Observational Study

Association Between Chronotype and Chronic Neuropathic Pain Sensitivity: A Pilot Prospective, Observational, Single-Center, Cross-Sectional Study

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Background: Chronotype defines an organism's biological preference for timing of activity and sleep. Being a morning chronotype (i.e., tending to wake up early and go to bed earlier at night) is associated with protection against chronic musculoskeletal pain and headaches, but the relationship between chronotype and neuropathic pain sensitivity remains unclear.

Objectives: The aim of this pilot study was to explore the relationship among chronotype, neuropathic pain sensitivity, and pain interference in patients with chronic neuropathic pain disorders.

Study Design: This was a prospective, observational, single-center, cross-sectional study.

Setting: Patients were recruited from pain management clinics.

Methods: The Morningness-Eveningness Questionnaire (MEQ) was used to evaluate circadian typology. Linear mixed-effects models, principal component analysis, and principal component regression were used to determine the predictors of pain intensity and pain interference evaluated by the Numeric Rating Scale (NRS) and Patient-Reported Outcomes Measurement Information System Pain Interference (PROMIS-PI) scores, respectively.

Results: We analyzed 38 adults who had at least one documented chronic neuropathic pain diagnosis. Morning-chronotype patients reported higher NRS scores over time and lower PROMIS-PI t-scores than did intermediate chronotypes. MEQ, depression, risk of sleep apnea, sleep quality, and body mass index (BMI) were all significant independent predictors of average NRS scores and PROMIS-PI t-scores.

Limitations: The population was small and homogeneously white, with an average age of 57 years. However, this population was representative of our pain clinic.

Conclusions: Morning chronotypes are more sensitive to chronic neuropathic pain, reporting higher pain scores than do intermediate chronotypes. However, in this study, morning chronotypes were more resistant to neuropathic pain interference, suggesting that they may experience less disturbance of their physical, mental, and social activities than intermediate chronotypes. Further, larger studies are needed.

Key words: Chronic pain, circadian rhythm, sleep, night owl, lark, morningness, eveningness, sleep, depression

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Chronic pain is a leading cause of disability and a frequent reason for visits to physicians (1). The incidence of chronic pain and severe chronic pain in the USA was recently estimated as 52.4 and 12.0 cases per 1,000 person-years, respectively (1). This incidence is greater than those of other common chronic conditions, such as diabetes, hypertension, and depression. Neuropathic pain, a type of chronic pain caused by lesions or diseases that impacts the somatosensory nervous system, affects 7-10% of the general population (2,3). Despite decades of prior preclinical and clinical work revealing that multiple factors are involved in the development and modulation of neuropathic pain, our current knowledge cannot fully explain the variation in pain sensitivity observed among individuals affected by the condition (2).

Chronotype is defined as an individual's biological preference for the timing of activity and sleep (4). Persons can be classified into 3 different chronotypes: morning, evening, and intermediate. Morning types (larks) wake up early and go to bed earlier at night. On the contrary, evening types (owls) wake up late and stay up late. Approximately 60% of the general population falls between these 2 extreme chronotypes and is described as the intermediate type (5). There is a relationship between chronotype and physical/psychological health, with evening/late-chronotype individuals being more susceptible to sleep and psychiatric disorders (6,7). However, the relationship between chronotype and pain has received less study and is less understood (8). Most evidence suggests that morning-chronotype individuals are less susceptible to pain, but the literature on the subject is concentrated on musculoskeletal and experimental heat pain specifically (9-16).

As far as we know, no study has examined the association between chronotype and chronic neuropathic pain conditions. Therefore, this study aimed to explore the association among chronotype, neuropathic pain sensitivity, and pain interference in patients with chronic neuropathic pain disorders. The research was conducted as a prospective observational single-center cross-sectional study at the affiliated chronic pain clinic of Banner—University Medical Center, Tucson, Arizona. Our initial hypothesis was that morning-chronotype individuals would experience less severe pain than would intermediate or late chronotypes.

Methods

Study Design

This study, designed to be prospective, observational, and cross-sectional and take place in a single-center setting, is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies (17). After we received approval (# 2104675201) from the University of Arizona's institutional review board (IRB), data were collected for a period of 12 months (October 30th, 2020 to October 25th, 2021).

Setting and Patients

The eligibility criteria were adult (≥ 18 years of age) patients being seen at the affiliated chronic pain clinic of Banner Health—Tucson with at least one documented chronic neuropathic pain diagnosis based on codes from the International Classification of Diseases (ICD-10-CM) (Appendix 1). A list of eligible patients was compiled using the electronic medical record (EMR), with the assistance of Banner Health's information technology department and NextGen® (n = 500). The charts were reviewed by MK to confirm the eligibility. The patients were then contacted individually by either phone or e-mail to gauge their interest in participating in the study. RedCAP was then used to both confirm the patients' consent and collect the pertinent data. If patients did not have Internet access or were unfamiliar with this technology, they were mailed a letter that included printed versions of the consent form and questionnaires. Of all the patients who were e-mailed a link to RedCAP or received printed material (n = 103), 59.2% (n = 60) agreed to participate in the study, and 36.8% (n = 38) completed all questionnaires. Patients who were unable to provide consent were excluded from the study.

Measurements

To ensure uniform data collection and accuracy, all variables were defined a priori and were recorded in a standardized format during the data collection process. Detailed definitions of all study variables are available in Appendix 1. The Morningness-Eveningness Questionnaire (MEQ) was administered once to evaluate the patients' previously described circadian typology (18). The MEQ is composed of 19 multiple-choice questions regarding sleep characteristics and preference for timing of sleep and work, with a possible final score ranging from 16 to 86. Patients were categorized into evening, intermediate, or morning chronotypes when their scores ranged from 16 to 41, 42 to 58, or 59 to 86, respectively.

Outcomes

We modeled 2 separate outcomes. The first was pain intensity at specific periods of the day. Pain intensity was evaluated on the Numeric Rating Scale (NRS), a validated self-reporting 11-point score scale (19), at 4 time points during the day (morning, afternoon, evening, and bedtime). We also calculated the average NRS score during the day, defined as the arithmetic mean of the 4 NRS scores obtained for each patient.

The second outcome measured was the Patient-Reported Outcomes Measurement Information System Pain Interference (PROMIS-PI) score. The PROMIS-PI is a validated item bank developed by the National Institutes of Health as a tool to measure the degree to which pain limits or interferes with individuals' physical, mental, and social activities (20,21). The PROMIS-PI Short Form 8a v1.0 uses 8 questions, the answer to each of which is scored on a 5-point Likert response scale, ranging from "never," scored as 1, to "always," scored as 5. These responses are added to obtain a raw score for each item bank and converted to a T-score. A T-score of 50 is the mean of a relevant reference population, and 10 is the SD of that population. Therefore, in our sample, higher scores indicated greater neuropathic pain interference. More information on the development, validation, and implementation of all PROMIS measures can be found at www.nihpromis.org.

Covariates

Sociodemographic covariates included age, gender, and ethnicity. Depression, obesity, risk of obstructive sleep apnea, and sleep quality are known to modulate pain intensity and sensitivity (8,22,23). Therefore, we adjusted for depression, body mass index (BMI), obstructive sleep apnea, and sleep quality using the Patient Health Questionnaire-9 (PHQ-9) (24), the STOP-Bang (25), and the Pittsburgh Sleep Quality index (PSQI) (26), respectively (Appendix 1). BMIwas calculated from self-reported weight and height and expressed as weight/height^2.

Statistical Analysis

Since we were conducting a pilot study, our focus was on establishing the estimation of parameters. Our post hoc analysis showed that a sample size of 38 would produce a 2-sided 95% CI, with the distance from the mean no wider than 0.33 standard deviations for a continuous outcome and an exact (Clopper-Pearson) 95% CI with a width no greater than 0.33 for a binary outcome.

Continuous variables were summarized as mean ± SD, ordinal variables were summarized as the median plus interquartile range (IQR), and categorical variables were summarized as frequency (%). Unpaired t-tests with Welch's correction were performed to compare continuous variables, Mann-Whitney tests were used to compare ordinal variables, and Fisher's exact tests were performed to compare categorical variables between chronotype groups. A linear mixed-effects model with random intercepts was used to compare pain scores over time among chronotypes, accounting for within-subject correlation and repeated measures. For the adjusted analysis, sociodemographic covariates, NRS time of measurement, and PROMIS-PI, STOP-Bang, PSQI, and PHQ-9 scores were controlled in the linear mixed-effects model. Morning NRS scores were also controlled for the analysis, based on the percentile change from the morning pain score to the later pain scores. Principal component analysis (PCA) and subsequent principal component linear regression (PCR) were done to control for multicollinearity among independent variables. These types of analysis were also carried out to determine the significance of the relationship of each independent variable to the average pain during the day and the patients' reported PROMIS-PI scores. The two-tailed significance level was set a priori at $P < 0.05$. GraphPad Prism 10.1 (GraphPad Software, LLC) and SAS version 9.4M7 (SAS Institute, Inc.) were used for calculations and graphing results.

Results

Patients' demographic and baseline characteristics are shown in Table 1. The neuropathic pain conditions diagnosed were isolated mononeuropathy (n = 11), unspecified polyneuropathy (n = 11), diabetic peripheral neuropathy (n = 8), idiopathic peripheral neuropathy (n = 6), drug-induced peripheral neuropathy (n = 2), postherpetic neuropathy (n = 1), and mononeuritis multiplex (n = 1). The most common comorbid chronic pain conditions were lumbar or cervical radiculopathy (n = 20) and myofascial pain (n = 12). Although 61.11% of patients had only one chronic pain diagnosis, diagnoses do not exclude one another, so 22.22% of the patients reported 2 chronic pain conditions and 16.67% reported 3 or 4 chronic pain diagnoses. The patients' average age was 57.11 ± 13.97 years. Of the patients, 60.3% were women, 81.58% were white, and 26.32% were Hispanic. Based on their MEQ scores, 16 patients were classified as the morning chronotype, 21 as the intermediate chrono-

type, and only one as the evening chronotype. Only 7 patients had opioid prescriptions (18.4%) in addition to other multimodal treatments. The patients who had these prescriptions were evenly distributed among the chronotypes (Table 1), and daily doses were lower than 30 morphine milligram equivalents (MME) every 24 hours. Other medications prescribed to the patients included gabapentin, pregabalin, duloxetine, celecoxib, meloxicam, aspirin, ibuprofen, amitriptyline, baclofen, acetaminophen, naproxen, diclofenac, and rizatriptan. None of the patients had been prescribed phase-altering medications such as melatonin or ramelteon. In the morning group, 11 patients were on one medication; one was on 2; another was on 3, and 3 patients were on 4 medications for controlling pain. In the intermediate group, 12 patients were on one medication; 6 were on 2; one was on 3, and 2 patients were on 4 medications designed to control pain. The patient in the evening group was on 2 pain medications. Since we had only one patient in the evening group, post-hoc analysis was done with just the patients in the morning and intermediate groups.

The results showed that the groups showed significant differences in their PROMIS and PHQ9 scores (Table 1). Intermediate-chronotype patients had significantly higher PHQ-9 scores than did morning-chronotype patients. In addition, morning-chronotype patients had significantly lower PROMIS-PI t-scores than did patients in the intermediate group. Other baseline characteristics did not differ between these chronotype groups.

Reported NRS scores significantly increased during the day in all chronotype groups, being higher in the afternoon, evening, and bedtime periods than in the morning period (Fig. 1). Linear mixed models identified that patients in the morning group had significantly greater pain scores than did patients in the intermediate group (Table 2a). Similarly, the increase in MEQ scores was positively correlated with the worsening of pain throughout the day (Table 2b). We also performed PCA followed by PCR to better determine the relationship of each independent variable to the patients' average reported pain score during the day (Table 3). The overall regression was statistically significant (R^2 = 0.254, F(3,28) = 3.185, P = 0.039). Our model showed that BMI, age, and MEQ, PHQ-9, PROMIS-PI, STOP-Bang, and PSQI results were all significant predictors of average NRS scores (Table 3). Therefore, this model confirmed that morning-chronotype patients reported significantly higher average NRS scores than did intermediate-chronotype patients, but the same model also showed that the characteristic similarly applied to patients with higher BMI and PHQ-9, PROMIS-PI, STOP-Bang, and PSQI scores.

Pain perception is complex and multifactorial. Individuals reporting the same NRS scores can experience extremely different limitations on their physical, mental, and social activities. Hence, we also explored the relationship between MEQ scores and pain interference by performing PCA and fitting a PCR model to our data, using PROMIS-PI as the dependent variable. The overall regression was statistically significant (R^2 = 0.549, F(3,28) = 11.39, $P \leq 0.0001$). Table 4 shows that MEQ scores were inversely related to PROMIS-PI scores, indicating that morning-chronotype patients reported less pain interference than did intermediate-chronotype patients. In addition, it was found that average NRS scores, age, BMI, PHQ-9, STOP-Bang, and PSQI scores significantly predicted scores on the PROMIS-PI.

Table 1. *Baseline characteristics of ≥ 18-year-old patients by chronotype.*

Variable	Overall (n = 37)	Morning (n = 16)	Intermediate (n = 21)	*P* value
Age	57.92 ± 13.21	61.00 ± 13.47	55.57 ± 12.84	0.26
Female Gender	22 (59.46%)	8 (50.00%)	14 (66.67%)	0.49
Race				
White	30 (81.08%)	13 (81.25%)	17 (80.95%)	> 0.99
Hispanic	10 (27.03%)	5 (31.25%)	5 (23.81%)	0.90
Other	5 (13.51%)	2 (12.50%)	3 (14.29%)	> 0.99
NA	1 (2.70%)	0 (0.00%)	1 (4.76%)	> 0.99
PROMIS-PI	62.89 ± 8.32	58.92 ± 8.99	65.73 ± 6.65	0.015
STOP-Bang	3.76 ± 1.66	3.47 ± 1.46	4.00 ± 1.81	0.47
PSQI Total	11.68 ± 5.20	9.71 ± 5.04	13.05 ± 4.97	0.076
PHQ9 Total	8.62 ± 7.03	5.94 ± 7.12	10.67 ± 6.38	0.017
MEQ Total	57.19 ± 8.41	65.12 ± 4.79	51.14 ± 4.63	< 0.001
Opioid Use	7	2 (12.5%)	5 (23.8%)	0.433

n = number of patients; NA = Native American; Pain conditions = number of pain conditions reported; BMI = body mass index; PSQI = Pittsburgh Sleep Quality index; PHQ-9 = Patient Health Questionnaire-9; PROMIS-PI = Patient-Reported Outcomes Measurement Information System pain interference t-score; data represented as n (%), mean (± standard deviation), or median (interquartile range); *P*-values related to comparisons between morning and intermediate chronotypes; * = $P < 0.05$.

Discussion

In this single-center prospective observational cross-sectional study, morning-chronotype patients with neuropathic pain reported significantly higher NRS scores than did intermediate-chronotype patients after controlling for covariates. However, morning-chronotype patients also reported significantly lower pain interference than did intermediate-chronotype patients. These associations were independent of other risk factors known to modulate chronic pain perception, such as depression, obesity, obstructive sleep apnea, and sleep disturbance.

Our initial finding that morning-chronotype patients reported higher levels of neuropathic pain stands in contrast to the current paradigm in the field that intermediate- and evening-chronotype individuals are more susceptible to pain (10,11,13-15,27). Notably, those studies did not concentrate on chronic neuropathic pain specifically and were instead focused on musculoskeletal pain and migraine headaches. A more recent study failed to show a relationship between chronotypes and heat pain threshold in healthy patients (16). In addition, literature on migraine and tension-type headaches mentions that morning-chronotype individuals experience more intense migraines in the morning while evening-chronotype individuals experience more

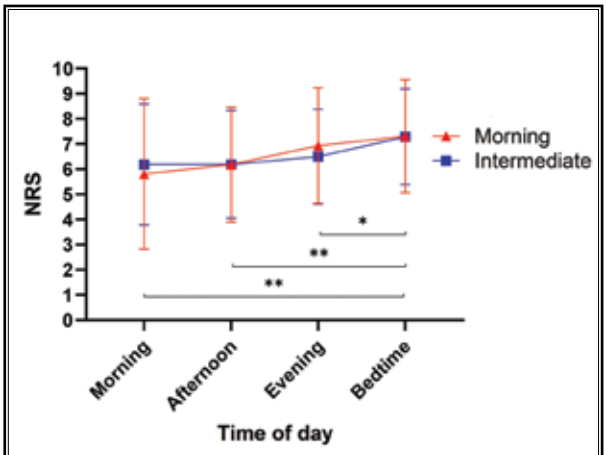

Fig. 1. *Numeric Rating Scale overtime in morning and intermediate chronotype.*
NRS, nermeric rating scale; *$P < 0.05$; **$P < 0.001$

Table 2a. *Comparison of pain score over time between chronotypes. Results from linear mixed effects model.*

	Unadj Coeff	SE	Unadj P	Adj Coeff	SE	Adj P
Intermediate vs. Morning	-0.094	0.744	0.9010	-2.751	0.834	0.0060

Table 2b. *Relationship between pain score over time and MEQ score. Results from linear mixed effects model.*

	Unadj Coeff	SE	Unadj P	Adj Coeff	SE	Adj P
MEQ	0.012	0.039	0.761	0.1	0.043	0.037*

Coeff, regression coefficient; SE, standard error; Unadj, unadjusted; Adj, adjusted; *$P < 0.05$

Table 3. *Relationship between average pain score during the day and independent predictors. Results from linear regression and principal component linear regression.*

	UnadjCoeff	SE	Unadj p	Adj Coeff	SE	Adj P
MEQ	0.003	0.036	0.935	0.016	0.007	0.033*
PHQ-9	0.077	0.043	0.081	0.027	0.012	0.033*
STOP-Bang	0.152	0.200	0.454	0.042	0.019	0.033*
PSQI	0.089	0.061	0.153	0.040	0.018	0.023*
BMI	0.069	0.044	0.128	0.015	0.007	0.023*
PROMIS-PI	0.111	0.034	0.002*	0.025	0.011	0.033*
Age	<-0.001	0.022	0.994	-0.008	0.003	0.033*
Gender	N/A	N/A	N/A	-0.924	0.626	0.151
Race	N/A	N/A	N/A	1.006	0.7696	0.201

Coeff, β coefficient; SE, standard error; Unadj, unadjusted; Adj, adjusted; MEQ, Morningness-Eveningness Questionnaire; BMI, body mass index; PSQI, Pittsburgh Sleep Quality index; PHQ-9, Patient Health Questionnaire-9; PROMIS-PI, Patient-Reported Outcomes Measurement Information System pain interference t-score; *$P < 0.05$

Table 4. *Relationship between PROMIS-PI score and independent predictors. Results from linear regression and principal component linear regression.*

	UnadjCoeff	SE	Unadj p	Adj Coeff	SE	Adj P
MEQ	-0.486	0.160	0.004*	-0.160	0.039	< 0.001*
PHQ-9	0.491	0.114	<0.001*	0.263	0.047	< 0.001*
STOP-Bang	0.152	0.200	0.454	0.042	0.019	0.033*
0.051	0.034	0.146	0.254	0.047	0.001*	0.023*
PSQI	0.415	0.082	<0.001*	0.378	0.074	< 0.001*
BMI	0.321	0.140	0.029*	0.125	0.037	0.002*
Average NRS	0.111	0.034	0.002*	0.787	0.125	< 0.001*
Age	-0.425	0.281	0.140	-0.096	0.019	< 0.001*
Gender	N/A	N/A	N/A	-1.747	2.057	0.4027
Race	N/A	N/A	N/A	1.381	2.545	0.5917

Coeff, regression coefficient; SE, standard error; Unadj, unadjusted; Adj, adjusted; MEQ, Morningness-Eveningness Questionnaire; BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; PHQ-9, Patient Health Questionnaire-9; PROMIS-PI, Patient-Reported Outcomes Measurement Information System pain interference t-score; average NRS, arithmetic mean of the 4 Numeric Rating Scale scores obtained for each patient; *$P < 0.05$

intense migraines in the evening (28,29). Therefore, neuropathic pain may have a different relationship with chronotypes than other types of pain do, with morning-chronotype persons being more sensitive to pain than intermediate-chronotype persons.

Patient-reported pain severity measures such as NRS scores remain the prime outcome in most clinical pain studies (19). However, measuring a complex construct like pain with a single-item scale such as an NRS may lead to more measurement error than the use of multi-item scales like PROMIS-PI. Despite being more prone to report higher NRS scores, morning-chronotype patients had lower levels of pain interference when compared to intermediate-chronotype patients. Pain experience can vary greatly among individuals reporting equal NRS scores; whereas one may function poorly in several areas, another may experience minimal pain interference (30). Psychological factors such as pain catastrophizing and coping strategies such as self-efficacy play a prominent role in the experience and response to chronic pain (30,31). Previous studies have shown greater resistance to psychological distress in morning-chronotype persons (10,32,33), so one possible explanation for our findings is that morning-chronotype individuals may have better coping mechanisms than do intermediate-chronotype individuals.

Multiple neuropathic pain conditions, including diabetic polyneuropathy, postherpetic neuralgia, small-fiber neuropathy, and phantom limb pain, display diurnal variation in their intensity, with peak pain intensity reported in the evening hours (between 18:00 and 23:59) (34). Those observations were confirmed by our study, showing that afternoon, evening, and bedtime NRS scores were significantly higher than those reported for the morning period. Additionally, in our sample, BMI and PHQ-9, STOP-Bang, and PSQI scores were independent predictors of average scores on the NRS and PROMIS-PI. These findings agree with previous studies showing that obstructive sleep apnea, obesity, depression, and sleep disturbances are associated with increased sensitivity to chronic pain (8,22,23,33).

Limitations

Our study has several limitations. The response rate of the study was 36.8%, which may have caused some selection bias. The homogeneity of our sample, composed mainly of white adults in their late 50s and early 60s, limits the generalizability of our results. Nonetheless, this cohort represents the typical population evaluated in a traditional pain clinic in the USA. Moreover, the vast majority of patients consisted of morning- and intermediate-chronotype persons, which was most likely due to the age of the patients in our sample, since the evening chronotype is more prevalent in young (< 40-year-old) men (35). The sample size was small, but this was a pilot study. Further, larger studies are needed to confirm our findings and establish their generalizability.

The cross-sectional design of this study did not allow the researchers to draw causal inferences. Future analyses of longitudinal data are needed to verify this study's findings. Finally, although the researchers adjusted for multiple factors (e.g., sociodemographic, obesity, and sleep disturbance) known to modulate pain perception, the authors cannot exclude the possibility of residual con-

founding. It is important to note that we did not control the use of opioid pain medications in this study. However, only 7 patients had opioid prescriptions (18.4%) as well as other multimodal treatments. Those prescriptions were distributed evenly among chronotypes (Table 1), and the prescribed daily doses of those medications were lower than 30 MME every 24 hours. Additionally, we did not include information on other factors that might have affected the patients' neuropathic chronic pain sensitivity and interference, such as physical activity, smoking status, and alcohol consumption (33).

Conclusion

In summary, our single-center prospective observational cross-sectional study demonstrates for the first time that morning-chronotype persons are more sensitive to chronic neuropathic pain than are persons of other chronotypes, reporting higher pain scores than intermediate-chronotype individuals. However, morning-chronotype patients were more resistant to neuropathic pain interference, suggesting that they may experience less disturbance of their physical, mental, and social activities than intermediate-chronotype persons do. Given the scarcity of literature on this topic, more studies are needed to clarify the mechanisms behind the relationship between chronotypes and neuropathic pain sensitivity in different populations.

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Appendix 1

ICD-10 CM Codes Used for Subject Identification
Neuropathy G 62.9
Chronic G 62.89
Diabetic E 11.40
Entrapment G 58.9
Hereditary G 60.9
Motor and sensory G 60.0
Sensory G 60.8
Idiopathic G 90.09
Radiculopathy 54.1
Polyneuropathy, unspecified (G62.9)
Drug-induced polyneuropathy (G62.0)
Mononeuropathies of upper limb (G56)
Mononeuropathies of lower limb (G57)
Other specified diabetes mellitus with diabetic neuropathy (E13.40)
Hereditary and idiopathic neuropathy, unspecified (G60.9)
Radiation induced polyneuropathy (G62.82)
Alcoholic peripheral neuropathy G 62.1

Study Covariates

1. Patient Health Questionnaire-9 (PHQ-9)

This test is a validated questionnaire for measuring depression, consisting of 9 questions with responses ranging from 0 to 3 for each question and a total score range of 0 to 27. Higher scores suggest higher depressive symptoms, and scores above 5 are indicative of depression.

2. The Pittsburgh Sleep Quality Index (PSQI)

This index is a self-reported measure of the patient's sleep quality over the last month. The PSQI includes 19 questions resulting in 7 component scores and a global score that ranges from 0-21, with higher scores suggesting greater sleep problems.

3. STOP-Bang questionnaire

This questionnaire is an 8-question survey developed to screen patients for obstructive sleep apnea (OSA). The response to each question can be either "yes" or "no." The score is calculated from the number of "yes" responses. A score of 2 or lower is normal, and 5 or more is suggestive of a moderate-to-high risk of OSA.