**Cover Page:**

Personalized Integrated Chronotherapy for Perinatal Depression NCT04364646
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**Background:**

Increasing evidence suggests a connection between mood disorders and circadian dysfunction, or dysfunction of the 'internal body clock' that helps regulate 24-hour cycles of sleep and wakefulness.[1] Integrated chronotherapy is a treatment approach that integrates bright light therapy, an advance in timing of the sleep-wake schedule, sleep schedule stabilization, and sleep scheduling, to address circadian dysfunction and thus ameliorate symptoms of mood disorders.[2] Chronotherapy has been used and established as an effective treatment for patients with unipolar[3,4] and bipolar[5-9] depression outside of the perinatal period.[2]

This multi-site study aims to assess the efficacy of personalized, integrated chronotherapy (PIC) in treating perinatal depression with or without concomitant anxiety. We hypothesize that women who suffer from depression/anxiety during their third trimester who receive PIC in addition to usual care (UC), (in comparison to women who receive UC only), will show improvement in depressive and anxiety symptoms throughout the remainder of their pregnancy into the postpartum period. Secondary hypotheses are that the women receiving PIC along with UC will in fact demonstrate changes to their circadian rhythms, and that these changes will mediate, or explain, any improvements in depression and anxiety symptoms.

This R01 study aims to recruit 220 women across 5 sites to complete at least 176 participants. (This will accommodate a 20% screening failure and attrition rate.) Women with major depression will be recruited in the third trimester of pregnancy as verified by diagnostic measures. Subjects will be randomly assigned to UC or PIC+UC. PIC will entail that the subjects use a bright light box to expose themselves to light for 15-60 ~~30~~ minutes each morning, follow an individualized sleep/wake schedule, keep a sleep/wake journal, and wear an actigraph (a wrist device resembling a wristwatch) to measure activity and light exposure throughout the day. Subjects in both groups will also have seven visits during their study enrollment, which will extend from 24-28 weeks' gestation to eighteen weeks postpartum; At these visits, subjects will complete self-report measures and participate in mood assessments administered by a blinded clinician, their actigraph data will be downloaded and collected, and their prescribed sleep schedule will be adjusted as needed. At the beginning, middle, and end of the study, subjects will complete a sleep diary as well as provide three sets of saliva samples for evaluation of biological markers of circadian rhythm changes. The aim of this study is to assess the feasibility of integrating PIC into routine clinical care and to test whether the outcome of PIC is beneficial to both mother and infant.

**Specific Aims:**

*Specific Aim 1*: Examine the efficacy of PIC, acting through chronobiologic targets, to improve mood in women with major depression during third trimester (N=220). Hypothesis: Compared to women receiving UC for depression during pregnancy, women in the PIC+UC group will show greater improvement in dependent measures of depression (HAMD) and anxiety (HAMA) at pregnancy week 36 and postpartum week 6.

*Specific Aim 2*: Examine hypothesized mechanisms of change to confirm that PIC engages and alters the RDoC domains targeted by chronotherapy (specifically DLMO, Sleep Onset, Sleep Offset, Phase Angle (PA), Light Levels), and to determine whether changes in targeted domains are associated with antidepressant response. Hypothesis 2a: Compared to UC, PIC+UC patients will have earlier circadian phase and bed/wake times and shorter PA at pregnancy week 36 and postpartum week 6. Hypothesis 2b: Decrease in HAMD and HAMA scores will be mediated by changes in DLMO, sleep onset, sleep offset, phase angle, and light levels.

*Exploratory Aims*: (a) In 100 mother-infant pairs, examine if maternal DLMO is related to (i) melatonin levels and onset in breastmilk at postpartum week 6, and (ii) infant sleep measured with ankle actigraphy at 18 weeks; (b) Explore factors relevant to future widespread dissemination of perinatal PIC, including health care utilization in UC vs. PIC+UC groups and quality of PIC delivery by different health care providers.

**Eligibility Criteria**:

The study team intends to enroll 220 subjects, females who are 24 to 28 weeks pregnant at screening and who are seeking treatment for depressive/anxiety symptoms. This time frame was selected for both scientific and practical reasons (i.e., most pregnancies that gestate to this time point are viable, sleep disturbances are common at this stage, it is early enough in pregnancy to have an impact, and the resulting study duration is not a burden for participants). We will include pregnant women aged 18-45 years old inclusive, with a baseline Hamilton Depression Rating Scale (HAMD-17) score ≥ 14 and a current DSM-5 diagnosis of MDD as determined with the Current Major Depressive Episode Module of the Structured Clinical Interview for DSM disorders (SCID-I/P) during the Screening Visit (V1). The rationale for involving the protected population of pregnant women in this study is that we are investigating the utility of a non-pharmacologic antidepressant treatment option in the specific population of perinatal women

and, therefore, must involve these women in the study. This will allow us to longitudinally gauge the efficacy of Integrated Chronotherapy in reducing perinatal depressive/anxiety symptoms. We will allow women with tobacco dependence to enroll. Furthermore, women's preferred choice of either bottle feeding or breastfeeding will not affect her eligibility. We anticipate some participants will take antidepressant, anxiolytic, and/or mood stabilizing medications as part of usual care (UC). We will allow women who are taking medications to enroll because medication use for mood disorders during pregnancy reflects current medical practice and will improve generalizability. Integrated Chronotherapy as administered through this research study will merely supplement any clinical care women are receiving. However, the team will be mindful to only enroll participants who start an antidepressant before at least four weeks of scheduled Screening Visit. This measure is only to control for any prolonged onset of action that could lead to decreased depressive symptoms due to the antidepressant, rather than the study intervention(s). We will also enroll women who are not taking medications. Our goal is to recruit patients who can participate in the PIC intervention safely and who will be representative of women who present with depression/anxiety during pregnancy.

The following factors will exclude participants from the study: active psychosis or suicidality contraindicating outpatient treatment as determined by the clinical judgement of the research team and as assessed with the B/C module of the SCID-I/P and the Columbia-Suicide Severity Rating Scale (C-SSRS), respectively; bipolar disorder (because sleep restriction can increase risk of conversion to mania); seizure disorder (because sleep restriction can increase seizure risk); self-report of frequent migraines/headaches precipitated by bright light or sleep deprivation; preexisting eye/skin disorders contraindicating light therapy; use of photosensitizing medications; primary Axis I diagnosis other than major depressive disorder (MDD); high risk pregnancy (e.g., conditions requiring mandatory bed rest or complex medical regimens that will interfere with study participation or conditions where poor infant outcomes are anticipated); starting antidepressants within four weeks prior to enrollment (see above); current employment as nightshift worker; Alcohol Use Disorders Identification Test (AUDIT) score $\geq$ 8 and/or Drug Abuse Screening Test (DAST) > 1 indicating current alcohol or drug use disorders; women whose infants will not be living in the home or who will have a nighttime caregiver; Pittsburgh Sleep Quality Inventory (PSQI) < 5 (i.e., those who report no sleep complaints during third trimester of pregnancy and for whom an intervention targeting sleep might not be indicated; the PSQI has been validated in pregnant women); women who do not speak and read English because PIC research instruments are only available in English at this time. Women who experience fetal loss or stillbirth, as well as mothers whose infants are born before 36 weeks gestation or have NICU stays longer than five days, will be discontinued from the study but will continue to receive UC.

**Study Procedures**:

Following the initial pre-screening process to ascertain a woman's eligibility, interested participants will be scheduled for Visit 1 (Screening) at 24-28 weeks gestation. The duration of this visit will be up to three hours. Study staff will thoroughly review the informed consent form with subject prior to the initiation of any protocol-specific procedures. If the woman provides her consent, she will be randomized to receive personalized bright light therapy and a prescribed sleep schedule (PIC) in addition to usual care (UC) (i.e. medications, talk therapy, etc.) or usual care (UC) alone. The PIC treatment will include both daily bright light therapy and personalized sleep prescriptions.

Subjects will be required to complete a total of seven study visits as described below. Whenever possible, these visits will place at the research offices at the respective sites. Visits may be performed as virtual visits via telephone and/or video if necessary.

| **Study Outline** | | | |
|---|---|---|---|
| **Visit** | **Time** | **Scheduling Window** | **Measures** |
| ***Pregnancy Phase*** | | | |
| *Visit 1 (Screening, Consenting, and Randomization)* | 24-28 Weeks Pregnancy | N/A | Screening Interview and Forms |
| *Visit 2 (Baseline)* | 28-30 Weeks Pregnancy | 28 Weeks, 0 Days – 30 Weeks, 6 Days | Home Sleep and Light Monitoring, Mood, Circadian Phase 1 |
| *Visit 3* | 33 Weeks Pregnancy | 33 Weeks, 0 Days – 33 Weeks, 6 Days ***(+/- 6 Days)*** | Home Sleep and Light Monitoring, Mood |
| *Visit 4* | 36 Weeks Pregnancy | 36 Weeks, 0 Days – 36 Weeks, 6 Days ***(+/- 6 Days)*** | Home Sleep and Light Monitoring, Mood, Circadian Phase 2 |
| ***Postpartum Phase*** | | | |
| *Visit 5* | 2 Weeks Postpartum | 2 Weeks, 0 Days Postpartum – 2 Weeks, 6 Days Postpartum | Home Sleep and Light Monitoring, Mood |
| *Visit 6* | 6 Weeks Postpartum | 6 Weeks, 0 Days Postpartum – 6 Weeks, 6 Days Postpartum ***(+/- 6 Days)*** | Home Sleep and Light Monitoring, Mood, Circadian Phase 3 |

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|---|---|---|---|
| *Visit 7* | 18 weeks postpartum | 18 weeks, 0 days postpartum to 18 weeks, 6 days postpartum (+/- 6 days) | Home Sleep and Light Monitoring, Mood assessment; debriefing. |

Throughout the study treatment (beginning after completing the baseline data collection at Visit 2), women in the PIC+UC group will be asked to sit with a bright light box every morning. The starting prescription is to use the light box for 30 minutes within the first 45-60 minutes after waking. Personalized prescriptions will take into account individual participants' schedules and morning responsibilities. Light duration may be adjusted within the range of 15-60 minutes depending on participant's response. Women will be instructed to use the light every day with the light box positioned approximately 12-24 inches from the eyes. She may be permitted to read, watch TV and do other activities so long as it does not block her eyes from the light. Although the light box therapy has no known adverse effects to newborns, participating women will be instructed not to hold their newborn infants while they are undergoing bright light therapy. Language regarding this is included in the sleep prescription that will be completed by study staff and provided to the participant.

Women will also be specifically prescribed a personalized sleep schedule based on their reported sleep patterns and constraints related to specific schedules.

Continuous sleep and light monitoring through an actigraph will occur to estimate sleep times and light exposure. Women will be instructed to wear the actigraph at all times throughout study enrollment except in instances where it may be damaged (i.e. water exposure while showering/bathing).

On weeks where melatonin saliva sampling is scheduled (baseline, pregnancy week 36 and postpartum week 6, see below), women will complete a daily sleep diary. Once the mother has delivered, the infant's sleep patterns may also be collected on the diary.

A total of three saliva sample sets will be collected as a part of this study at 28 Weeks Gestation, 36 Weeks Gestation and 6 Weeks Postpartum (weeks of Visit 2, 4 and 6). This is to measure melatonin concentrations. Women will be asked to collect twelve saliva samples each evening every half hour at a time that is assigned based on their sleep patterns during the visit week.

Infant assessments will be conducted at Postpartum Week 18, requiring participants to complete questionnaires on their infants' sleep/behavior. Infants will also wear an actigraph on their ankle for one week to obtain an objective measure of sleep patterns.

The 7 study center visits will include downloading of wrist monitor data, examination of sleep and activity data as measured through the actigraph versus what was reported in the sleep diary (during applicable weeks). Treatment sleep schedules will also be assigned and adjusted at study center visits. Questionnaires and blinded clinical assessments will be administered to measure mood, safety measures (e.g. suicidality and manic symptoms).
**Analytic Strategy Registered with AsPredicted.org**

1) **Data collection:**
**Have any data been collected for this study already?**

It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid **pre**-registration nevertheless.
(Note: Choices are 'Yes, we already collected the data.', 'No, no data have been collected for this study yet.' and the answer above. Also, *'Yes'* is not an accepted answer.)

2) **Hypothesis:**
**What's the main question being asked or hypothesis being tested in this study?**

The primary aim of this single-blinded RCT is to test whether adding a personalized integrated chronotherapy intervention (PIC) to usual care (UC) for perinatal depression improves mood better than UC alone in individuals who meet criteria for major depression during 3rd trimester of pregnancy. Participants are females ages 18-45 years recruited at 24-28 weeks' gestation across 5 study sites. They are enrolled between 28-30 weeks of gestation and take part in the study through postpartum week 18. After the screening and consenting visit (V1), they are randomized to UC or PIC+UC and have 6 more study visits: baseline (V2), gestational week 33 (V3), gestational week 36 (V4), postpartum week 2 (V5), postpartum week 6 (V6) and postpartum week 18 (V7). Sleep and mood are measured at Visits 2-7 and dim light melatonin onset is measured at Visits 2, 4, and 6.

Hypothesis: Compared to women receiving UC for depression during pregnancy, women in the PIC+UC group will show greater improvement in dependent measures of depression (HAMD) at postpartum week 6

3) **Dependent variable:**
**Describe the key dependent variable(s) specifying how they will be measured.**

The primary dependent variable is the score on the Hamilton Depression Rating Scale (HAMD-17) which is evaluated by blinded raters at the end of each study week. We are also measuring the Hamilton Anxiety Rating Scale (HAMA).

**4) Conditions:**
**How many and which conditions will participants be assigned to?**

Participants are randomized to usual care (UC) or personalized integrated chronotherapy (PIC)+UC. We are using urn randomization to allocate women to UC or PIC+UC while balancing for expectant mothers' parity and whether women self-identify as declining pharmacologic treatment for perinatal depression.

**5) Analyses:**
**Specify exactly which analyses you will conduct to examine the main question/hypothesis.**

Changes in HAMD from baseline will be compared using generalized estimating equations, treating follow-up points as discrete time points, having correlated error within patient. All study time points will be in the model, but our main hypothesis will be tested as an interaction involving the baseline time point and postpartum week 6. This will be carried out within the model using orthogonal linear contrasts. Distributions for each dependent variable will be based on: a) real-world constraints, and b) model residual diagnostics. We will adjust for additional model misspecification using classical sandwich estimation.

**6) Outliers and Exclusions**
**Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.**
We will identify a data point as an outlier that should be excluded only if the value is impossible/implausible biologically or if there is corroborating evidence independent of the observation value that indicated a protocol deviation or concern related to data collection.

**7) Sample Size How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.**

We will continue enrolling through April 2024 and accept the sample size accrued at that point.

**8) Other Anything else you would like to pre-register?**
**(e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)**

The official start date of this study was 02/02/2020. Required COVID restrictions and the relocation of one of our study sites limited participant recruitment. Thus, we have changed our analytic strategy. Our original plan was to conduct an interim two-tailed analysis after 100 participants completed the study to test for early signs of confirmatory efficacy, with the plan to switch all patients to PIC+UC if the HAMD reduction between groups was significantly different at alpha=0.005 either at 36 weeks of pregnancy or 6 weeks postpartum. Absent that, we planned to use two-tailed tests of the HAMD change using an alpha of 0.02 at 36 weeks of gestation and 6 weeks postpartum. To avoid an underpowered study, we will now test a one-tailed hypothesis at 6 weeks postpartum. We are therefore registering our one-tailed hypothesis while we are still enrolling participants and collecting data to establish our new *a priori* analytic plan.

Our secondary aim is to examine putative mechanisms of change to confirm that PIC engages and alters the RDoC domains targeted by chronotherapy (specifically DLMO, Sleep Onset, Sleep Offset, Phase Angle (PA), and Light Levels) and to determine whether changes in targeted domains are associated with antidepressant response. For this aim, we hypothesize that (a) compared to UC, PIC+UC patients will have earlier circadian phase and bed/wake times and shorter PA at pregnancy week 36 and postpartum week 6; and (b) decrease in HAMD scores will be mediated by the changes in DLMO, Sleep Onset, Sleep Offset, Phase Angle, and Light Levels.

**9) Name**
**Give a title for this AsPredicted pre-registration**

Personalized Integrated Chronotherapy for Perinatal Depression NCT04364646

**10) Type of study**

Experiment

**11) Data source**

Field experiment / RCT