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# Sleep and circadian rhythm disturbances as risk and progression factors for multiple chronic overlapping pain conditions: a protocol for a longitudinal study

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## Abstract

**Introduction:** Chronic overlapping pain conditions (COPCs), such as chronic low back pain (cLBP) and fibromyalgia, frequently cooccur and incur substantial healthcare costs. However, to date, much focus has been placed on individual anatomically based chronic pain conditions, whereas little is known about the mechanisms underlying progression to multiple (more than 1) COPCs. This study aims to address the gap by investigating the role of common and modifiable risk factors, specifically sleep and circadian rhythm disturbances, in the development of multiple COPCs.

**Methods:** The study will enroll 300 participants with cLBP, including 200 with cLBP only and 100 with cLBP plus other COPCs (ie, fibromyalgia, temporomandibular disorders, irritable bowel syndrome, and chronic headaches) and follow them up for 12 months. Sleep and circadian rhythms will be assessed using wireless sleep electroencephalography, 24-hour evaluation of the rhythm of urinary 6-sulfatoxymelatonin, actigraphy, and sleep diaries. Pain amplification using quantitative sensory testing, psychological distress using validated self-report measures, and the number of pain sites using a pain body map will also be assessed.

**Perspectives:** This research aims to (1) comprehensively characterize sleep/circadian disturbances in individuals with single and multiple COPCs using multimodal in-home assessments; (2) examine the associations between sleep/circadian disturbances, changes in pain amplification, and psychological distress; and (3) investigate the relationship among these factors and the progression in the number of pain sites, a proxy for multiple COPCs. The findings will provide insights into the mechanisms leading to multiple COPCs, potentially informing treatment and prevention strategies for these complex conditions.

**Keywords:** Pain, Chronic overlapping pain conditions, Sleep, Circadian rhythms, Quantitative sensory testing, Stress

## 1. Introduction

Chronic overlapping pain conditions (COPCs) are specific chronic pain conditions that are mostly idiopathic, frequently co-occur and share common risk factors.[77] Examples include chronic low back pain, fibromyalgia, temporomandibular disorders, irritable bowel syndrome, and chronic headaches. The cooccurrence of

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multiple COPCs (ie, 2 or more COPCs) affects 48% to 62% of individuals with a COPC.[31,44,51] Although coexistence of multiple COPCs is associated with increased pain, disability, increased emotional distress, and reduced quality of life,[29,36,56,65,75] prior research has primarily focused on individual COPCs. This inattention to multiple COPCs has substantially limited efforts to develop and refine effective treatment and prevention strategies.

Two key factors, pain amplification and psychological distress, are proposed as primary risk factors for COPC development.[44] Pain amplification, a pronociceptive pain modulatory balance, characterized by enhanced pain facilitation (eg, temporal summation) and diminished pain inhibition (eg, conditioned pain modulation), is notable in individuals with COPCs.[19,44,84] The OPPERA-2 (Orofacial Pain: Prospective Evaluation and Risk Assessment-2) study showed a significant positive association between number of COPCs and pain amplification.[24]

Psychological distress, which refers to elevated levels of anxiety, depression, and perceived stress,[43] represents another domain of an established risk factor for onset and progression of COPCs. Studies show heightened depression, anxiety, and stress levels in individuals with a COPC compared with healthy controls.[44] Psychological distress experienced before the onset of a COPC is also a robust predictor of such a condition.[1,18,25,42] Importantly, our recent study found that as the number of co-occurring COPCs increases, psychological distress profiles are also elevated incrementally.[21]

Identifying common risk factors that influence pain amplification and psychological distress is crucial for developing targeted treatments and prevention strategies in COPCs. Sleep and circadian rhythm disturbances are among such critical factors (**Fig. 1**). A review of longitudinal studies indicates a stronger effect of sleep disturbances on pain than vice versa.[22] Laboratory studies also support the causal role of sleep deprivation in increased pain severity and pain amplification.[22,35,38] The link between sleep disturbances and psychological distress is also well-documented. Insomnia is an important risk factor for the onset and recurrence of depressive and anxiety disorders.[4,48,52,62] Most relevantly, a laboratory study found that partial sleep deprivation led to a significant increase in psychological distress among patients with rheumatoid arthritis.[32]

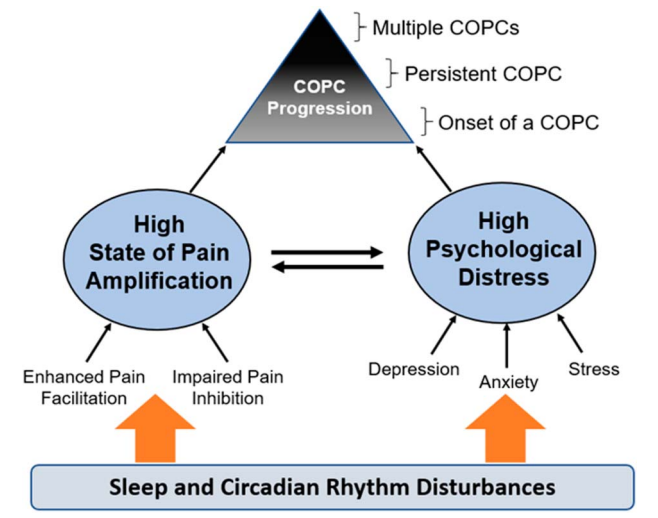


Figure 1. Conceptual model of factors influencing the onset and progression of COPCs. This figure is adapted from Maixner et al.[44] COPC, chronic overlapping pain conditions.

Similarly, circadian disturbances, such as shifted and/or blunted circadian rhythms—near-24h oscillations in physiology and behavior controlled by a central pacemaker (ie, the suprachiasmatic nucleus [SCN])[3]—can modulate pain perception. This is evidenced by experimental circadian disruptions in animal studies leading to increased nociceptive sensitivity.[11,16,79] Human studies support this, showing increased pain sensitivity in night-shift workers.[45,61] In addition, synthesis of both preclinical and clinical studies suggests a strong connection of circadian disturbances with anxiety and depression.[78]

Although studies to date indicate that both sleep and circadian disturbances may be important common and modifiable risk factors for pain amplification and psychological distress in the context of multiple COPC progression, some critical gaps remain. First, most studies examining these relationships have focused on healthy adults. Second, although neurobiological mechanisms underlying sleep and circadian rhythms are closely intertwined[64] and each can play a unique role in pain amplification and psychological distress, their coassessment is scant in the field of pain research.[50] Third, most previous studies that have investigated the effects of sleep and circadian disturbances on COPCs used self-report or a single method (eg, actigraphy) rather than employing a multimodal assessment.[81]

This study, funded by the National Institutes of Health (NIH), aims to fill significant gaps in previous research and provide answers to several key questions. We chose chronic low back pain (cLBP) as the index condition, given that it is arguably one of the most prevalent[26] and debilitating[70] COPCs. First, based upon 200 individuals with cLBP only and 100 individuals with cLBP and other COPCs, we will cross-sectionally examine a hypothesized dose-response–like associations between the number of COPCs and the severity of sleep and circadian disturbances at baseline (Aim 1). We hypothesized that individuals with greater number of COPCs will exhibit greater sleep and circadian disturbances than those with fewer COPCs. Second, we will prospectively examine whether differences at baseline and change over time (0–6 months) in sleep and circadian disturbances are associated with change (0–6 months) in pain amplification and psychological distress (Aim 2). We hypothesized that greater baseline values of and increased severity in sleep and circadian disturbances from 0 to 6 months will predict greater changes in pain amplification and psychological distress. Third, we will longitudinally examine whether pain amplification and psychological distress at 6 months and later change (6–12 months) are related to the progression in the number of pain sites, while controlling for the effects of baseline sleep and circadian disturbances (Aim 3). We hypothesized that greater 6-month values of and increased severity in pain amplification and psychological distress from 6 to 12 months will predict an increase in the number of pain sites, over and above the effects of baseline sleep and circadian disturbances. Finally, as an exploratory aim, we will examine whether baseline and change (0–6 months) in sleep and circadian disturbances, pain amplification, and psychological distress are associated with new COPC onset over 12 months.

## 2. Methods

### 2.1. Study design

We are conducting a single-site, longitudinal, cohort study. All participants will be followed for 12 months and divided into 2 groups: (1) those with cLBP only and (2) those with cLBP along with other COPCs (referred to as the "multiple COPCs" group). The study design varies between the groups to align with our objective of examining the progression single COPC to multiple

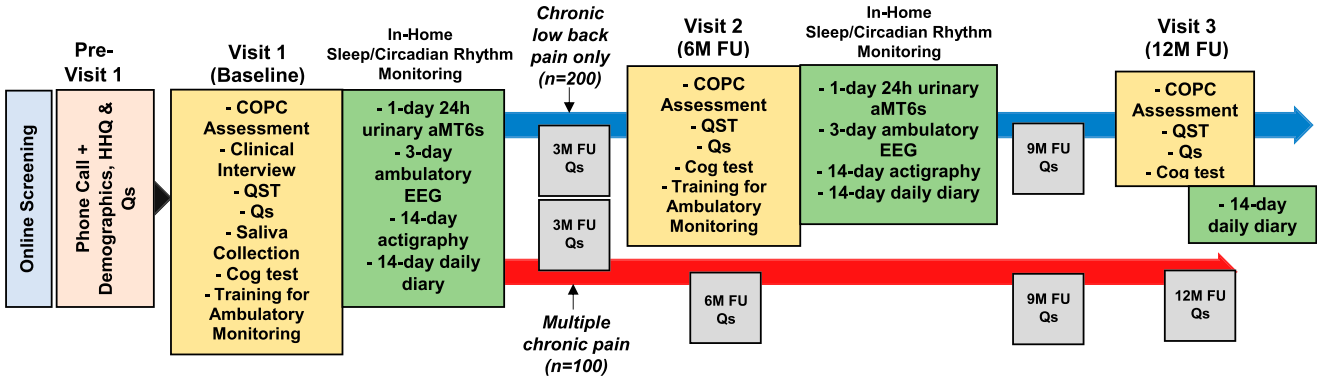


Figure 2. Study design and procedures. Blue and red thick lines indicate the duration of the study. Cog test, cognitive function test; EEG, electroencephalography; FU, follow-up; HHQ, Health History Questionnaire; M, months; Qs, questionnaires; QST, quantitative sensory testing; urinary aMT6s, urinary 6-sulfatoxymelatonin.

COPCs. Specifically, the cLBP-only group will undergo more extensive in-person assessments and sleep and circadian rhythm assessments. All data collection will take place at Arizona State University in the United States. This study's protocol has been approved by the Institutional Review Board (IRB) at Arizona State University (STUDY00017799), ensuring that all procedures are in accordance with the Declaration of Helsinki. Informed consent will be obtained from all participants.

### 2.2. Participants and recruitment

The recruitment of participants for this study started in December 2023. A total of 300 participants with cLBP (ie, 200 with cLBP only; 100 with multiple COPCs) will be recruited. Note that when we refer to participants with multiple COPCs, we are describing individuals who have cLBP along with at least 1 of 4 other COPC conditions (ie, fibromyalgia, temporomandibular disorders, irritable bowel syndrome, and chronic headache) that are described in the section below. Inclusion criteria for this study are (1) age between 18 to 65 years; (2) ability to speak, write, and read English; (3) classified as having cLBP based on the criteria established by an NIH task force[17] (ie, endorsement of pain in the space between the lower posterior margin of the rib cage and the horizontal gluteal fold indicated by figure drawing; duration of back pain for at least the past 3 months; and presence of back pain as an ongoing problem for at least half the days in the past 6 months); and (4) willing to participate in sleep/circadian rhythm assessments and pain assessments.

Exclusion criteria for this study are (1) having had lumbar surgery in past year; (2) having back pain from fracture or trauma (eg, car accident); (3) having been hospitalized within past month for mental illness; (4) self-reporting of chronic malignant pain (eg, cancer and HIV); or systemic inflammatory disease (eg, rheumatoid arthritis, ankylosing spondylitis, lupus, sarcoidosis); (5) currently using melatonin or immunosuppressant medications (eg, steroids); (6) currently pregnant, trying to get pregnant, or breastfeeding; (7) experiencing recent shift work (in previous 2 months) or travel across multiple time zones (in previous 2 weeks); and (8) planning to relocate within next year.

We recruited participants using multiple strategies, including but not limited to distributing flyers in community hospitals, clinics, and the Phoenix Veterans Affairs (VA) Health Care System; posting flyers online and through social media (eg, Facebook, Instagram); and advertising through radio and newspapers.

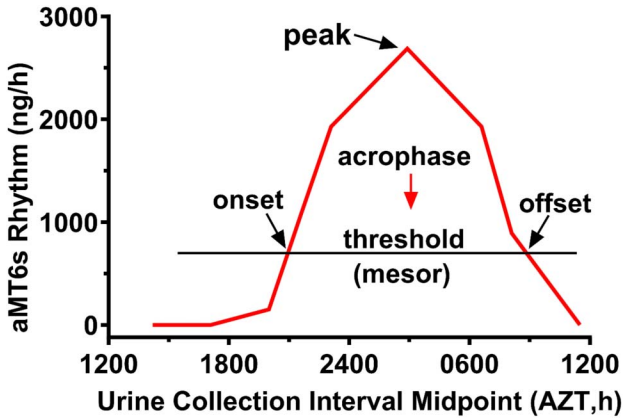


Figure 3. Schematic illustration of the circadian rhythm of urinary 6-sulphatoxymelatonin excretion rate (aMT6s, ng/h). The red curve plots calculated aMT6s ng/h excretion rates (at collection interval midpoints) for a continuous time series spanning approximately 24 hours. Arrows point to parameters important for characterizing potential health-related changes in the rhythm.

### 2.3. Study procedures

**Figure 2** visually summarizes the study procedures. Individuals who are interested in participating in the study will complete a brief online screening survey through REDCap online data management platform[27] to establish their initial eligibility. Eligible participants will be invited to an in-person visit to the laboratory (Visit 1). During Visit 1, participants who consent to study participation will complete a final screening procedure (ie, a urine pregnancy test for female participants only) to establish study eligibility.

Those who meet eligibility criteria and consent to participate will then complete a series of data collection procedures, including self-report measures and clinical interviews (eg, Structured Clinical interview for Sleep Disorders-Revised[74]), sleep apnea assessment with STOP-Bang,[14] brief computerized cognitive function assessments (ie, Auditory Digit Span Test and Trail Making Tests), and quantitative sensory testing (QST) procedures to assess pain amplification. Participants will also have the option to complete a one-time saliva collection procedure for an optional ancillary study, which aims to investigate the potential associations between salivary biomarkers, sleep patterns, circadian rhythms, and chronic pain. After completing these assessments, research staff will conduct

a training session to acclimate participants to study procedures for in-home sleep/circadian rhythm monitoring procedures involving (1) 24h assessment of urinary 6-sulfatoxymelatonin (aMT6s), (2) 3-night ambulatory sleep electroencephalography (EEG) assessment, (3) 14-day wrist actigraphy assessment, and (4) 14-day daily diary assessment through a smartphone app (for further details on participant training, please refer to the online supplement, http://links.lww.com/PR9/A251).

Participants will begin in-home monitoring of sleep and circadian rhythm starting the night when they arrive home from the in-person visit. For the 24h urinary aMT6s assessment, study staff will coordinate with participants to find a specific period in the next 14-day assessment period when they will collect urine samples continuously for 24h following the protocol outlined below. After all in-home monitoring assessments are completed, participants' urine samples and devices will be collected by a research team member. Note that the probability and magnitude of harm or discomfort anticipated in the both in-laboratory and home assessments are not greater than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations. In addition, participants can withdraw from the study at any time, as their participation is voluntary.

After the in-home monitoring is completed at baseline, all study participants will be followed for longitudinal assessments across the next 12 months. The nature of the longitudinal assessments will differ between those with cLBP only vs those with multiple COPCs. Each group's follow-up procedures are described below.

#### 2.3.1. Follow-up procedures for chronic low back pain only group

Six months after Visit 1, cLBP only participants will be invited for Visit 2, which includes self-report measures and QST assessments, as well as computerized cognitive tasks. These in-person assessments will be immediately followed by the same sleep and circadian rhythm assessments completed after Visit 1. Participants will be invited for Visit 3 (12-month follow-up) 6 months after Visit 2 completion. During Visit 3, the same assessments will be conducted in addition to verification of COPCs to examine the number of new COPCs. In addition, participants will complete a 14-day daily diary assessment after Visit 3. In addition to these in-person visits, participants will be invited to complete a 3- and 9-month online follow-up assessment that includes key self-report outcome measures (eg, pain, sleep, psychological distress, etc).

#### 2.3.2. Follow-up procedures for multiple chronic overlapping pain conditions group

After completing Visit 1 and in-home sleep and circadian rhythm assessment procedures, participants in this group will not undergo additional in-person follow-up assessments. Instead, they will be invited to complete a 3-, 6-, 9-, and 12-month online self-report follow-up assessments.

### 2.4. Assessment of other chronic overlapping pain conditions classifications

In addition to cLBP, 4 other COPCs will be classified in this study: fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, and chronic headache. We focus on these 4 COPCs because they are some of the most prevalent COPCs,[44,72] and they occur in both men and women. Assessment of these COPC conditions will be based on self-reports using well-validated measures (see online supplement, http://links.lww.com/PR9/A251 for further details).

### 2.5. Assessment of sleep

#### 2.5.1. Wireless sleep-electroencephalography assessments

The Sleep Profiler (Advanced Brain Monitoring, Carlsbad, CA)[40] will be used to for 3 consecutive nights. Single-use, gelled, snap electrodes are attached to the participant's forehead record 3-channel frontopolar-EEG (roughly FPZ, AFP7 and AFP8). Participants' data will be autoscored by the company's proprietary spectral scoring algorithm and manually edited by trained research staff to ensure that sleep staging corresponds to American Academy of Sleep Medicine scoring criteria.

#### 2.5.2. Actigraphy assessment

Participants will also be wearing a triaxial wrist accelerometer (Actigraph GT3X+; ActiGraph LLC, Pensacola, FL) on their nondominant wrist for 24 h/d for 14 days. Movement data will be collected in 60-second intervals. Based on the actigraphy monitoring guideline from the Society of Behavioral Sleep Medicine,[2] sleep periods will be first autoscored using the Cole–Kripke algorithm and then they will be manually verified by trained research staff using the consensus sleep diary data. Changes will be made to the autoscored sleep periods based on a standardized procedure that has been used in previous studies (see online supplement for details, http://links.lww.com/PR9/A251).[66,67]

#### 2.5.3. Daily sleep diary

Each morning, using the MetricWire smartphone app (MetricWire Inc., Waterloo, Ontario, Canada), participants will complete the consensus sleep diary,[13] which includes questions about time of getting into bed, time attempting to sleep, sleep latency, final wake time, out of bed time, wake time during the night, and sleep quality.

### 2.6. Primary sleep measures

We chose total sleep time (TST), wake after sleep onset (WASO), and slow wave sleep (SWS) measured by Sleep-EEG (Sleep Profiler) as primary measures because most laboratory studies investigating the effects of sleep on pain and psychological distress have been based on a sleep deprivation paradigm reducing TST or SWS, or increasing WASO.[22,38,69]

### 2.7. Assessment of circadian rhythms

#### 2.7.1. 24h home assessment of urinary aMT6s excretion

Participants will record the time of their last urination before starting their 24h home urine collection. Then, a urine sample will be collected from every instance of urination (approximately every 2-3h during wakefulness). Participants will first collect each urine sample in a specimen collector to record total volume and collection time and will then pipette duplicate 2-mL aliquots from each voiding to 2 prelabelled specimen tubes. Samples will be frozen (or refrigerated) at home for later pick up or drop off and storage in a −20°C freezer until assay of aMT6s. Participants will be asked to drink extra fluids (~200 mL every 2h) to promote frequent voiding. Concentration of aMT6s (ng/mL) will be

measured using aMT6s ELISA kits (NovoLytiX GmbH, Switzerland).

Guided by previous studies, all samples from an individual will be run initially at the same time on the same plate with reassays performed only as required to improve the clarity of the calculated circadian rhythm excretion (ng/h).[34,82] Based on aMT6s concentration, urine volume, and collection times, the aMT6s excretion rate (ng/h) will be computed for each collection interval and subsequently associated with each 5-minute interval within each collection interval. From this time series of 5-minutes interval, a least-squares best-fit 24h cosine function will establish the acrophase (ie, fitted time of peak), mesor (ie, fitted mean), and amplitude (ie, 50% of the difference between fitted peak and trough) of the circadian rhythms of aMT6s excretion. For each participant, we will also estimate circadian timing of evening rise (onset) and morning decline (offset) of the nocturnal aMT6s peak algebraically from upward and downward crossings of the calculated cosine mesor of the raw (ng/h) data curve connecting midpoints of each collection interval (**Fig. 3**).

#### 2.7.2. Actigraphy assessment

Circadian rest-activity rhythm will be measured by the triaxial wrist accelerometer described above. Using R software (eg, *ActCR* package),[83] we will extract the following circadian rest-activity rhythm features: interdaily stability, acrophase, amplitude, sleep midpoint (to evaluate social jetlag), circadian fit, and relative difference between activity during the sleep and wake periods (ie, dichotomy index).

### 2.8. Primary circadian rhythm measures

We selected amplitude, acrophase, aMT6s onset and offset from aMT6s analysis, and interdaily stability from actigraphy analysis as primary measures. These circadian indices are among the most important and widely studied and are closely associated with health-related outcomes.[30,57,58,76]

### 2.9. Assessment of pain amplification

Trained research team members will perform QST to measure pain amplification. The central sensitization inventory (CSI)[47] will be assessed to complement QST-measured pain amplification.

#### 2.9.1. Temporal summation

Temporal summation will be assessed using thermal stimuli and punctate mechanical stimuli. Thermal temporal summation (TTS) is measured by response to 3 series (temperatures: 45, 47, and 49°C) of 5 heat pulses. The temperature of each phasic stimulus remains the same. Within each sequence, successive thermal pulses will be delivered for a duration of approximately 0.5 seconds each, with an approximately 1.5-second interpulse interval. Participants will verbally rate the perceived intensity of each thermal pulse on a 0 to 100 numerical rating scale (NRS). Thermal temporal summation is calculated as the difference between the highest rated thermal stimulus and the first stimulus.[12,20] For mechanical temporal summation (MTS), a weighted pinprick stimulator with a flat contact area of 0.2-mm diameter and variable forces (both a 256-mN and a 512-mN probe) will be used to deliver punctuate noxious stimulus. The probes are applied perpendicular to the middle phalange of the middle finger. We will apply both single stimuli and 10-stimulus trains at 1 Hz and will subsequently record subjects' pain ratings (0–100 NRS). Single pinprick stimuli are alternated with trains of 10 stimuli. The difference between pain rating to the train of stimuli and the single stimulus is then calculated as MTS.[63]

#### 2.9.2. Conditioned pain modulation

A baseline pressure pain threshold at the trapezius muscle will be measured through a pressure algometer (AlgoMed; Medoc, Ramat Yishai, Israel) before participants undergo a cold pressor task (ie, the conditioning stimulus) consisting of immersion of the contralateral hand in an 8°C circulating cold-water bath (ARTIC-A25; Thermo Fisher Scientific, Waltham, MA, USA). Thirty seconds after initial hand immersion, participants' pressure pain threshold will be again assessed, whereas their hand remains in the cold water. A conditioned pain modulation index is quantified as the average percent change in pressure pain threshold during cold pressor tasks relative to baseline pressure pain threshold.[80]

### 2.10. Assessment of psychological distress

The total score of the *Depression, Anxiety, and Stress Scale–21 (DASS-21)*[43] will be used to quantify psychological distress. DASS-21 has excellent psychometric properties across cultures and is the most widely used measure of psychological distress.[53,54,55] We will also administer the PCL-5,[8] a well-validated measure of post-traumatic stress disorder (PTSD) symptom severity, as a part of psychological distress.[9,59]

### 2.11. Assessment of the number of pain sites

The online version of the revised Michigan Body Map (rMBM)[10] will be used to assess the number of pain sites. Participants will mark any of 35 body areas at which they have experienced persistent or recurrent pain for the last 3 months or longer.

### 2.12. Power analysis

The sample size was determined based on our previous study[68] and preliminary data because there are no other studies available for power analysis. For further power analysis details, please refer to the online supplement, http://links.lww.com/PR9/A251.

### 2.13. Data analytic plan

Aim 1 includes 8 dependent variables. As such, alpha will be set at 0.01 (2 tailed) to keep a reasonable lid on the inflation of the type I error rate, whereas an alpha of 0.05 will be used for all other analyses. Sex, age, and race/ethnicity will be included in all regression models as common a priori covariates, as there are established sex, age, and racial/ethnic differences in pain, sleep, and circadian rhythms.[5,7,28,39,52,60,79] In addition, the STOP-Bang score for sleep apnea risk and medication use, which can impact sleep and circadian rhythms, will be included as additional a priori covariates in the models for Aims 1 and 2. Mplus software, with parameters obtained through maximum likelihood estimation and standard errors that are robust to violations of normality (ie, MLR), will be used for all analyses.

#### 2.13.1. Plan for aim 1 analysis

Multiple regression models will be estimated for the baseline sleep and circadian rhythm outcome variables (ie, TST, WASO, SWS, acrophase, amplitude, melatonin onset and offset, and

interdaily stability). Each model will include the focal predictor (ie, the number of COPCs) and a priori covariates.

#### 2.13.2. Plan for aims 2 and 3 analyses

For Aim 2, separate multiple regression models will be estimated for the outcomes of baseline to 6-month change in pain amplification and psychological distress. Here, the focal predictors are the baseline and 6-month assessments of the sleep and circadian disturbance variables. Note that the regression coefficient for the 6-month assessment of a given focal predictor, while controlling for the baseline of the focal predictor, is equivalent to the baseline-to-6 months change scores. This allows for an interpretation of change associated with the focal predictor. As recommended,[46] we will include the baseline measure of a given outcome as a covariate in the model. The overall multiple regression model for Aim 3 is consistent with those for Aim 2. For Aim 3, the outcome is the 6- to 12-month change in the number of pain sites, and the focal predictors are the 6- and 12-month assessments of pain amplification and psychological distress. Again, same as Aim 2 analysis, regression coefficient for the 12-month assessment of a given focal predictor, while controlling for the 6-month of the focal predictor is equivalent to the 6-to-12 months change scores. The models will also include the baseline values of the sleep and circadian disturbance variables and the number of pain sites, and a priori covariates.

#### 2.13.3. Plan for exploratory aim analysis

Binary logistic regression will be used to assess whether baseline and baseline to 6-month changes in sleep and circadian disturbances, pain amplification, and psychological distress predict new COPC incidence over the 12-month period. If the incidence rate is very small, Bayesian MCMC estimation will be used, which can remove bias in the regression estimates and their standard errors in the presence of sparse outcome data.[15,71]

#### 2.13.4. Missing data analysis

The regression models described above treat incomplete response data with maximum likelihood estimation, which is the state-of-the-art missing data treatment.[6] We will also conduct missing data analysis to identify variables that are related to missingness and include them as auxiliary variables in the models, which can significantly reduce parameter estimation bias and increase statistical power.[23,37]

## 3. Discussion

Multiple COPCs exact an enormous toll on individuals and society. Recognizing common and modifiable risk factors of multiple COPCs is essential in developing interventions to treat and prevent these vexing conditions. Existing evidence suggests that sleep and circadian disturbances are common modifiable risk factors that may be associated with progression of multiple COPCs. Given that evidence-based strategies already exist to improve sleep and circadian rhythm disturbances (eg, cognitive behavioral therapy for insomnia, bright light therapy, and chronotherapy), clarifying the link between sleep and circadian disturbances, and multiple COPCs through this study may inform readily implementable and testable interventions.

Our study has several methodological strengths. First, this study will integrate both sleep and circadian markers to understand progression of multiple COPCs. To our knowledge, this study will be the first of its kind in human pain research to incorporate well-validated and reliable measures of sleep and circadian rhythms and assess them prospectively in ecologically valid home settings. Second, this study will be one of the first to assess 24h urinary aMT6s excretion rates among individuals with chronic pain, which provides reliable measures of endogenous melatonin onset and offset, peak, and amplitude that are relatively impervious to external factors (eg, physical activity, stress, and carbohydrate intake).[33,41] Third, this study will stand as the largest of its kind in the pain research field to employ a rigorous, medical-grade, wireless, sleep-EEG device, which will significantly enhance ecological validity in assessing objective sleep markers.

In summary, the proposed study holds the potential to provide significant insight into whether sleep and circadian rhythm disturbances underlie the progression from a single to multiple COPCs. If successful, key findings from this study could inform existing strategies and the development of novel intervention and/or prevention strategies aimed at improving the care of millions of adults with multiple COPCs.

## Disclosures

M.J.R. has a patent pending for a sleep neural network-based sleep-stage classifier with intended applications to wireless sleep-EEG devices. None of the other authors have conflicts of interests.

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Data availability: Upon the completion of primary outcome papers, datasets and associated documentation will be released to the Arizona State University (ASU)'s Research Data Repository. The institutional repository enables ASU-affiliated, interdisciplinary researchers to share, store, preserve, cite, explore, and make research data accessible and discoverable. For researchers at other institutions, a Data Use Agreement (DUA) will be completed as established by ASU.

## Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A251.

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