toward a delayed activity peak. In terms of affective symptoms, patients with CM presented more severe depressive symptoms; however, there were no differences in symptoms related to state and trait anxiety. To the best of our knowledge, this is the first study to report an association between the rest-activity rhythm and anxiety and depression symptoms in patients with CM. In addition, the present study is also novel regarding the specific set of actimetric variables used to characterize the rest-activity rhythm.

The data revealed that, although the majority of patients with CM were of the intermediate chronotype, the activity peak (acrophase) of patients with CM was later than in the NH group. These findings corroborate previous studies which observed that patients with more frequent migraine attacks tend to have more vespertine habits.[33] Other researchers found that most migraine attacks begin in the early morning.[34] One possible explanation for this phenomenon may be due to sleep disruption in individuals, given the more vespertine activity as demonstrated by their later acrophase.

The typical characteristics of insomnia presented by patients with CM in this study ($\%AUC_{Sleep}$) corroborate findings of previous actimetric studies which reported that patients with episodic migraine had insufficient sleep[35] and difficulty initiating sleep.[36] However, another study of patients with episodic migraine reported that there was no change in sleep characteristics after the headache crisis.[37] This suggests that migraine attacks do not predict the sleep problems commonly reported by people with

migraine. Instead, disruption of the rest-activity rhythm could be a trigger of migraine attacks. Therefore, good sleep quality may provide relief from migraine.[4,38]

Because better sleep quality leads to symptom relief, CM patients may take more naps throughout the day, which could explain our findings of lower activity among CM patients (MESOR, amplitude, L5, fSoD). Such sleep fragmentation throughout the day predisposes to a reduction in nocturnal sleep and leads to variation in sleep-onset and wake-up times,[28] as shown by CVAON, CVAOF, and SRI. This may explain the lower rhythmicity of the patients with CM in the present study (%V; IS, CFI).

Similar to our findings, an actigraphy study of women with breast cancer receiving adjuvant chemotherapy demonstrated that increased motor activity (MESOR, amplitude, and peak activity) and disrupted circadian quotient were related to higher levels of anxiety.[39] Corroborating our results related to fragmented sleep, an actigraphy study in middle-aged and older adults found that anxiety was associated with greater sleep fragmentation.[40] Thus, the disruption of the internal temporal organization along with alteration of the stability between biological rhythms, as seen in our study, allows for the emergence of anxious and depressive symptoms.[41] The mechanisms underlying the association between rhythm disruption and anxiety are not well known, but monoamine signaling, metabolic peptides,[42] and melatonin levels[43] may be implicated.

The present study found that circadian desynchronization (fragmented sleep, higher activity over 24h, a less expressive and robust rhythm) would have a greater association with anxiety symptoms in CM when compared to NH group. We hypothesized that this would occur because migraines are also sensitive to changes in biological rhythmicity per se. Several triggers for migraine, such as bright lights, meal timing, and stress-related cortisol, are known to affect the circadian system directly. On the other hand, melatonin, which is an important indicator of circadian rhythmicity, is low in individuals with migraine, and the administration of melatonin facilitates migraine treatment.[44] In a study of mice, exposure to sustained misaligned-time feeding led to an altered rest-activity rhythm and greater sensitivity to pain, with recovery after the administration of melatonin.[45] It is also postulated that painful conditions would occur with a certain rhythm, probably due to the homeostatic sleep drive and circadian rhythms modulating pain neural pathways.[46]

We are unaware of other studies which have investigated a physiological rationale for the fact that rest-activity rhythm is differently associated with anxiety symptoms in individuals with CM than in healthy individuals. However, it has already been verified that anxiety symptoms can be responses to alterations in biological rhythms.[14] Thus, we suggest that the rationale behind the present study is that the rest-activity rhythm (specifically circadian desynchronization) would be associated with anxiety symptoms in individuals with CM due to the misalignment of the circadian timing system of migraine patients.[10]

An interesting point to consider is that there was no difference in trait or state anxiety between individuals with and without CM, as reported in previous studies.[47] Therefore, how would the rest-activity rhythm be differently associated with the trait anxiety of individuals with CM than in the NH group? Patients with CM in the present study may have social support or coping strategies that counterbalance the interference of rhythm on trait anxiety, such as being optimistic.[48] On the other hand, individuals in the NH group may have presented other challenges associated with trait anxiety, such as being pessimistic. Furthermore, the fact that there was no influence of the rest-activity rhythm on depressive symptoms or anxious state during the course of this study may be because these symptoms would be triggered by long-term desynchronization.[49]

For example, Luik et al.[40] found that sleep fragmentation was associated with anxiety disorders. The present study goes further by pointing out that rest-activity rhythm influences anxiety in patients with CM. This demonstrates that the use of more practical tools, such as actigraphy, can be an important element in acquiring parameters to help define the therapeutic strategy for anxiety in CM, whether it consists of behavioral therapies,[50] adequate light exposure, or pharmacological treatment.[51] This can facilitate synchronization of the rest-activity rhythm of these patients and improve their prognosis.

Thus, further studies in this area aiming at a better understanding of the underlying mechanisms by which the rest-activity rhythm influences the affective symptoms of patients with CM are needed. To generalize findings, such studies should assess differences between genders and take body mass index into account. Additionally, techniques such as neuroimaging, analyses of melatonin and cortisol levels, polysomnography, and single-pulse transcranial magnetic stimulation can provide deeper insight into the rest-activity rhythm and brain activity of patients during sleep and wakefulness.

The present study has some limitations. First, the cross-sectional design precluded any causal inferences. Second, some variables included in the linear regression were not normally distributed, which could influence the regression residuals. Finally, due to the relatively small sample size, multiple comparisons could not be made. Despite these limitations, we found that the rest-activity rhythm (specifically RA, $AUC_{Activity}$, $\%AUC_{Sleep}$, and CFI) could contribute to the anxiety symptoms of patients with CM, as seen in the regression model. In addition to analyzing STAI-State and STAI-Trait data, our group decided to conduct a more in-depth analysis and ascertain whether the rest-activity rhythm presented a differential relationship between statements that show anxiety and the statements which do not. We consider that this approach has scientific importance for unraveling which aspects are involved in the association of rest-activity rhythm and anxiety and thus instigate critical reading, as well as motivating other research groups to consider such outcomes in their studies. In addition, this subdivision is useful and clinically significant, as it can

help elucidate which aspects health professionals should prioritize when treating anxiety in patients with CM.

In summary, our study, in conjunction with the literature (especially longitudinal studies), showed that there is a bidirectional comorbidity between rest-activity rhythm and migraines. In addition, we have shown that there is also an association between rest-activity rhythm and anxiety in CM. It is worth noting that these associations were found even considering 15 continuous days, meaning days with and without migraine attacks. Thus, it is important to assess the rest-activity rhythm of these individuals, including on non-attack days, since each day is influenced by the previous days when we consider biological rhythms. Therefore, we suggest that the evaluation and monitoring of patients with migraine should include a chronobiological assessment, especially of the rest-activity rhythm. Through such an assessment, individualized treatments can be developed to adjust the rest-activity rhythm and reduce sleep fragmentation, aiming to reduce the anxiety of individuals with CM. Furthermore, double-blind longitudinal studies are needed to test for causal association between the variables assessed herein. It is also necessary that future studies analyze how the medications used by individuals with migraine affect actigraphy data and other outcomes.

The findings of this study point to the coexistence of chronic migraine, impaired rest-activity rhythm, and mood changes. In this association of pathological conditions, the rest-activity rhythm can influence trait anxiety in patients with CM. However, the rest-activity rhythm did not influence state anxiety or depressive symptoms.

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Disclosure

The authors report no conflicts of interest.

References

1 Rammohan K, Mundayadan SM, Das S, Shaji CV. Migraine and mood disorders: prevalence, clinical correlations, and disability J Neurosci Rural Pract. 2019;10:28-33.
2 Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. Sleep Med Rev. 2013;17:173-83.
3 Pires GN, Bezerra AG, Tufik S, Andersen ML. Effects of acute sleep deprivation on state anxiety levels: a systematic review and meta-analysis. Sleep Med. 2016;24:109-18.
4 Uhlig BL, Engstrøm M, Ødegård SS, Hagen KK, Sand T. Headache and insomnia in population-based epidemiological studies. Cephalalgia. 2014;34:745-51.
5 Lin YK, Lin GY, Lee JT, Lee MS, Tsai CK, Hsu YW, et al. Associations between sleep quality and migraine frequency: a cross-sectional case-control study. Medicine (Baltimore). 2016;95:e3554.
6 Leocadio-Miguel MA, Fontenele-Araújo J. Actigraphy. In: Frange C, Coelho FMS, editors. Sleep medicine and physical therapy: a comprehensive guide for practitioners. Cham: Springer; 2022. p. 411-24.
7 Smith MT, McCrae CS, Cheung J, Martin JL, Harrod CG, Heald JL, et al. Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: an American academy of sleep medicine systematic review, meta-analysis, and GRADE assessment. J Clin Sleep Med. 2018;14:1209-30.
8 Ong JC, Taylor HL, Park M, Burgess HJ, Fox RS, Snyder S, et al. Can circadian dysregulation exacerbate migraines? Headache. 2018; 58:1040-51.
9 Kottwitz MU, Gerhardt C, Schmied S, Elfering A. Sleep, work stress and headache in printing business: an actigraphy study. Sleep Vigil. 2019;3:9-15.
10 Gori S, Morelli N, Maestri M, Fabbrini M, Bonanni E, Murri L. Sleep quality, chronotypes and preferential timing of attacks in migraine without aura. J Headache Pain. 2005;6:258-60.
11 Zurak N. Role of the suprachiasmatic nucleus in the pathogenesis of migraine attacks. Cephalalgia. 1997;17:723-8.
12 Vecchierini MF, Kilic-Huck U, Quera-Salva MA; Members of the MEL consensus group of the SFRMS. Melatonin (MEL) and its use in neurological diseases and insomnia: recommendations of the French Medical and Research Sleep Society (SFRMS). Rev Neurol (Paris). 2021;177:245-59.
13 Salva MAQ, Hartley S. Mood disorders, circadian rhythms, melatonin and melatonin agonists. J Cent Nerv Syst Dis. 2012;4:15-26.
14 Pilz LK, Carissimi A, Oliveira MAB, Francisco AP, Fabris RC, Medeiros MS, et al. Rhythmicity of mood symptoms in individuals at risk for psychiatric disorders. Sci Rep. 2018;8:11402.
15 Canazei M, Weninger J, Pohl W, Marksteiner J, Weiss EM. Effects of dynamic bedroom lighting on measures of sleep and circadian rest-activity rhythm in inpatients with major depressive disorder. Sci Rep. 2022;12:6137.
16 Valentinuzzi VS, Oda GA. The timekeeping system: a key organizational element. In: Vallentinuzzi ME, editor. Further understanding of the human machine: the road to bioengineering. Vol 9. Singapura: World Scientific Publishing Company; 2017. p. 357-89.
17 Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629-808.
18 Cline ME, Herman J, Shaw ER, Morton RD. Standardization of the visual analogue scale. Nurs Res. 1992;41:378-80.
19 Kosinski M, Bayliss MS, Bjorner JB, Ware JE Jr, Garber WH, Batenhorst A, et al. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res. 2003;12:963-74.
20 Horne JA, Östberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 1976;4:97-110.
21 Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193-213.
22 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540-5.
23 Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck depression inventory: twenty-five years of evaluation. Clin Psychol Rev. 1988;8:77-100.
24 Biaggio AMB, Natalício L, Spielberger CD. Desenvolvimento da forma experimental em português do Inventário de Ansiedade Traço-Estado (IDATE) de Spielberger. Arq Bras Psicol. 1977;29:31-44.
25 Nelson W, Tong YL, Lee JK, Halberg F. Methods for cosinor-rhythmometry. Chronobiologia. 1979;6:305-23.
26 Gonçalves BSB, Adamowicz T, Louzada FM, Moreno CR, Araujo JF. A fresh look at the use of nonparametric analysis in actimetry. Sleep Med Rev. 2015;20:84-91.
27 Ortiz-Tudela E, Martinez-Nicolas A, Campos M, Rol MA, Madrid JA. A new integrated variable based on thermometry, actimetry and body position (TAP) to evaluate circadian system status in humans. PLoS Comput Biol. 2010;6:e1000996.
28 Phillips AJK, Clerx WM, O'Brien CS, Sano A, Barger LK, Picard RW, et al. Irregular sleep/wake patterns are associated with poorer

academic performance and delayed circadian and sleep/wake timing. Sci Rep. 2017;7:3216.
29 Lim ASP, Yu L, Costa MD, Buchman AS, Bennett DA, Leurgans SE, et al. Quantification of the fragmentation of rest-activity patterns in elderly individuals using a state transition analysis. Sleep. 2011; 34:1569-81.
30 Fekedulegn D, Andrew ME, Shi M, Violanti JM, Knox S, Innes KE. Actigraphy-based assessment of sleep parameters. Ann Work Expo Health. 2020;64:350-67.
31 Lockley SW, Skene DJ, Arendt J. Comparison between subjective and actigraphic measurement of sleep and sleep rhythms. J Sleep Res. 1999;8:175-83.
32 Hammad G, Reyt M, Schmidt C. PyActigraphy: actigraphy made simple [Internet]. 2020 [cited 2022 Jun 08]. zenodo.org/record/2537921#.YqCkVKjMLIU
33 Viticchi G, Falsetti L, Paolucci M, Altamura C, Buratti L, Salvemini S, et al. Influence of chronotype on migraine characteristics. Neurol Sci. 2019;40:1841-8.
34 van Oosterhout W, van Someren E, Schoonman GG, Louter MA, Lammers GJ, Ferrari MD, et al. Chronotypes and circadian timing in migraine. Cephalalgia. 2018;38:617-25.
35 Kim J, Cho SJ, Kim WJ, Yang KI, Yun CH, Chu MK. Insufficient sleep is prevalent among migraineurs: a population-based study. J Headache Pain. 2017;18:50.
36 Bruni O, Russo PM, Violani C, Guidetti V. Sleep and migraine: an actigraphic study. Cephalalgia. 2004;24:134-9.
37 Vgontzas A, Li W, Mostofsky E, Rueschman M, Mittleman MA, Bertisch SM. Associations between migraine attacks and nightly sleep characteristics among adults with episodic migraine: a prospective cohort study. Sleep. 2020;43:zsaa001.
38 Smitherman TA, Walters AB, Davis RE, Ambrose CE, Roland M, Houle TT, et al. Randomized controlled pilot trial of behavioral insomnia treatment for chronic migraine with comorbid insomnia. Headache. 2016;56:276-91.
39 Berger AM, Wielgus K, Hertzog M, Fischer P, Farr L. Patterns of circadian activity rhythms and their relationships with fatigue and anxiety/depression in women treated with breast cancer adjuvant chemotherapy. Support Care Cancer. 2010;18:105-14.
40 Luik AI, Zuurbier LA, Direk N, Hofman A, Van Someren EJW, Tiemeie H. 24-hour activity rhythm and sleep disturbances in depression and anxiety: a population-based study of middle-aged and older persons. Depress Anxiety. 2015;32:684-92.
41 Miguel MAL, Menna-Barreto L. Sleep pressure and time perception in university students. Biol Rhythm Res. 2016;47:731-42.
42 McClung CA. How might circadian rhythms control mood? Let me count the ways. Biol Psychiatry. 2013;74:242-9.
43 Comai S, Gobbi G. Unveiling the role of melatonin MT2 receptors in sleep, anxiety and other neuropsychiatric diseases: a novel target in psychopharmacology. J Psychiatry Neurosci. 2014;39:621.
44 Burish MJ, Chen Z, Yoo SH. Emerging relevance of circadian rhythms in headaches and neuropathic pain. Acta Physiol (Oxf). 2019;225:e13161.
45 Xu F, Zhao X, Liu H, Shao X, Chu S, Gong X, et al. Misaligned feeding may aggravate pain by disruption of sleep–awake rhythm. Anesth Analg. 2018;127:255-62.
46 Hagenauer MH, Crodelle JA, Piltz SH, Toporikova N, Ferguson P, Booth V. The modulation of pain by circadian and sleep-dependent processes: a review of the experimental evidence. In: Layton A, Miller L, editors. Women in mathematical biology. Vol 8. Cham: Springer; 2017.
47 Russo A, Santangelo G, Tessitore A, Silvestro M, Trojsi F, De Mase A, et al. Coping strategies in migraine without aura: a cross-sectional study. Behav Neurol. 2019;2019:58086210.
48 Peres MFP, Oliveira AB, Mercante JP, Kamei HH, Tobo PR, Rozen TD, et al. Optimism, pessimism, and migraine: a cross-sectional, population-based study. Headache. 2019;59:205-14.
49 Baron KG, Reid KJ. Circadian misalignment and health. Int Rev Psychiatry. 2014;26:139-54.
50 Garland SN, Johnson JA, Savard J, Gehrman P, Perlis M, Carlson L, Campbell T. Sleeping well with cancer: a systematic review of cognitive behavioral therapy for insomnia in câncer patients. Neuropsychiatr Dis Treat. 2014;10:1113-24.
51 Cheng DCY, Ganner JL, Gordon CJ, Phillips CL, Grunstein RR, Comas M. The efficacy of combined bright light and melatonin therapies on sleep and circadian outcomes: a systematic review. Sleep Med Rev. 2021;58:101491.