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Interpersonal and Social Rhythm Therapy for Perinatal Women at Risk for Bipolar Disorder

Aubrey Presnell
Yale Physician Associate Program, aubrey.presnell@yale.edu

INTERPERSONAL AND SOCIAL RHYTHM THERAPY FOR PERINATAL WOMEN AT RISK FOR BIPOLAR DISORDER

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Aubrey Presnell, PA-SII
Class of 2022
Yale Physician Associate Program
Yale School of Medicine

Hilary Blumberg, M.D.
John and Hope Furth Professor of Psychiatric Neuroscience
Professor of Psychiatry, Radiology and Biomedical Imaging, and in the Child Study Center; Director, Mood Disorders Research Program
Yale School of Medicine

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Nota bene

Existing literature on perinatal bipolar disorder and postpartum mood disturbances focuses on cis-gendered "women" and "mothers." In keeping with the prior body of evidence to support our study design and rationale, the reader will notice that we utilize those terms in the same manner. It is important to note that trans men, gender-fluid, and non-binary people can also experience pregnancy, childbirth, and postpartum mood disturbances. Though not addressed in the study to be outlined below, it is a much-needed area of further research.

The reader will also note that we use the words "convert/conversion/new-onset" to denote individuals previously deemed at-risk for bipolar disorder who now meet diagnostic criteria for the disorder. We acknowledge that ongoing research may identify biomarkers of disease or new evidence that enables earlier detection and diagnosis in individuals now considered to be at-risk, but asymptomatic. Therefore, when we use the above terms, we use them to mean an individual who previously did not meet criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition who now meets criteria for the disorder, i.e. a manic episode for bipolar I disorder or a hypomanic episode for bipolar II disorder. The full criteria can be found in Appendix D.

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List of Abbreviations

A-LIFE: Adolescent Longitudinal Interval Follow-up Evaluation

ASRM: Altman Self Rating Mania Scale

BAR: Bipolar at-risk criteria

BARS: Bipolar at-risk states criteria

BD: Bipolar disorder

BD-OS: Other specified bipolar disorder

BRIAN: Biological Rhythms Interview of Assessment in Neuropsychiatry

BSRS: Brief Social Rhythm Scale

C-SSRS: Columbia Suicide Severity Rating Scale

CBT: Cognitive Behavioral Therapy

Co-I: Co-investigator

CSQ: Client Satisfaction Questionnaire

DBT: Dialectical Behavioral Therapy

DIR: Data-informed referral

DLMO: Dim light melatonin onset

DSM: Diagnostic and Statistical Manual of Mental Disorders

E-TAU: Enhanced treatment-as-usual

EPDS: Edinburgh Postnatal Depression Scale

FFT: Family-Focused Therapy

FH-RDC: Family History Research Diagnostic Criteria

HAM-D: Hamilton Depression Rating Scale

HCL-32: Hypomania Checklist

HIC: Human Investigations Committee

HIPAA: Health Insurance Portability and Accountability Act

IPSRT: Interpersonal and Social Rhythm Therapy

IPT: Interpersonal Therapy

IQ: Intelligence Quotient

IRB: Institutional Review Board

IS: Interdaily stability

IV: Intradaily variability

L5 activity: Sleep quality

LIFE: Longitudinal Interval Follow-up Evaluation

M10 activity: Day-time activity

MDD: Major Depressive Disorder

MINI: Mini-International Neuropsychiatric Interview

NDCT: National Database for Clinical Trials

NIMH: National Institute of Mental Health

OB/GYN: Obstetrics and Gynecology

PHI: Personal Health Information

PI: Primary Investigator

PPD: Postpartum Depression

PQ-16: Psychosis Prodromal Questionairre-16

PSQI: Pittsburgh Sleep Quality Index

RA: Relative Amplitude

SAFE-T: Suicide Assessment Five-Step Evaluation and Triage

SCID: Structured Clinical Interview for DSM Disorders

SE: Sleep efficiency

SES: Socioeconomic Status

SOL: Sleep Onset Latency

SRM-5: Social Rhythm Metric-5

SRT: Social Rhythm Therapy

TST: Total sleep time

WASO: Wake after sleep onset

YCCI: Yale Center for Clinical Investigation

YMRS: Young Mania Rating Scale

PSR: Psychiatric Status Rating

RCT: Randomized Control Trial

Abstract

Bipolar disorder is a lifelong diagnosis with high morbidity. The perinatal period represents a high-risk interval for conversion to bipolar disorder, thought to be amplified by the destabilizing effects of sleep and daily rhythm disruption. Interpersonal and social rhythm therapy, an effective adjunctive treatment for bipolar disorder, also shows promise as an intervention for adolescents at familial risk for bipolar disorder; however, it has not been evaluated in at-risk perinatal women. **Utilizing a randomized control trial, we will investigate the benefit of interpersonal and social rhythm therapy in reducing symptom burden among perinatal women at risk for bipolar disorder.** We hypothesize that women receiving our intervention will spend, on average, more weeks symptom-free compared to enhanced treatment-as-usual. This study addresses the current lack of clinical options in pregnancy for women at risk for bipolar disorder and may elucidate methods to moderate or prevent the morbidity associated with new diagnosis.

CHAPTER 1: INTRODUCTION

1.1 Background

Bipolar disorder (BD) is a mood disorder characterized by significant fluctuations in mood, energy, and activity level with discrete periods of emotional highs (mania or hypomania) and lows (depression). Most individuals with BD experience symptom onset between adolescence to early adulthood. Mood episodes can be frequent and debilitating, conferring a high degree of functional impairment.[1] Often, depression is the presenting episode and predominant mood state which can lead to misdiagnosis and a delay in appropriate treatment.[2-4] Recurrent mood episodes put individuals at risk of negative sequelae, including development of comorbid psychiatric conditions, neurobiological deterioration, cognitive impairment, functional disability, and premature death by suicide.[5-7] The significant morbidity and mortality associated with BD, along with its early presentation, has made it one of the main causes of disability in working-age adults.[8]

Recent evidence has supported the concept of BD as a neuroprogressive disorder with discrete stages of disease.[9,10] Initially, there is a significant latent period during which individuals may be entirely asymptomatic. This is followed by the emergence of prodromal or subthreshold symptoms and ultimately by fully syndromal disorder. Greater numbers of subsequent episodes are associated with increasing treatment resistance and worsening prognosis, functional impairment, and cognitive changes.[9,11-13] Studies have also shown that mood episode recurrence in BD is associated with structural brain changes,[14-17] with the progression of these changes correlated with increased number of recurrences. Brain abnormalities can present early in BD,[18] and even before fully syndromal BD, with abnormalities in corticolimbic regions and connectivity evident as early as adolescence in

youth at risk for the disorder.[19] This indicates that prompt detection and intervention may play a critical role in ameliorating the course of BD. This is particularly important early in the disease when global brain structure is still relatively preserved.[20] At this point, interventions may be able to effectively address functional abnormalities,[21] potentially slowing or halting neuroprogression. Together, these findings underscore the importance of early intervention to prevent or mitigate the course of BD and future negative sequelae.

For early intervention and prevention strategies to be feasible and beneficial, they must be effectively targeted to those at highest risk for conversion to BD. While numerous factors contribute to increased risk in any one individual, the most strongly associated risk factor is a family history of BD. Life events (positive or negative), disrupted daily rhythms, disturbed sleep, anxiety, depression, and subsyndromal (hypo)manic symptoms have also been associated with increased risk for conversion to fully syndromal BD.[10,22-24]

Interestingly, research also suggests that the peripartum may represent a high-risk interval for diagnostic conversion to BD. Numerous studies have established childbirth as a significant precipitator of a first episode of BD.[25-27] In the international BRIDGE (Bipolar Disorders: Improving Diagnosis, Guidance and Education) study, postpartum women presenting with a first episode of major depression were nearly three times more likely to meet Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for BD than women presenting outside of the postpartum.[28] A Danish national cohort study noted similar findings, reporting a 4.26 times increased risk of subsequent conversion to BD for women experiencing onset of mood symptoms within the first two weeks after delivery.[25] The reasons for increased risk of diagnostic conversion following childbirth are not entirely understood but may reflect underlying genetic vulnerability exacerbated by hormonal

changes, environmental stressors, and daily rhythm disruptions unique to the peripartum.[27,29] Risk factors for conversion to BD in the postpartum are similar to those of the general population and include most prominently a family history of BD in a first-degree relative.[27] Additional risk factors include history of an anxiety, obsessive-compulsive, or substance use disorder, history of subthreshold depressive or (hypo)manic symptoms, or history of major depressive disorder.[29]

1.2 Statement of Problem

Currently, research on early intervention and prevention of BD has focused predominantly on at-risk adolescent and young adult populations. Several studies investigating both pharmacologic and psychotherapeutic interventions have shown promise in ameliorating mood symptoms with the potential to alter the course of BD.[13] However, to date, there have been no published studies conducted in perinatal populations. Consequences of a delayed or missed diagnosis of BD in the peripartum can be significant and severe. Postpartum psychosis, a rare but significant psychiatric emergency, can be a first manifestation of BD in some women.[30,31] In addition, risk of suicide, a leading cause of maternal mortality, is increased in BD and though infrequent, risk of infanticide is also increased.[30,32-35] BD in the peripartum caries risk of negative sequelae not only for the mother but for her family as well in the form of reduced family cohesion,[36] poor maternal-infant bonding,[37-40] and increased risk of psychopathology in offspring.[41]

Thus, it is clear that the perinatal period represents a critical interval for prevention and early intervention in those at highest risk of conversion. Moreover, the peripartum may represent an opportune interval for engagement of at-risk women. Women are routinely under the care of a health professional both during and after pregnancy and may be more

likely to engage in primary prevention strategies. Additionally, risk for conversion seems to be highest in the immediate postpartum,[27,30] making it easier to implement brief, targeted interventions. It is particularly critical that any intervention designed for the peripartum take both mother and the developing fetus/newborn infant into account. Psychotherapeutic interventions may have a more favorable risk profile in populations lacking threshold symptoms and therefore may be more acceptable to perinatal women.

Interpersonal and Social Rhythm Therapy (IPSRT) is one such psychotherapy which has been more recently studied in the prevention of BD in at-risk adolescents.[42,43] Originally developed for adults with BD, IPSRT improves regularity of social rhythms, preventing or delaying episode recurrence.[44] IPSRT focuses on addressing psychosocial stressors, stabilizing daily rhythms, and developing good sleep hygiene to promote mood stability. This may be especially important in the context of childbirth which represents a significant life event accompanied by marked disruption of sleep and previously established daily rhythms, each of which can increase the risk for a BD episode.[22,23] Women at risk for BD may benefit from the additional support during this period along with tools to develop new daily rhythms and improved sleep hygiene. Interpersonal Therapy (which constitutes one component of IPSRT) has already been found to be an acceptable and effective intervention for perinatal women at risk for or suffering from unipolar postpartum depression.[45,46] Therefore, there is reason to believe that IPSRT will also be acceptable to perinatal women and may prevent or mitigate the course of BD.

1.3 Goals and Objectives

This randomized control trial aims to assess the benefit of IPSRT versus enhanced treatment-as-usual (E-TAU) in reducing postpartum symptom burden among perinatal

women at risk for BD. Furthermore, it will assess the acceptability and feasibility of IPSRT in this population. In so doing, this study aims to address the current lack of clinical options in pregnancy for women at risk for BD.

Multiple secondary measures will be also assessed including 1) the relationship between group assignment and mood, 2) the relationship between group assignment and daily rhythms measures, 3) the relationship between daily rhythms measures and mood, 3) pre- to post-treatment changes in mood symptoms and 4) the proportion of women who diagnostically convert to BD within each group. These will help elucidate the role of daily rhythms disruption on postpartum mood and how efforts to stabilize these rhythms might prevent or mitigate postpartum mood disturbances and conversion to BD.

1.4 Hypothesis

We hypothesize that perinatal women at risk for BD who receive IPSRT will experience a statistically significant difference in average number of weeks well (Psychiatric Status Rating[47] ≤ 2) over a 16-week postpartum period when compared to women receiving E-TAU.

1.5 Definitions

Perinatal period*:* Used herein to denote the period encompassing pregnancy and the postpartum period, up to 1 year postpartum.

Interpersonal and Social Rhythm Therapy (IPSRT): psychotherapy that focuses on addressing psychosocial stressors, stabilizing daily rhythms, and developing good sleep hygiene to promote mood stability

Psychiatric Status Rating: Scale used to assess the overall severity of psychiatric symptoms each week over the course of a predetermined follow-up period; usually administered in conjunction with the Longitudinal Interval Follow-up Evaluation

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CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Introduction

During the period of August 2021 to May 2022, we conducted repeated searches of PubMed, Ovid Medline, Scopus, and Cochrane Library databases with the assistance of the librarians at the Yale School of Medicine. Broad primary searches were conducted using combinations of the MeSH terms "Bipolar Disorder" and "Pregnancy" along with keywords "bipolar," "hypomania," "mania," "bipolar depression" and "pregnancy," "perinatal," "antenatal," "postpartum." Additional search terms included "sleep," "social rhythm*," "daily rhythm*," "circadian," "mood," "bipolar, at risk," "prevention," "mood disorder," and "postpartum depression." Results were initially screened based on the relevance of the title and abstract to our proposed study. Articles were limited to those written in the English language. We also examined the reference lists of articles to further identify relevant papers. Preference was given to recently published articles, systematic reviews, meta-analyses, and randomized clinical trials (RCTs). In the absence of RCTs, observational studies were included with a preference given to prospective cohort studies.

This literature search demonstrates the dearth of evidence on effective methods to prevent BD in the perinatal period. By analyzing the state of the literature, we demonstrate how our study will help fill this research gap and further the field of perinatal mental health.

2.2 Review of Empiric Literature

2.2.1 New-Onset Bipolar Disorder and the Perinatal Period

A substantial body of evidence now exists to indicate that the peripartum is a high-risk interval for new-onset (hypo)mania or conversion to bipolar disorder. Since 1994 when a subclinical postpartum phenomenon known as "the highs" was first described,[1] attention

has increasingly turned to the commonality of hypomanic symptoms in the early postpartum. A recent systematic review notes that between 9.6 - 49.1% of women, both with and without mood disorders, experience hypomanic symptoms in the postpartum period.[2] The review also notes several studies draw an association between early hypomanic symptoms and subsequent onset of postpartum depression (PPD), although findings are mixed.[2] One such study by Pingo et al. found that mixed mood states at postpartum day 3 (i.e. a positive screen on both hypomania and depression scales) were associated with greater depressive symptoms at week 6 than early hypomanic ($p=0.010$) or depressive ($p=0.035$) symptoms alone.[3] This relationship between early hypomania and/or mixed states and subsequent PPD have led some to postulate that the highs may actually reflect a BD diathesis.[2] This is particularly troubling given that mixed episodes confer the greatest risk for suicide in the postpartum period (OR=41.50, 95% CI: [12.11- 142.16]).[4] Suicide is a leading cause of maternal mortality.[4] While suicide prevention in the context of PPD has been extensively researched, effective prevention of mixed episodes remains understudied. Interventions that could address BD symptomology in the postpartum period, specifically mixed states, are much needed to prevent the tragic consequences of suicide.

The postpartum period also represents a particularly high-risk interval for new onset of fully syndromal BD in women. In a prospective, register-based cohort study of the entire Danish population, Munk-Olsen et al. found that first-time psychiatric contact for any mental health concern in the postpartum period significantly predicted conversion to BD. Over a 15-year follow-up, 14% ultimately developed BD versus just 4% of non-postpartum women.[5] Early onset of symptoms (0-14 days postpartum) was associated with increased risk of conversion (RR=4.26, 95% CI [3.1-5.85]).[5] A follow-up study using the same

registry looked at first-time antidepressant prescription as a proxy for first-onset affective disorder. [6] They found the risk of BD conversion to be greater in those with a postpartum onset (RR=1.66, 95% CI [1.12-2.48]) and greater still in those whose persistent symptoms required subsequent treatment with anxiolytics (RR=10.15, 95% CI [7.13-14.46]) or mood stabilizers and/or antipsychotics (RR=22.48, 95% CI [15.30–33.03]). Risk was also significantly elevated in those with a parental history of BD (RR=4.68, 95% CI [3.28–6.69]).[6] These studies highlight the importance of screening for familial risk and intervening early when women present with postpartum mood disturbances as these can represent an underlying BD diathesis and present key opportunities to intervene and possibly alter the course of BD.

Though the aforementioned literature repeatedly supports the link between childbirth and new onset of BD or BD symptomology, these studies are limited by their largely cross-sectional nature and methodological differences in assessment of BD symptoms and diagnosis (several utilize screens rather than confirmation of a DSM diagnosis). Few studies prospectively investigate the rate of postpartum conversion to BD, and even fewer rigorously investigate both antenatal and postpartum diagnoses to confirm diagnostic conversion. A study by Sharma et al. utilized the Structured Clinical Interview for DSM Disorders (SCID) to determine antenatal diagnoses and the Mini-International Neuropsychiatric Interview (MINI) to determine subsequent diagnoses at 1, 3, 6, and 12 months postpartum. In a sample of 92 women with major depressive disorder (MDD), they found that 6.52% converted to BD within 6 months postpartum.[7] This was an 11-fold higher rate than that reported in the non-postpartum population,[8] indicating that childbirth may represent a potent trigger for conversion. Of the baseline characteristics assessed,

Sharma et al. note that a only a positive family history of BD in a first-degree relative significantly predicted diagnostic conversion (p=0.05).[7] This is consistent with findings from other studies showing history of BD in a first-degree relative to be the strongest risk factor for postpartum psychiatric disorders (HR=2.86, 95%CI [1.88-4.35]).[9] This argues that women with a familial history of BD may particularly benefit from interventions in the postpartum to reduce BD symptomology and possibly prevent new onset of BD.

2.2.2 The Role of Sleep and Daily Rhythms in Peripartum Mood Disturbance

Pregnancy and the postpartum period are characterized by significant disruptions in maternal sleep and daily rhythms understandably necessitated by the needs of a newborn. Various physiologic and mechanical factors are also implicated, including variations in reproductive hormone levels, altered respiratory physiology, disordered breathing, and discomforts associated with pregnancy.[10] Sleep is generally worse in the third trimester and early postpartum with decreases in sleep duration and efficiency observed on actigraphy and self-report.[11] In healthy women, sleep steadily improves over the postpartum as infant circadian rhythms are established and synchronize with those of the mother. In their 2015 review, Miller et al. posit that these sleep and rhythm disruptions, new stressors, and social role transitions may partially underlie the high rates of postpartum relapse seen in BD.[12]

Most papers investigating the relationship between sleep and BD in the postpartum actually examine the incidence of postpartum psychosis. This phenomenon, though diagnostically distinct, is more common in women with BD and, for some, can represent a first episode of BD.[13] Despite the well-documented relationship between sleep disturbance and mania onset in nonpregnant populations, there is a scarcity of high-quality literature involving perinatal women. Papers mostly rely on case reports,[14,15] chart reviews,[16] and

cross-sectional studies[17] to draw relationships between sleep and onset of postpartum psychosis. Bilszta et al. sought to prospectively investigate the role of sleep in perinatal women at risk of a postpartum psychotic episode (i.e. with a personal history of BD or postpartum psychosis).[18] During the study, three women in the at-risk group experienced a relapse. However, there were no significant differences in sleep/wake activity between at-risk women and healthy controls. This study was limited by small sample size and missing data which prevented analyses of the relationship between measures of sleep and mood scores as well as between sleep and subsequent relapse in the at-risk group. The study also did not include analyses for the confounding effect of mood stabilizing medication.

Though not specifically addressing BD, a great deal of research addresses the relationship between postpartum mood and measures of sleep and daily rhythms. Daily rhythms consist of a variety of external social "cues" that regulate a person's internal biological clock (biological rhythms or circadian rhythms). These "cues" include items such as sleep, activities, social interactions, and eating patterns.[19-21] Disturbances in these daily rhythms are known to precipitate mood episodes in vulnerable individuals, particularly in those with BD.[22] In a prospective cohort study, Krawczak et al. found that women with mood disorders (BD or MDD) self-reported significantly greater sleep and daily rhythm disturbances over the perinatal period when compared to healthy controls ($p<0.001$).[23] Additionally, for both groups, changes in daily rhythm scores predicted changes in depressive symptom scores from pregnancy to postpartum ($R^2=0.21$, $p=0.01$ and $R^2=0.13$, $p=0.03$ respectively).

In the initial study, subjective measures of sleep (Pittsburgh Sleep Quality Index - PSQI) and daily rhythms (Biological Rhythms Interview of Assessment in

Neuropsychiatry - BRIAN) were used to approximate objective sleep deprivation and circadian changes. However, subjective measures of sleep poorly correlate with objective measures in pregnant populations, with subjective measures often overestimating total sleep time and sleep efficiency.[24,25] It may be that subjective measures such as the PSQI, which assess sleep quality over a 30-day period, are ill-equipped to capture the frequent variablity that occurs in perinatal sleep. Therefore, Krawczak et al. obtained actigraphic measures of rest and activity (proxies of sleep) in a subsample of the population in order to investigate the association of objective changes in sleep and daily rhythms with postpartum mood.[26] They found that postpartum sleep efficiency (a percentage measure of actual time asleep over the sleep period) was significantly worse in those with a history of a mood disorder ($p=0.05$). Additionally, changes in sleep efficiency and interdaily stability (a marker of daily rhythm stability over time) were associated with changes in Edinburgh Postnatal Depression Scale (EPDS) scores ($p=0.04$ and $p=0.05$ respectively). Krawczak et al. also noted a discrepancy between subjectively reported and objective measures of sleep.

Together, these studies indicate that those with a history of mood disorders seem to be particularly vulnerable to disrupted sleep as well as alterations in daily rhythms during the postpartum period. These disruptions can have a substantial impact on the manifestation of postpartum depressive symptoms. Unfortunately, Krawczak et al. only reported EPDS scores. Young Mania Rating Scale (YMRS) scores, a measure of (hypo)manic symptomology, were obtained at the postpartum time point but not reported except to note that no participant developed a manic or hypomanic episode.[26] Given that sleep deprivation and daily rhythm disturbances can be a potent trigger for (hypo)manic symptomology in individuals with or at-risk for BD,[27,28] future studies are needed to measure correlations

between daily rhythm disruptions and YMRS scores. A larger sample size and longer study period, sampling at multiple points throughout the postpartum, could enhance the ability to study relationships between sleep, daily rhythms, and postpartum mood disturbances.

A more recent prospective cohort study by Obeysekare et al. addresses some of the shortcomings of prior studies, assessing transdiagnostic psychiatric symptoms (including manic, depressive, and obsessive-compulsive symptomology) across multiple time points in pregnancy and the postpartum.[29] Additionally, they utilized objective measures of rest/activity and endogenous measures of circadian rhythms (measured by dim light melatonin onset - DLMO) to assess relationships between sleep, rhythms, and postpartum mood disturbances. Within their sample (51 euthymic women with a previous diagnosis of unipolar or bipolar depression), they found that those in the late-to-bed group experienced significantly more (hypo)manic and depressive symptoms at postpartum week 2. Delayed sleep (represented by a longer phase angle between DLMO and actual sleep onset) was also associated with increased (hypo)manic symptoms at week 2. This is one of the first studies to measure multiple psychiatric outcomes across a large number of perinatal timepoints. However, it is limited by its small, heterogeneous sample size (they did not control for medication use although they note that numbers were similar between groups) as well as by its post-hoc determination of "late-to-bed" and "early-to-bed" sleep groups.

Currently, there is much evidence to support the theory that sleep disruption in the perinatal period is associated with development of PPD.[30] The above studies further support that perinatal disruptions in sleep and daily rhythms are associated with worsened postpartum depressive symptoms, with the most recent study suggesting the same may be true of (hypo)manic symptomology.[29] Sleep and daily rhythm disturbance is a

characteristic prodrome and feature of BD and has been associated with worse course of illness, increased symptom severity, and functional impairment outside of the context of childbirth.[28] The perinatal period is associated with marked disruptions in both sleep and daily rhythms and thus may represent a key interval for intervention in order to alter the course of BD. The findings discussed above suggest that interventions targeting sleep and daily rhythm stabilization in pregnancy may protect women against postpartum worsening of mood symptoms, including onset/worsening of BD symptomology.

2.2.3 Stabilization of Daily Rhythms for Prevention of Bipolar Episodes

Individuals with BD are particularly sensitive to daily rhythm disruptions, which can elevate risk of first-onset BD or episode recurrence.[22,31,32] The Social Zeitgeber Theory of mood disorders presents a mechanism by which this occurs, positing that life events can lead to disruptions of social zeitgebers ("time givers"), destabilizing social and circadian rhythms and provoking mood episodes in vulnerable individuals.[20] Interpersonal and social rhythm therapy (IPSRT) was born of this theory and combines the relational aspects of interpersonal psychotherapy (IPT) with social rhythm therapy (SRT). By stabilizing daily rhythms, the creators theorized one could reduce risk of mood episode relapse.

Indeed, IPSRT has been shown to significantly increase regularity of daily rhythms, improve time to clinical stability, and protect against relapse, with the degree of relapse protection related to the degree to which participants successfully regularize their daily rhythms.[33,34] Multiple studies have established that IPSRT offers broad benefits as an adjunctive treatment for BD, preventing relapse and aiding recovery from *both* manic and depressive episodes.[33-36] IPSRT also lessens psychopathological burden in non-acutely ill individuals,[37,38] reducing depressive ($p<0.007$), anxious ($p<0.001$), and manic ($p<0.004$)

symptomology.[38] Given these promising findings of IPSRT in the treatment of BD, there is interest in whether interventions to stabilize daily rhythms may be of benefit in the amelioration of subsyndromal symptoms and prevention of initial BD onset.

Research assessing the effectiveness of early intervention and prevention strategies is still young. A recent systematic review by Saraf et al. identified just sixteen trials assessing interventions (predominantly psychotherapeutic strategies) in individuals at risk for BD.[39] However, there was significant heterogeneity in definitions of at-risk populations (which included familial and/or symptom-based risk criteria), study outcomes, and study duration, making the data unamenable to meta-analysis and difficult to compare. Of note, nearly all of the study populations were restricted to children and/or adolescents ≤18 years of age,[39] with only one study including at-risk young adults up to age 30 years.[40] Many of the studies also had significant methodological limitations including non-blinded outcomes assessment and failure to control for concomitant medication usage.

Only two studies purposefully investigated stabilization of sleep and daily rhythms for the prevention of BD in at-risk individuals.[41,42] Both were conducted by Goldstein et al. with at-risk adolescents, ages 12-18 years. At-risk status was determined based on a first-degree relative with history of BD ascertained via record review or administration of the SCID with the affected family member.

In their initial study, Goldstein et al. recruited thirteen at-risk adolescents for a trial of twelve sessions of IPSRT delivered over 6 months.[41] Measures of mood, subjective sleep, and functioning were obtained at pre-treatment, 3 months, and 6 months. At post-treatment there were no significant differences in mood; however, there was a significant effect on daily rhythm stabilization, with earlier weekend wake-time and less oversleeping.

Additionally, clinician ratings reflected decreased illness severity ($p<0.01$) and pre- to post-treatment improvement in overall psychiatric illness (not significant).[41] Given the small sample size and low symptom burden at presentation, it is not surprising that the study did not detect pre- to post-treatment mood changes. However, it did demonstrate high treatment satisfaction with IPSRT, with adolescents providing an average rating of 5.8±1.3 and parents 6.2±0.8 on a Likert scale of 1 [very dissatisfied] to 7 [very satisfied].[41]

Goldstein et al. subsequently conducted a RCT to better assess the potential benefit of IPSRT and included a component of data-informed referral (DIR) in a two-pronged approach to addressing at-risk status.[42] IPSRT + DIR (N=21) was compared to DIR alone (N=21) to assess effects on measures of mood and subjective and actigraphic measures of sleep. Though not statistically significant, the IPSRT+DIR group did see a trend towards improvement in wake-after-sleep-onset from pre- to post-treatment. There were no statistically significant differences between groups on self-reported mood measures which, again, could be attributed to low symptom scores at baseline. However, participants in IPSRT+DIR were significantly less likely to display subthreshold symptoms of (hypo)mania over follow up ($p=0.03$) and spent a significantly lower rate of weeks with symptoms ($p=0.0009$) as determined from the Psychiatric Status Rating Scale (PSR) on the Adolescent Longitudinal Interval Follow-up Evaluation (A-LIFE).[42]

These promising results of IPSRT in a sample of youth at risk for BD indicate that IPSRT may confer similar benefits to other at-risk populations, particularly those that experience significant disruptions in sleep and daily rhythms as do perinatal women.

2.2.4 Early Intervention and Prevention of Mood Disorders in Pregnancy

A majority of the literature on management of BD during pregnancy focuses on pharmacotherapeutic interventions.[43-45] Given that up to 85.5% of women who discontinue mood stabilizing medications will relapse during the perinatal period,[46] research on safety, efficacy, and best practices is much needed in this realm. However, in women without fully syndromal BD, psychotherapeutic interventions may represent a promising alternative to pharmacotherapy given their potential for lower risk to the fetus/newborn. Yet psychotherapy remains vastly understudied in perinatal populations both with and at-risk for BD. A majority of the literature establishing the efficacy of IPSRT in individuals with BD specifically exclude for pregnancy.[33,34,36] The same is true of research in at-risk populations. Of the seventeen trials reported by Saraf et al., fourteen had the potential to include women of reproductive age based on age inclusion criteria. Of these, five explicitly excluded for pregnancy;[47-51] the remainder, including the previously discussed trials of IPSRT in at-risk youth, either did not list exclusion criteria or failed to mention perinatal status.[40-42,52-57] This highlights the great need for study of psychotherapeutic interventions in perinatal women in order to assess to what degree benefits seen in non-pregnant populations are translatable and whether IPSRT remains effective in the peripartum.

Review of the literature did reveal one pilot RCT of IPSRT in perinatal women with BD identified on the Cochrane Central Register of Controlled Trials (NCT02402738).[58] In this trial, Weinstock aimed to investigate the effect of adjunctive IPSRT on mood and psychotic symptoms up to 16 weeks postpartum when compared to an enhanced treatment-as-usual control. However, the study was terminated in 2019 in favor of enhancing an initial open trial, and no results have yet been published.

One other study investigating IPSRT in pregnancy was identified on an abstract for presentation at the 2010 Annual Meeting of the American Psychiatric Association.[59] While the full study did not reveal statistically significant differences between IPSRT and specialist support care (both groups experienced mood symptom improvement),[37] a subset analysis of thirteen pregnant and postpartum women showed significantly lower than expected symptoms, mood episodes (including postpartum psychosis), medication use, and hospitalizations.[59] Though not optimized to investigate the effects of IPSRT in pregnancy, these findings nevertheless suggest that interventions to stabilize daily rhythms may be particularly beneficial in the perinatal period for management of BD symptomology.

The remaining literature on the role of psychotherapy in the peripartum has focused largely, if not exclusively, on unipolar postpartum depression. A series of systematic reviews and meta-analyses by Sockol show that IPT and cognitive behavioral therapy (CBT) are effective for both treatment and prevention of perinatal depression.[60,61] Notably, preventive psychotherapy was beneficial for both universal and targeted prevention, and interventions initiated during the postpartum were more effective at reducing depressive symptoms than those initiated during the antenatal period. For CBT, the greatest effect was seen when therapy was delivered over pregnancy *and* the postpartum (OR=0.29, $p<0.01$).[60] These findings support that intensive psychotherapeutic interventions delivered during the perinatal period can successfully prevent postpartum mood disturbances, specifically depression, and that timing of delivery can affect efficacy.

In fact, the well-established benefit of psychotherapeutic interventions during pregnancy led the US Preventative Services Task Force to issue a class B recommendation that individuals at increased risk of perinatal depression be referred to counseling

services.[62] However, no similar recommendation exists for individuals at increased risk of BD. To date, perinatal research has focused largely on depressive symptomology without differentiation of unipolar versus bipolar depression. Further studies are needed to elucidate the role that psychotherapy may play in preventing BD in the postpartum.

2.3 Possible Confounders and Covariates in Development of Mood Symptomology

Numerous factors have been associated with increased risk of developing a postpartum mood disturbance. Lower social support and socioeconomic status (SES) have been consistently related to subsequent PPD.[63] Lane et al. found that at three days postpartum these same measures were associated with greater depressive symptoms (EPDS) *and* (hypo)manic symptoms (Highs Scale).[64] Whether these factors also correlate with increased risk of a postpartum BD episode has not been studied. Although association is inconsistent, parity, the number of times a woman has delivered, is another maternal baseline factor commonly included in studies on PPD and conversion to BD.[6,7,64-66]

Studies investigating the role of maternal age in PPD onset also show largely mixed results, and some find no association at all.[63] Studies investigating postpartum onset of BD symptomology have been similarly mixed, with some showing it to be more common in younger women[66] and others, in older women.[3] Neither study investigated cases of new BD diagnosis, and inclusion criteria and measures of (hypo)mania were different between studies making comparison difficult. However, given that onset of BD most commonly occurs in adolescence/young adulthood, it is reasonable to believe age may play a role in postpartum development of BD. In a meta-analysis investigating age at onset of BD, Bolton et al. found that a majority of studies described a trimodal distribution of onset: early (μ = 17.3 years, SD = 1.19), mid (μ = 26.0 years, SD = 1.72), and late (μ = 41.9, SD = 6.16).[67]

Most new diagnoses occurred in the early-onset group (45%), with reductions in new diagnoses occurring at later ages (35% mid-onset, 20% late-onset). Given the decreased incidence of new diagnosis with increased age, we expect maternal age may be a possible confounder if not appropriately controlled for during randomization.

Psychiatric comorbidities and symptom overlap may also confound our ability to detect difference between groups or to attribute mood symptom differences to BD symptomology. Psychiatric comorbidities are common in individuals with and at-risk for BD[39,41,42,68,69] and may constitute a prodrome that increases risk of future conversion. In particular, anxiety disorders and externalizing disorders (such as attention deficit hyperactivity disorder - ADHD) are common in high-risk youth and are predictive of later onset of major affective disorders.[70,71] Depressive disorders and disorders characterized by subthreshold BD symptomology (cyclothymia, other specified BD) are also common antecedent disorders in at-risk youth and increase risk for conversion to BD.[70,72] Though inclusion of psychiatric comorbidities may introduce confounding, given their frequency in at-risk populations, we will include participants with depressive disorders, bipolar-related disorders, ADHD, and/or anxiety disorders to improve generalizability.

It is also common for individuals at risk for BD to be on medication management for subsyndromal symptoms or independent psychiatric diagnoses. Antidepressants are of particular concern in our study as some studies suggest that antidepressant use, particularly antidepressant monotherapy, puts individuals with BD at risk of a triggered (hypo)manic episode.[73] It is worth noting, however, that Sharma et al. did not find an association between antidepressant monotherapy and diagnostic conversion to BD in the postpartum.[7] Use of mood stabilizers would also reduce our ability to see an effect given the proven

benefit of mood stabilizers in reducing postpartum relapse in women with existing BD.[43] However, there are ethical concerns in requiring participants to discontinue medication, which can increase risk of mood worsening and suicide. Instead, inclusion of medications will minimize ethical concerns and increase generalizability/feasibility of our study.

2.4 Relevant Methodology

2.4.1 Study Design and Recruitment

Our study is an outcomes-assessor blinded RCT investigating the effect of IPSRT versus E-TAU in ameliorating mood symptoms in perinatal women at risk for BD. We will assess the acceptability, feasibility, and initial benefit of IPSRT in this population. Acceptability and feasibility of psychotherapeutic interventions are commonly studied prior to developing larger and longer studies that rigorously assess effectiveness.[41,74-76] Additionally, RCTs are the gold standard for study of therapeutic interventions, reducing bias and confounding and increasing internal validity of the study.[77] While the aforementioned literature suggests that stabilization of daily rhythms may successfully ameliorate mood symptoms in perinatal women at risk for BD, studies are needed to assess whether such interventions are acceptable, feasible, and beneficial in this population.

In keeping with the practices of other studies, we will utilize a combination of consecutive sampling and self-referral to recruit participants from multiple venues,[75,78,79] including Connecticut clinics and hospitals that offer prenatal care and outpatient psychiatric services. This is a similar method used in the RCT conducted by Goldstein et al. which recruited adolescents from multiple sites, including outpatient psychiatric services, ongoing studies, adult BD support groups, and advertisements.[42] While nonprobability sampling methods may fail to recruit a sample representative of the general

population, we anticipate this will be less likely given our multisite recruitment and use of consecutive sampling. Additionally, these sampling methods are commonly used in mood disorders research to recruit adequate sample sizes when the population of interest may be small. BD is a relatively common psychiatric diagnosis with an annual prevalence of 2.8% and lifetime prevalence of 4.4% in US adults.[80] While there are no prevalence estimates of BD at-risk status in pregnant women, conversations with Dr. Kimberly Yonkers, a pioneer of postpartum psychiatric research, lead us to estimate about 1% of the pregnant population will meet inclusion criteria thus necessitating recruitment from multiple venues.

Randomization and allocation will occur in a 3:2 ratio. The process will be similar to that of comparable studies investigating psychotherapeutic interventions in pregnant women[75,78,79] and will utilize a computer-generated and non-stratified allocation sequence with varying block sizes concealed to the researchers. Due to the nature of the intervention, participants and the therapists who deliver the intervention cannot easily be blinded to allocation. However, the research staff who collect and analyze the data will be blinded.

2.4.2 Selection Criteria

Multiple studies have been conducted that assess psychotherapeutic interventions in youth at risk for BD. Unfortunately, in intervention studies, there remains a lack of consensus on at-risk identifiers (studies often use a combination of familial and/or clinical risk identifiers); therefore, there is a lack of homogeneity regarding inclusion criteria in these studies. The literature consistently shows that family history of BD in a first-degree relative confers the greatest risk,[81] and indeed, this was the only factor found to be significantly associated with onset of postpartum psychiatric disorders[9] and subsequent conversion to BD.[5-7] In 2010, Bechdolf et al. assessed and synthesized additional risk

factors, developing a set of bipolar at-risk (BAR) criteria.[82,83] An expanded version of this criteria, the Bipolar at-risk states (BARS), coupled with a semi-structured interview was later developed and validated to have adequate prognostic accuracy in at-risk youth ages 15-35 years (Harrell's C = 0.742).[72] The expanded BARS criteria divide individuals into one of six at-risk groups based on 1) subthreshold mania, 2) depression ± cyclothymic features, 3) depression ± genetic risk, 4) cyclothymic features + genetic risk, 5) subthreshold mixed episode, 6) mood swings.[72] While there are no validated measures in pregnant women, Sharma et al. has proposed a similar set of criteria based on the BARS criteria to determine at-risk status in pregnancy.[84] These include any woman with a history of BD or postpartum psychosis in a first-degree relative in addition to the risk groups defined above. Inclusion in this study will be guided by these risk factors. Whenever possible, family history will be confirmed by interviewing the first-degree relative using the SCID. If this is not possible or agreeable to the study participant, then the study participant will be interviewed using the Family History Research Diagnostic Criteria (FH-RDC) in keeping with prior studies of BD conversion conducted in perinatal women.[7] Similar to other studies,[55-57] we will require participants to be at least minimally symptomatic at baseline in order to optimize our ability to discern a treatment effect. These criteria will be based on the International Society of Bipolar Disorder's definition of subsyndromal symptoms.[85] Recruitment will occur during the second trimester in order to allow adequate time to complete the initial therapy sessions prior to delivery and is similar to a previous clinical trial of IPSRT in pregnant women (NCT02402738).[58] Exclusion criteria are modeled after prior studies with individuals at risk for BD,[42] trials of IPSRT in pregnant women with BD (NCT02402738),[58] and trials of IPT in pregnant populations.[75]

Of particular note, we will exclude for any Axis I or Axis II disorder other than ADHD, anxiety disorders, or those specified for inclusion (depressive or bipolar-related disorders). Each of these represent common antecedent psychiatric diagnoses in at-risk populations and may increase risk of conversion to BD. Although a history of postpartum psychosis is also associated with increased risk of conversion to BD,[86] it also significantly increases risk for maternal suicide or infanticide.[13] Thus, we will exclude for any history of psychosis and include enhanced safety measures to monitor for emergence of psychotic symptoms and suicidal or homicidal ideation over the study period. A full description of inclusion and exclusion criteria can be found in Section 3.2 and have been selected to optimize generalizability, feasibility, and safety while minimizing attrition and confounding.

2.4.3 Baseline Characteristics

Numerous factors are associated with risk of postpartum mood disturbances and conversion to BD; these are discussed in detail in Section 2.3. We also discussed baseline characteristics that are routinely assessed in studies of perinatal populations and individuals at risk for BD. Drawing on this information, the following baseline characteristics will be obtained in our sample population: age, race/ethnicity, socioeconomic status (Hollingshead Index of Social Status[87]), parity, marital status, level of social support (Multidimensional Scale of Perceived Social Support[88]), pregnancy intention, current community mental health treatment, psychiatric diagnoses, psychiatric medication, and baseline mood symptoms. These are discussed in more detail in Section 3.5.

2.4.4 Intervention

Our study will randomize pregnant women at risk for BD to receive either IPSRT or E-TAU. The design of the intervention will be based on prior studies of IPSRT

conducted in youth at risk for BD[41,42] and in pregnant women with BD (NCT02402738).[58] IPSRT consists of four phases: the initial phase, intermediate phase, maintenance phase, and termination phase. During the initial phase, the patient and therapist focus on history taking, psychoeducation, and the interpersonal inventory, with the goal being to identify one mutually agreed upon interpersonal problem area to be the focus of the IPT portion of IPSRT. These focus areas can be either unresolved grief, role transition, role dispute, or interpersonal deficits.[89] The perinatal period is unique in the manner in which role transitions very clearly contribute to social, emotional, biological, and psychological stress.[90] Prior studies of IPT alone have shown that the ability to address interpersonal stress may be one change mechanism by which IPT is effective at treating perinatal depression.[91] Thus, role transition in the context of new motherhood will be the main interpersonal focus of our intervention in this study.

In a study of IPSRT for pregnant women with BD, Weinstock intended to deliver up to twenty sessions, beginning in pregnancy and continuing through the postpartum (NCT02402738).[58] Our intervention will be similarly designed, with the first twelve sessions delivered weekly to ideally allow completion prior to the infant's birth. These sessions will follow the structure of *IPSRT for At-Risk Youth*, outlined by Goldstein et al.[41] Following the 12-week treatment phase, bimonthly maintenance sessions will be offered up to 8 weeks postpartum. PPD research has shown that women benefit from delivery of psychotherapeutic interventions in the postpartum when they may be more equipped to identify and address challenges associated with motherhood.[60,61] Preventative interventions demonstrated the largest effect size when delivery was mixed (i.e. over the antenatal and postpartum period).[60] The duration of therapy (up to 8 weeks postpartum) is based on the

finding that a majority of women who convert to BD postnatally do so within the first month, making the early postpartum a critical interval for support and intervention.[7]

Unlike the prior trials of IPSRT outlined above, our intervention will be delivered via telehealth. In both an open trial and RCT, Goldstein et al. noted poor attendance with only about 50% of sessions attended.[41,42] Often, missed sessions were attributable to BD illness severity in the parent which prevented the adolescent from making their appointment times.[41] Similar attendance difficulties have plagued engagement of the perinatal population with mothers citing lack of time, transportation, and childcare issues as barriers to seeking care for PPD.[92] Telehealth interventions have proven to be acceptable and feasible in perinatal women and are effective at reducing symptoms of depression while simultaneously providing the flexibility needed to expand access and reduce barriers to engagement with care.[79,93] A large trial of telephone-based IPT found low attrition (<20%) as well as high adherence (86.7% attended ≥10 out of 12 sessions) among perinatal women.[79] A recent study investigating the implementation of SRT for adolescents and young adults with BD, delivered predominantly via telehealth, also revealed high satisfaction, retention, and therapeutic alliance achieved with the therapy.[74] Together, these findings support the use of telehealth for delivery of IPSRT in the perinatal population.

2.4.5 Control Group

The control group for our study will receive E-TAU. This is consistent with prior interventions conducted in individuals at risk for BD[42] and pregnant women with BD (NCT02402738)[58] as well as numerous interventions looking at the use of IPT for treatment of PPD.[75,78,79,90] Women will have access to all routine antenatal and postpartum care available in the community. However, strict treatment-as-usual risks ethical concerns if a

participant were to become psychiatrically symptomatic. Thus, as with the intervention group, subjects will receive enhanced monitoring of their symptoms via weekly self-report mood scales (EPDS,[94] Altman Self Rating Mania Scale; ASRM[95]), psychosis screens (Prodromal Questionnaire-16; PQ-16),[96,97] and suicide risk assessments (Columbia Suicide Severity Rating Scale; C-SSRS).[98] As noted by Goldstein et al. in their pilot open trial, many individuals at risk for BD have multiple psychiatric diagnoses identified at intake for which they have not previously been treated.[41] In keeping with the methodology of their subsequent RCT,[42] referrals will be made as necessary for both groups based on mood symptoms and any new psychiatric diagnoses identified at intake or during subsequent pre-scheduled clinical interviews.

2.4.6 Primary Outcome

In a review of early interventions for individuals at risk for BD, primary outcomes varied, with a majority assessing changes in mood, sleep, or functioning from pre- to post-intervention.[39] Though the ultimate goal of early intervention and prevention research is to prevent diagnostic conversion to BD, few studies report this as a primary outcome due to time-frame and sample size restraints.[39] Instead, initial studies tend to focus on reduction of symptom burden. The Longitudinal Interval Follow-up Evaluation (LIFE) Psychiatric Status Rating (PSR) enables researchers to assess cumulative (hypo)manic and depressive symptom burden over a follow-up interval. LIFE PSR scores have been used as an outcome measure in previous trials of IPSRT in individuals both with[37] and at-risk[41,42,56] for BD and were an intended primary outcome measure in Weinstock's clinical trial of IPSRT in pregnancy (NCT02402738).[58] In keeping with these prior studies, our primary outcome will compare average number of weeks well (LIFE PSR $\leq$2) between groups over the study

period, up to 16 weeks postpartum. The 16-week postpartum follow-up period was determined by time constraints of our study and is aligned with Sharma et al.'s finding indicating that the early postpartum (1-3 months) is the highest risk for BD conversion.[7]

Our study will also assess acceptability and feasibility of this intervention in a perinatal population. Client Satisfaction Questionnaire (CSQ) scores are commonly used to assess the acceptability of psychotherapeutic interventions, including in perinatal populations.[74,75] Additional measures of acceptability and feasibility include participant retention and session attendance.[41,42,74-76,78,79] Given that the total number of sessions a woman receives may vary depending on her delivery time, we will consider 12 sessions (the number outlined in Goldstein et al.'s adaptation of IPSRT for at-risk youth[41]) as a full course of treatment. Thus, acceptability and feasibility will be defined by a mean CSQ score of ≥24 and retention of 75% of participants who receive a full course of therapy.

2.4.7 Secondary Outcomes

Secondary outcomes will include several measures assessing daily rhythms of rest and activity, mood, and diagnostic conversion to BD. Actigraphy measures of rest/activity include total sleep time (TST), wake after sleep onset (WASO), sleep efficiency (SE), sleep onset latency (SOL), sleep quality (L5 activity), day-time activity (M10 activity), relative amplitude (RA), intradaily variability (IV), and interdaily stability (IS) and will be assessed for one week at baseline and all study time points. The PSQI[99] will also be collected at these time points and will enable analysis of subjective measure of sleep. These measures are commonly utilized in studies of sleep, daily rhythms, and mood in pregnant women[11,26,29,30,100] and in individuals with and at-risk for BD.[42,101,102] Daily rhythms will be further assessed using the self-report Social Rhythm Metric-5 (SRM-5), a diary measure

which is commonly used both as a therapy tool and in IPSRT research.[34,103] The SRM-5 demonstrates good correlation (r=0.866) with the longer SRM-17,[21] the gold standard in measures of lifestyle regularity. Additionally, it is both sensitive (74%) and specific (95%) for detecting rhythm irregularity.[103] The Brief Social Rhythm Scale (BSRS),[104] a questionnaire format developed from the longer SRM-17, will also be collected as an additional measure of daily rhythms and has been utilized as an outcome measure in intervention studies of SRT for adolescents with BD.[74]

We will also acquire multiple measures of mood at baseline and throughout the study period. EPDS and clinician-acquired YMRS and Hamilton Depression Rating Scale (HAM-D) scores will be obtained at baseline and at 2, 9, and 16 weeks postpartum. Review of psychotherapeutic interventions in both perinatal populations and individuals at risk for BD supports the use of these scales as common outcome measures of mood.[39,85,90]

Diagnostic conversion to BD will be assessed via administration of the MINI at all study time points. In a systematic review of early interventions in individuals at risk for BD, five studies reported outcomes of diagnostic conversion to BD.[41,42,47,57,105] Saraf et al. argue that more early intervention studies need to assess conversion to BD as prevention is the ultimate goal;[39] thus, we will assess conversion as a secondary outcome.

2.4.8 Determination of Sample Size

In the absence of published trials of IPSRT in perinatal populations, our sample size was calculated from data derived from studies conducted in individuals at risk for BD. Goldstein et al. reported a between-groups difference in weeks spent with subsyndromal symptoms over a follow-up period of 6 months. Odds were greater that youth in the control would display subthreshold symptoms of depression (OR = 4.2) and hypomania (OR=14.7)

when compared to youth receiving IPSRT. This yields Cohen's d effect sizes of d=0.79 and d=1.48 respectively.[106] Given that we will pool depressive and hypomanic symptoms to determine total weeks well, we assume our effect size will lie somewhere between the two values reported by Goldstein et al. Though utilizing a different therapy (Family-Focused Therapy - FFT), Miklowitz et al. also report significant group differences in weeks symptomatic (depressed and/or (hypo)manic) in a population of individuals at risk for BD ($\chi^2[1]=15.08$, $p<0.0001$). Youth in the intervention group spent an average of 26.80 weeks (95% CI = [24.03-29.89]) in full remission from symptoms versus an average of 19.50 weeks (95% CI = [17.19-22.11]) for youth in the control. This correlates to a Cohen's d effect size of 1.25 (see Appendix B for calculation). We will conservatively utilize an effect size of d=0.85 for our sample size calculation. This is less than the effect size determined by Miklowitz et al. and also lies on the lower end of the two effect sizes calculated by Goldstein et al. Assuming a two-tailed $\alpha=0.05$ and $\beta=0.20$ and with a 3:2 allocation of intervention to control, this will yield a sample size of N=29 and N=19.

In several studies examining the role of IPT in perinatal populations, loss-to-follow-up ranged from approximately 10 to 15%.[75,78,79] We will conservatively assume a 15% drop-out rate in our study in order to recruit an adequate sample size. This brings our final sample size to 55 individuals: 33 in the intervention group and 22 in the control.

Assuming this 15% loss to follow up with a two-tailed $\alpha=0.05$, we will also be 80% powered to detect medium effect sizes (Cohen's $d \geq 0.56$) in pre- to post-treatment changes in mood symptoms among women receiving IPSRT. In a study of FFT in at-risk youth, Garrett et al. observed a medium effect size of treatment on change in depressive symptoms (Cohen's d=0.56) and (hypo)manic symptoms (Cohen's d=0.59).[54] A recent trial of

predominantly telehealth-delivered SRT in youth with BD found similar pre-/post-treatment effect sizes (0.86 for HAM-D scores and 0.49 for YMRS score).[74] These findings are slightly lower than findings of IPT trials in perinatal women, which yield within-group effect sizes of 0.96–1.86 for improvement of depressive symptoms.[61] Though pre-/post-treatment differences in mood symptoms are not our primary outcome, these are commonly reported in initial acceptability and feasibility trials with individuals at risk for BD. With our proposed sample size, we will have adequate power to assess these changes.

2.5 Conclusion

The data presented above support the great need for perinatal mental health research as relates to BD. As discussed previously, the postpartum period is a high-risk interval for mood disturbance and conversion to BD, particularly for women with a positive family history in a first-degree relative. Prior research has shown the importance of daily rhythm regulation in those with a diagnosis of BD, a concept now gaining traction in the field of early intervention and prevention in at-risk adolescents. However, similar studies investigating strategies to reduce postpartum symptom burden and ultimately prevent BD conversion have not yet been conducted. The success of psychotherapeutic interventions in ameliorating postpartum unipolar depressive symptoms and the promise shown by IPSRT and other intensive psychotherapies in at-risk adolescents indicate that similar interventions may be effective in pregnant women. The proposed study will investigate whether early intervention with IPSRT exerts a protective effect on women at risk for BD during the vulnerable perinatal period. If successful, this study may better inform best clinical practice for these at-risk women, helping to reduce symptom burden and possibly prevent conversion to BD along with the accompanying ramifications for mother and baby.

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CHAPTER 3: STUDY METHODS

3.1 Study Design

The proposed study will be an outcomes-assessor blinded RCT which will investigate the effect of IPSRT versus E-TAU in reducing postpartum mood symptom burden (as measured by LIFE PSR scores) in perinatal women at risk for BD.

After determination of eligibility, women will be randomized to either treatment (IPSRT) or control (E-TAU) in a 3:2 allocation ratio. The control group will receive enhanced monitoring of their symptoms via weekly self-report mood scales, psychosis screens, and suicide risk assessments. At intake and at postpartum week 2, 9, and 16, control participants will have the opportunity to discuss symptoms with a trained clinician. Referrals will be placed as necessary if the clinical interview suggests symptoms meeting diagnostic criteria for which a mental health referral would be beneficial. With the study participant's permission, her primary care provider, obstetrician, and/or community mental health provider will be informed in order to reinforce the referral. Additional contact with study staff and determination of need for referral outside of these time points will be guided by the weekly self-report assessments.

Those assigned to the treatment group will receive all of the enhanced monitoring of the control group along with up to 22 sessions of IPSRT. The first 12 sessions will be offered weekly with the goal that these sessions be completed prior to the delivery of the infant. This 12-week treatment series will be followed by maintenance therapy on a bimonthly basis up to 8 weeks postpartum. The total number of maintenance sessions will vary depending on the time at which the participant enters the study. The structure and content of the sessions can be found in Table 3.1.

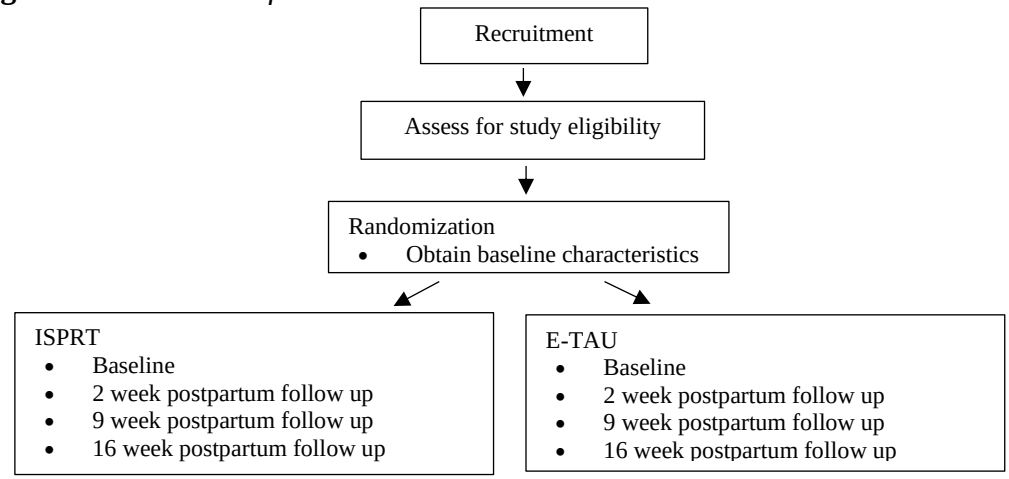
Table 3.1: *Interpersonal and Social Rhythm Therapy for Perinatal Women at risk for BD*

Phase	Primary Focus	Session	Content
Treatment Phase: Initial	Develop rapport Conduct psychoeducation about risk for BD	1-2 3-4	• Conduct the interpersonal inventory • Construct "family trees" with familial psychiatric disorders • Review symptoms of BD • Introduce biopsychosocial model of BD • Discuss association between stress and mood (with focus on role transitions) • Introduce the SRM-5
Treatment Phase: Intermediate	Enhance social rhythm regularity Resolve interpersonal problem area	5-8	• Establish target times on SRM-5 for sleep and social rhythms; discuss how target times will change over perinatal period • Develop strategies to regularize sleep patterns and stabilize daily rhythms (both now and in the postpartum) • Explore feelings about being at risk for BD • Link stressful family/interpersonal events and mood and social rhythm disruptions
Treatment Phase: Final	Continue work from prior sessions Plan for end of initial treatment phase	9-12	• Review goals and progress • Identify strategies for future management with focus on anticipated changes specific to the postpartum • Create plan for management of emergent mood symptoms
Maintenance Phase/ Termination	Continue work from prior sessions Termination	13-… Final 2 sessions	• Adjust target times of SRM-5 • Continue to problem solve and identify strategies for current and anticipated sleep and daily rhythm pattern disruptions • Readjust plan for management of emergent symptoms as needed

* Note: This table is drawn directly from Goldstein et al. IPSRT Treatment Content for at-risk Youth with slight modification for the perinatal population.[1] IPSRT sessions will be offered up to 8 weeks postpartum.

Measures of mood (EPDS, HAM-D, YMRS) as well as daily rhythm metrics (actigraphy measures, PSQI, SRM-5, BSRS) will be obtained at baseline and at postpartum week 2, 9, and 16. At these time points, confirmation of psychiatric diagnoses or conversion to BD will be made using the SCID (baseline) or MINI (postpartum time points). Participants in both groups will have the opportunity to discuss symptom burden at this time and will receive referrals as necessary. Any changes in medications or engagement with community mental health treatment will also be recorded at this time. At the final time point, total symptom burden over the 16-week postpartum period will be assessed using the PSR LIFE score. Participant satisfaction with the treatment will be assessed using the CSQ. The schedule of events can be seen in Figure 3.1.

Figure 3.1: *Schedule of Events*



* Measures obtained at all timepoints: EPDS, YMRS, HAM-D, SCID/MINI, PSQI, SRM-5, BSRS, actigraphy measures, psychiatric medications, engagement with community mental health treatment

* CQS and LIFE PSR scores will additionally be obtained at 16 weeks

3.2 Study Population and Sampling

This study will enroll perinatal women at risk for BD. At-risk status will be determined based on a combination of clinical and familial risk factors including 1) positive family history of BD or postpartum psychosis in a first-degree relative and 2) past or current diagnosis of a depressive or bipolar-related disorder (e.g. cyclothymia, other specified BD). Participants included in this study must be 18-44 years of age, in their second trimester at the time of recruitment (18-26 weeks gestation), able to speak and write in English, and be mildly symptomatic at intake (YMRS>8 and/or HAM-D>8). Past and current psychiatric diagnoses will be confirmed using the SCID. When possible, family history will be confirmed via direct interview of the affected family member using the SCID. Otherwise, the study participant will be interviewed using the FH-RDC.

The selection criteria set forth aims to recruit a sample that balances control for possible confounds with safety concerns, generalizability, and feasibility. Thus, we will exclude any Axis I or II disorder except for a select few known to be common in individuals

at risk for BD including anxiety disorders and ADHD. Depressive and bipolar-related disorders will also be included as specified above since these diagnoses may represent antecedent conditions that predict risk of future conversion to BD. We will not exclude for psychiatric medication use as discontinuation can lead to symptom worsening and increased suicide risk. However, this information will be collected at baseline and at each study timepoint to be included as a covariate in exploratory analyses. A list of inclusion and exclusion criteria are provided in Table 3.2. We will employ consecutive sampling to enroll all women who are referred to our study and meet selection criteria.

Table 3.2: *Selection Criteria*

Inclusion Criteria	Exclusion Criteria
1. Family history of BD-I, BD-II, or postpartum psychosis in a first-degree relative 2. Current or past diagnosis of a depressive disorder or bipolar-related disorder (cyclothymia, other specified BD) 3. Age 18-44 years 4. 18-26 weeks gestation 5. Able to speak and write in English 6. Mildly symptomatic at intake (YMRS>8 and/or HAM-D>8)	1. DSM-5 diagnosis of BD-I or BD-II 2. Any alcohol or substance use (positive urine drug screen) in prior week or any substance use disorder meeting moderate to severe criteria on DSM-5 (excluding caffeine/nicotine) within past 6 months 3. Any Axis I or II disorder, including history of psychosis (exceptions include anxiety disorders, ADHD, or those specified for inclusion) 4. Current participation in a form of structured psychotherapy (CBT, IPT, IPSRT, SRT, FFT, DBT) 5. Inability to provide informed consent (IQ<70, too symptomatic to participate per PI's judgement, or YMRS>25) 6. Active suicidal, homicidal, or infanticidal thoughts or C-SSRS Category 4 risk (some intent to carry out plan) 7. High risk pregnancy (multiple gestation; history of >1 first trimester loss or any second or third trimester loss; history of preterm labor, abruption placentae, or severe or early onset preeclampsia; current serious maternal medical condition such as cardiac or renal failure)

* CBT = Cognitive Behavioral Therapy; IPT = Interpersonal Therapy; ISPRT = Interpersonal and Social Rhythm Therapy; SRT = Social Rhythm Therapy; FFT = Family Focused Therapy; DBT = Dialectical Behavioral Therapy; C-SSRS = Columbia Suicidal Severity Rating Scale

3.3 Subject Protection and Confidentiality

The study protocol and all recruitment materials will be reviewed and approved by the Human Investigation Committee (HIC) of the Yale University School of Medicine Institutional Review Board (IRB) prior to initiation of recruitment. Study staff and research assistants will be added to the HIC approved protocol and will be required to complete HIPAA (Health Insurance Portability and Accountability Act) compliance training prior to

participating in study-related activity and must maintain certification throughout the study. During the intake screening interview, participants will be assigned a unique identification number which will replace all identifying personal health information (PHI). The record used to relate PHI to a participant's unique identifier will be stored within password-protected, encrypted servers that comply with HIPAA standards and are accessible only to the PI and select study staff. All deidentified study data will likewise be stored in password protected and HIPAA compliant encrypted servers accessible only to research staff.

Videotelecommunication will only be performed using secure methods approved by the HIC. Therapy sessions will be completed over HIPAA compliant video/audio software (Yale Zoom). Computer monitors will be away from the view of anyone but the study treater, listened to in soundproofed rooms or by headphones, and the treaters will not leave the computer while participants are engaged. All participants who wish to participate in the study will be required to sign a written, informed consent form providing an overview of the research study as well as any anticipated risks or benefits. Participants will be made aware that they can withdraw from the study at any time. Participants will also be made aware that the PI reserves the right to withdraw an individual from the study and initiate escalation of care if it is determined that the participant is a risk to herself or others. A copy of the consent form can be found in Appendix A.

3.4 Recruitment

Subjects will be recruited from Connecticut clinics and hospitals offering prenatal care as well as by referral from community mental health providers. The primary recruitment site will be hospitals and clinics associated with the Yale New Haven Health System. Other suitable recruitment centers include Hartford Hospital, Norwalk Hospital,

and Saint Francis Hospital, amongst others. Obstetric providers affiliated with these hospitals will be provided study information and will be asked to provide appropriate patients with study information and study site contact information. Similar requests will be made of community mental health providers. We will also accept community/self-referral. Participants must identify a community health provider (e.g. obstetrician, primary care provider, mental health provider) in order to participate in this study. If subject flow is lower than anticipated, we will consult with the Yale Center for Clinical Investigation's (YCCI) Study Recruitment and Marketing unit in order to develop strategies to bolster participation. If subject accrual rates remain below target levels, we will consider expanding recruitment to the home institutions of collaborators Dr. Holly Swartz, University of Pittsburgh School of Medicine, and Dr. Crystal Clark, Northwestern Feinberg School of Medicine, both of whom have significant experience with BD research including IPSRT (Dr. Swartz) and perinatal BD (Dr. Clark).

A list of those individuals who endorse interest in the study will be stored in a secure database. Research staff will conduct initial screening over the phone to assess eligibility for the study based on the inclusion and exclusion criteria outlined in Table 3.2. If a participant is found to be eligible based on the initial screen, an intake visit will be scheduled to be completed in-person at the office space of the Mood Disorders Research Program (New Haven, CT). During this time, eligibility will be further assessed, and baseline and demographic data will be collected. Following intake, if all eligibility criteria are met, subjects will be randomized to either intervention or control. All future visits will be conducted over HIPAA compliant video software (Yale Zoom).

3.5 Study Variables and Measures

Several demographic, obstetric, and clinical characteristics will be collected at baseline and will be considered as covariates in exploratory analyses. These variables and their operationalization can be found in Table 3.3. Medication at baseline and at each study timepoint will be recorded with structured medication history forms, including the National Database for Clinical Trials (NDCT) Medication History and Clinical Trials: Other Medications Record. Current engagement with community mental health treatment will also be recorded at baseline and each study timepoint. Existing psychiatric disorders will be classified according to DSM-5

Table 3.3: *Baseline Characteristics*

	Intervention	Control	P-Value
Demographic			
Age	μ±SD	μ±SD	Student's t test
Race/Ethnicity			
American Indian or Alaskan Native	(n) %	(n) %	Chi-squared
Asian	(n) %	(n) %	Chi-squared
Black or African American	(n) %	(n) %	Chi-squared
White	(n) %	(n) %	Chi-squared
Native Hawaiian or Pacific Islander	(n) %	(n) %	Chi-squared
Hispanic/Latinx	(n) %	(n) %	Chi-squared
Married	(n) %	(n) %	Chi-squared
SES[1]	μ±SD	μ±SD	Student's t test
Level of Social Support[2]	μ±SD	μ±SD	Student's t test
Obstetrics			
Unplanned Pregnancy	(n) %	(n) %	Chi-squared
Primiparous	(n) %	(n) %	Chi-squared
Clinical			
Community Mental Health Treatment (Yes/No)	(n)%	(n)%	Chi-squared
Psychiatric Diagnoses			
Depressive Disorder	(n) %	(n) %	Chi-squared
Bipolar and Related Disorders	(n) %	(n) %	Chi-squared
Anxiety Disorders	(n) %	(n) %	Chi-squared
Obsessive Compulsive and Related Disorders	(n) %	(n) %	Chi-squared
Attention-Deficit/ Hyperactivity Disorders	(n) %	(n) %	Chi-squared
Baseline Psychiatric pharmacotherapeutics			
Lithium	(n) %	(n) %	Chi-squared
Anticonvulsants	(n) %	(n) %	Chi-squared
Antipsychotics	(n) %	(n) %	Chi-squared
Anxiolytics	(n) %	(n) %	Chi-squared
Psychostimulants	(n) %	(n) %	Chi-squared
Antidepressants	(n) %	(n) %	Chi-squared
Antidepressant monotherapy	(n) %	(n) %	Chi-squared
Baseline Mood Symptoms			
HAM-D	μ±SD	μ±SD	Student's t test
YMRS	μ±SD	μ±SD	Student's t test
EPDS	μ±SD	μ±SD	Student's t test

1. Hollingshead Index of Social Status
2. Multidimensional Scale of Perceived Social Support

diagnostic categories. Diagnoses will be confirmed by the SCID.

The independent variable is treatment assignment. Study participants will be randomly assigned in 3:2 ratio to receive either IPSRT or E-TAU throughout the peripartum (from assignment to 8 weeks postpartum).

The primary outcomes will assess acceptability and feasibility of IPSRT in perinatal women at risk for BD as well as the effect of treatment on postpartum symptom burden. Symptom burden will be operationalized as mean number of weeks well over the postpartum study period (up to 16 weeks postpartum). Weeks well will be defined as the total number of weeks with all PSR LIFE scores ≤ 2, indicating no to minimal symptoms. Acceptability and feasibility of IPSRT will be defined by a mean CSQ score of ≥ 24 and retention of 75% of participants who receive a full course of therapy (≥ 12 sessions).

Multiple secondary outcomes will be investigated that assess pre- to post- treatment changes in daily rhythms and mood as well as the stability of those changes after treatment completion. Sleep and daily rhythm measures will be acquired for 1 week at baseline and again at 2, 9, and 16 weeks postpartum. These include the PSQI, SRM-5, and BSRS as well as actigraphic measures of rest/activity, including TST, WASO, SE, SOL, L5 activity, M10 activity, RA, IV, and IS (see Appendix C for definitions). Available actigraphic data will be extracted for each day in the week and will be averaged to produce a single value for each measure. EPDS and clinician-acquired YMRS and HAM-D scores will also be obtained at baseline and postpartum weeks 2, 9, and 16. Finally, conversion to BD will be assessed via administration of the MINI at these same time points. This will allow for comparisons within and between groups in order to better understand the interrelated effects of our intervention, daily rhythms, and mood.

3.6 Methodology Considerations

3.6.1 Assignment of Intervention

After initial eligibility is confirmed and informed consent obtained, research staff will obtain baseline characteristics of all study participants (see Table 3.3). Participants will then be randomized to treatment or control utilizing a computer-generated and non-stratified allocation sequence with varying block sizes concealed to the researchers.

3.6.2 Blinding

Due to the nature of the intervention, it would be difficult to blind study participants and the therapists who will be delivering IPSRT. However, the research staff who collect and analyze the data will be blinded to treatment allocation.

3.6.3 Adherence

For participants assigned to the intervention group, the therapist will record attendance after each scheduled appointment. In the event a session is missed, a Qualtrics survey will be deployed seeking to obtain the reason for the missed session. The survey will be linked to that participant's unique study identifier and no personal health information will be associated with the results.

We anticipant that delivery of our intervention via telehealth will significantly reduce the burden of attendance. Nevertheless, we expect that participants will be unable to make all scheduled sessions and acknowledge that complications of pregnancy and childbirth may necessitate longer absences irrespective of a participant's desire to attend. Additionally, women may receive a different number of maintenance sessions depending on the gestational age of the pregnancy at the time of study enrollment. Because of this, we will consider attendance at 12 sessions (the treatment phase) a full course of therapy.

To ensure uniformity and fidelity of the treatment sessions between different therapists/participants, two raters will perform independent fidelity assessments. All sessions will be recorded with 25% of sessions randomly selected to be rated for fidelity. Of these, 10% will be rated by both raters to ensure inter-rater reliability.

3.6.4 Monitoring of Adverse Events

We do not anticipate adverse events as a result of the study protocol outlined here. However, participants will be asked to answer weekly mood questionnaires and engage in therapy sessions which may cause momentary discomfort to some participants.

Irrespective of treatment assignment, women may experience mood symptom worsening over the course of pregnancy and the postpartum period. Thus, mood symptoms will be closely monitored via the administration of weekly self-rating mood scales (ASRM, EPDS), psychosis screens (PQ-16), and suicide risk assessments (C-SSRS) which will be deployed via an online survey and analytics tool (Qualtrics). A score of ≥6 on the ASRM, ≥13 on the EPDS, or a raw score ≥6 on the PQ-16 will prompt a telephone call from the clinician on-call in order to triage the situation and offer referrals as necessary. On-call duties will rotate between the PI, therapists, and trained research personnel with at least a master's level education. If a participant shows evidence of worsening and/or psychotic symptoms that suggest a higher level of care is needed, then at the discretion of the PI, their participation in the study will be ended, and their case will be discussed with their community healthcare provider (OB/GYN, primary care, or mental health provider). If they do not have a community mental health provider, a referral will be placed.

If at any point during the study (including during initial screens, therapy sessions, or self-report monitoring) a participant indicates that she is actively homicidal or suicidal,

the licensed clinician on-call, the PI (Dr. Blumberg), and the co-I (Aubrey Presnell, PA-S) will be immediately notified. A secondary Suicide Assessment Five-Step Evaluation and Triage (SAFE-T) assessment will be performed by the on-call clinician or PI. If there is imminent risk to self or others, the EMS system/Police (911) will be activated, and study personnel will attempt to stay on the phone with the individual until EMS/Police arrive.

3.7 Data Collection

Potential study participants will meet with study personnel in person to determine eligibility and to perform intake screening and randomization if applicable. Prior to intervention start, study participants will participate in comprehensive interviews both to determine eligibility and obtain baseline characteristics. These include assessments of socioeconomic status (Hollingshead Index of Social Status), social support (Multidimensional Scale of Perceived Social Support), intelligence quotient, family psychiatric history (SCID with affected family member or Family History – Research Diagnostic Criteria), personal DSM-5 psychiatric diagnoses (SCID), and psychiatric medication history (NDCT Medication History and Clinical Trials: Other Medications Record form). Baseline mood symptoms will be assessed via clinician-administered EPDS, YMRS, and HAM-D. Additional baseline characteristics will be obtained via self-report. The participant will then receive instruction on how to complete the PSQI, BSRS, and SRM-5 and will be given a GENEActiv actigraph to be worn for one week during which period the participant will also complete the SRM-5. Actigraphic measures to be obtained include: TST, WASO, SE, SOL, L5 activity, M10 activity, RA, IV, and IS.

Subsequent interviews will be conducted via videotelecomunication with trained study personnel at weeks 2, 9, and 16 postpartum. Participants will receive their

GENEActiv device via USPS prior to the data collection timepoint along with instructions and a prepaid return shipping label. At each study point, diagnostic conversion will be assessed using the MINI and mood symptom scores will be obtained via clinician administered EPDS, YMRS, and HAM-D. The PSQI, BSRS, and seven days of actigraphic measures and SRM-5 data will also be obtained at these timepoints. At the conclusion of the study (16 weeks postpartum), study personnel will conduct the LIFE and record PSR scores to assess symptom burden over the course of the postpartum period. CQS scores will be obtained via a Qualtrics survey deployed to study participants in the intervention group at study conclusion. Adherence will be assessed as detailed in Section 3.6.3.

3.8 Sample Size Calculation

For a complete rationale regarding determination of sample size, refer to Chapter 2, Section 2.4.8. Sample size was calculated using G*Power Software.[2] Assuming a two-tailed α=0.05 with a 3:2 allocation of intervention to control, we will be 80% powered to detect large between-group effect sizes (Cohen's d≥0.85) in postpartum symptom burden with a total sample size of 55 individuals: N=33 in the intervention and N=22 in the control. This assumes a 15% loss-to-follow-up. Though not our primary outcome, we will also be >80% powered to detect medium effect sizes (Cohen's d≥0.56) in pre- to post-treatment changes in mood symptoms among women who are receiving IPSRT (Appendix B).

3.9 Analysis

Prior to hypothesis testing, descriptive statistics and graphs will summarize data. Data will be checked for adherence to normal distribution by the Kolmogorov-Smirnov test. If needed, transformations will be used to meet assumptions for analysis; otherwise, nonparametric methods will be used. Baseline characteristics will be analyzed using

Student's t-test for continuous variables and chi-squared test for categorical variables to determine effectiveness of randomization.

All hypothesis testing will be by intention-to-treat. Student's t-test will be utilized to test the primary hypothesis that the average number of postpartum weeks well (LIFE PSR≤2) will differ between our intervention and control groups. Exploratory analyses will assess sensitivity of conclusions by adding age, baseline mood scores, community mental health treatment, medication class, psychiatric diagnoses, and attended session number one at a time as covariates in a multiple linear regression model. Additional covariates from baseline characteristics will be considered as needed.

Secondary analyses will be conducted using linear mixed models with maximum likelihood estimation. These models allow greater flexibility in modeling the correlation structure of repeated measures and can better accommodate missing data. Step-down Bonferroni will be used to correct for multiple comparisons. The multiplicity adjustments will keep the family-wise error rate within each hypothesis at the target 0.05 level.

A series of linear mixed models will be examined in order to understand the interrelated effects of group assignment (IPSRT, E-TAU) and time (baseline, 2 weeks, 9 weeks, 16 weeks) on key outcomes of interest, including measures of mood (YMRS, HAM-D, EPDS) and daily rhythms (PSQI, BSRS, SRM-5, actigraphic measures). Group will represent the between-subjects factor and time, the within-subjects factor. Actigraphy data from the GENEActiv devices will be processed using the GGIR program to extract key daily rhythm values from accelerometry data for use as outcome measures in the model. The model will include a group variable, time variable, and group*time interaction variable to assess correlations with outcomes of interest. The individual participant will be

treated as the random effect. We will also analyze mood rating scales as an outcome of interest using time as within-subjects factor and daily rhythms measures as between-subjects factor. Least square means and standard errors will be estimated and plotted to assess statistical significance of observed correlations.

Exploratory analyses will assess sensitivity of results after adjustment for age, baseline mood scores, community based mental health treatment, medication class, antecedent psychiatric diagnoses, and attended session number. Additional demographic or obstetric covariates as outlined in baseline characteristics will be considered as needed in the models, one at a time. We will also perform exploratory analyses of the IPSRT group divided into subgroups with predominant depressive or (hypo)manic baseline symptoms and assess the magnitude of effects relative to E-TAU in each subgroup.

Pre- to post-treatment changes in mood (YMRS, EPDS, and HAM-D) will be assessed via paired-t test for normally distributed variables and Wilcoxin signed-rank test for nonnormally distributed variables. Differences in the proportion of women who convert to BD in both groups will be assessed using chi-squared tests. Multiple logistic regression will be used to assess sensitivity of results and conduct exploratory analyses using the covariates mentioned earlier. All analyses will be using SAS, version 9.4 (Cary, NC).

3.10 Timeline and Resources

The proposed study, including recruitment, intervention, and data collection, will be performed over a two-year period. The estimated timeline of data collection is based on assumption of a full-term pregnancy of 40 weeks. Because women will be recruited during the second trimester (18-26 weeks gestation) and followed to 16 weeks postpartum, the follow-up period will vary from 31-39 weeks. Therefore, recruitment will end with 10

months remaining in order to allow adequate time for data collection. If recruitment is lower than anticipated, then the study will be modified as described in Section 3.4. Data analysis will occur upon study completion. Proposed study personnel include:

- 1 Principal Investigator (Dr. Hilary Blumberg) to oversee all operations.
- 1 co-Investigator (Aubrey Presnell, PA-S) to help oversee operations, for IRB protocol submissions, and writing.
- 1 research assistant to assist with enrollment, obtaining informed consent, and data collection/organization.
- 2 therapists with at least a master's level of education and expertise in administration of IPSRT who will deliver treatment sessions and collect data. Therapists will receive training in proper administration of IPSRT for perinatal women at risk for BD and will not deliver treatment until they have conducted at least two training cases under the supervision of the PI/co-I. Dr. Blumberg (PI) and Aubrey Presnell, PA-S (co-PI) will closely supervise each therapist weekly. Research personnel assisting in data collection will be blinded to treatment allocation of study participants (i.e. they will not be the clinicians providing the study intervention).
- 1 postdoctoral researcher, fellow, or PhD candidate trained in administration of the SCID, MINI, YMRS, HAM-D, EPDS, and SAFE-T to assist with data collection.
- 2 independent raters with at least a master's level of education to perform independent fidelity assessments of therapy sessions following training by the PI.
- 1 statistician to perform statistical analyses once data collection has concluded.

Office space will be provided by the PI of this study (Dr. Blumberg) at the Mood Disorders Research Program Office (60 Temple Street, Suite 6B, New Haven, CT 06510).

3.11 References

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CHAPTER 4: CONCLUSION

4.1 Study Advantages

This study will be the first of its kind to investigate early intervention and prevention strategies targeted to perinatal women at risk for BD. It utilizes a psychotherapeutic intervention, IPSRT, which has already demonstrated effectiveness as adjuvant treatment in fully syndromal BD and has shown promise as early intervention in at-risk adolescents. The use of a psychotherapeutic intervention minimizes ethical concerns of prescribing pharmacologic interventions to women in whom the benefit may not outweigh the risk to the developing fetus/newborn. In addition, it directly targets role transitions and sleep and daily rhythm disruptions unique to the perinatal period.

The proposed study possesses additional advantages that increase the internal validity of conclusions, thus strengthening confidence to infer a causal relationship between IPSRT and postpartum symptom burden. The randomization of participants to either intervention or control will minimize selection bias, reduce confounding, and increase the probability that both arms are balanced with regard to baseline characteristics. Blinding of outcomes assessors will minimize the risk of detection bias in outcome measures as will the use of standardized, clinician-administered questionnaires and clinical interviews and objective measures of daily rhythms (via actigraphy). Assurance that therapy sessions conform to the manualized treatment and are consistent between therapists will be provided by the use of independent raters to assess treatment fidelity.

To enhance generalizability, this study will not exclude participants with anxiety disorders or ADHD and will deliberately include those with depressive or bipolar-related disorders as these diagnoses are commonly comorbid with BD and may constitute a

prodrome of conversion. Furthermore, study participants will not be required to discontinue any psychiatric medications as a condition of participation in the study. The delivery of the intervention via telehealth also expands access and may thus provide a more socioeconomically, culturally, and racially diverse set of participants while simultaneously reducing study burden and attrition.

4.2 Study Limitations

While this study possesses many strengths, there are several notable limitations. Foremost, is the potential difficulty in recruiting an adequate sample size in the proposed timeframe. Recruitment of pregnant participants may be complicated by the additional commitments imposed on women who are already juggling multiple obligations. Additionally, women may fear engaging in clinical trials that could impact the developing fetus. The nonpharmacologic nature of our study aims to reduce this anxiety. In addition, the delivery of our intervention and outcomes assessment via telehealth aims to increase flexibility for participants and reduce time burden and attrition. Nevertheless, given the small anticipated population, it may be difficult to recruit such a large sample size (N=55). If needed, we will pursue recruitment strategies with YCCI to meet study enrollment requirements. Expansion of study sites may also be considered as outlined in Section 3.2.

This study is powered to detect only medium to large effect sizes, limiting its ability to identify small effects of IPSRT on symptom burden reduction. Longer follow up may also be needed to see the full benefit of IPSRT as a preventative therapy. While studies point to the early postpartum as the highest-risk interval,[1] longitudinal prospective studies show that individuals who experience postpartum mood disturbances not meeting DSM criteria for BD may still convert years later.[2,3] This should be an area of future study.

Similar to previous studies, we expect significant subject heterogeneity which we will not be powered to definitively assess with our proposed sample size. While this increases generalizability and feasibility of the study, it has the potential to confound results and limit the strength of conclusions. As previously discussed, medication class may alter risk of a postpartum episode. Current psychiatric diagnoses, engagement with outpatient treatment, and age may similarly mediate any observed relationships. We anticipate that social support and the ability to meaningfully engage with therapy recommendations may also play a role, as single mothers may find it more difficult to consolidate sleep and regularize daily rhythms that those with the support of a partner or family member. Though we will assess sensitivity of results by including these variables as covariates in exploratory analyses, we will not be powered to assess to what degree these factors contribute to our findings or obscure effects.

Additionally, this study utilizes E-TAU as a control. While control participants will receive enhanced monitoring of their symptoms, their total contact time with clinicians will not equate to those in the intervention group. Thus, we cannot definitively conclude whether differences between groups are specifically due to IPSRT or rather due to increased therapist time or therapeutic alliance. While constraints on study timing and sample size prevent us from utilizing a psychoeducational comparison control to address these non-specific effects, future studies should utilize such a control matched for session number and therapist time in order to increase the strength of conclusions.

This study is also limited by the sometimes unpredictable nature of pregnancy and childbirth. Although we aim to complete the first 12 sessions of IPSRT prior to delivery, we cannot control for the possibility of premature birth. Additionally, complications of

pregnancy may require prolonged absence or withdrawal from the study. While the selection criteria exclude for high-risk pregnancies in an effort to minimize these obstacles, they remain a possibility. Attended session numbers will also not be consistent among participants secondary to recruitment occurring at varying gestational ages. The number and timing of sessions required to achieve therapeutic effect has not been studied in at-risk or perinatal populations. Though we will investigate the effect of number of attended sessions in exploratory analyses, we will not be powered to definitively comment on best practices. However, the information from this trial will be used to guide modifications for future studies that may improve acceptability and optimize therapeutic benefit.

4.3 Clinical and Public Health Significance

The Strategic Plan of the National Institute of Mental Health (NIMH) calls for increased research in early intervention and prevention strategies, with a focus on delivery during known sensitive periods and key transitions.[4] As previously discussed, this is particularly important in BD which is associated with significant lifelong morbidity and functional decline. The perinatal period is a well-documented, high-risk interval for new diagnostic conversion to BD, particularly among a subset of women at high risk for the disorder; yet efforts to prevent or mitigate the impact of new-onset BD during this period remain vastly understudied. While the USPSTF has issued recommendations for prevention of postpartum depression in at-risk individuals,[5] no such recommendations exist for women at risk for perinatal BD. This study constitutes a brief, preliminary trial to investigate the acceptability, feasibility, and initial benefit of IPSRT in this population of women. Ultimately, this study's findings will assist providers in better discussing risk for BD, both during preconception counseling and in the perinatal period, and will enable

clinicians to provide their patients with evidence-based information and referrals to help lessen risk. If successful, this study could lead to the development of an effective, low-risk treatment option that could prevent or mitigate the negative sequelae of BD.

4.4 Future Directions

This proposed trial is intended to serve as a foundation for further studies investigating perinatal BD. It is possible this study will reveal needed alterations to improve acceptability and scalability for delivery to peripartum women. Larger and longitudinal studies will be needed to rigorously assess effectiveness of IPSRT as a preventative intervention in this population. This study will obtain multiple secondary measures, raising questions for further research. In particular, the relationship between mood and various measures of sleep and daily rhythms will be investigated and may provide a target for future studies aimed to prevent or treat postpartum mood disturbances.

While this study focuses on IPSRT as a preventative intervention for women *at risk* for BD, IPSRT as an adjunctive treatment for perinatal women with fully syndromal BD merits exploration. Studies show that up to 23% of women with BD will experience a postpartum relapse despite being on appropriate maintenance medication.[6] Alternative strategies tailored to the peripartum are thus urgently needed. IPSRT has been shown to be an effective adjunctive treatment in adults with BD, but there is limited data on its effectiveness in perinatal women.[7] By conducting a preliminary, limited study in at-risk women, this study hopes to elucidate methods which may prove helpful in delivering this intervention to women with BD. Ultimately, it is our hope that the findings of this study will prompt further research and advance the field of perinatal mental health, helping to fill a critical need for perinatal women with and at-risk for bipolar disorder.

4.5 References

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APPENDICES

Appendix A: Consent Form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: *Interpersonal and Social Rhythm Therapy for perinatal women at risk for bipolar disorder*
Principal Investigator: *Hilary Blumberg, MD*
Co-Investigator: *Aubrey Presnell, PA-SII*
Funding Source: *Pending*

Invitation to Participate and Description of Project

You are invited to participate in a research study investigating mental health outcomes in pregnant and postpartum women at risk for bipolar disorder who receive either a structured telehealth psychotherapy (Interpersonal and Social Rhythm Therapy - IPSRT) or enhanced treatment-as-usual. You have been asked to participate because you are a pregnant adult (age 18-44) in your second trimester who has a family history of bipolar disorder or postpartum psychosis in a first-degree relative (parent, sibling, or child). Additionally, you have a past or current diagnosis of depression, cyclothymia, or other specified bipolar disorder. Approximately 55 people will be invited to participate in this study.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits, and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you are interested in the study, you will be asked information about your mental health and obstetric history in order to determine if you are eligible to participate. You will also be asked to provide a urine sample for a urine drug screen. If you agree to participate in this study, research personnel will ask you questions about your demographics, obstetric and mental health history. These will include questions about age, race/ethnicity, marital status, socioeconomic status, social support, whether your pregnancy was planned or unplanned, whether this is your first pregnancy, information about any current mental health diagnoses, treatment, or medications, and current depressive or hypomanic symptoms.

If you agree to participate in this study, you will be randomly assigned to one of two groups. Participants in both groups will receive enhanced monitoring of their mood symptoms throughout the course of study up to 16 weeks postpartum. All participants may continue to engage with regular care with their obstetrician, primary care provider, and, if applicable, their mental health provider. Additionally, for both groups, referrals will be placed as necessary if a need for additional treatment is identified by study staff. However, one group will receive IPSRT in addition to their usual care. Randomization will be done through a computer-based system in which you have an equal chance of being assigned to either group. Neither you, your providers, nor study personnel will have influence over which group you are

assigned to. Once you are assigned to a group, you will be assigned a unique study code that designates your place in the study. This code will be used to identify you throughout the study.

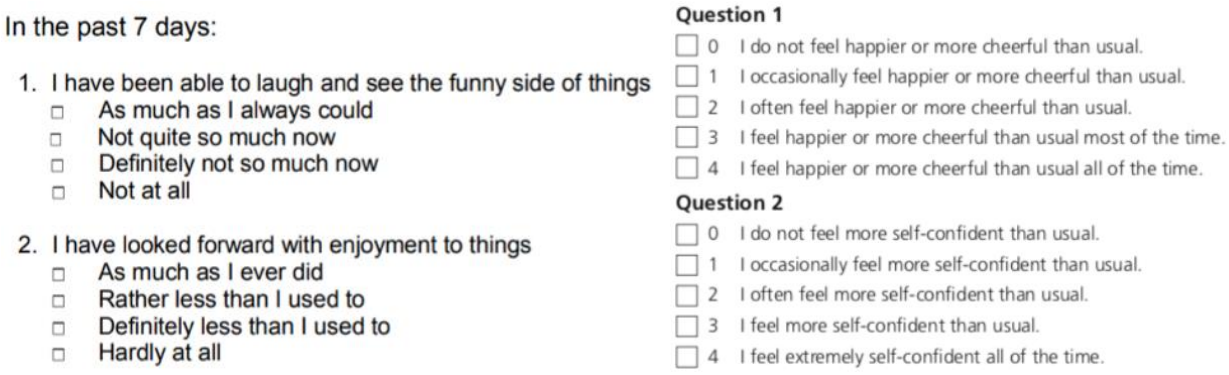
Once you have been randomized to one of the two groups, you will be contacted by study personnel to inform you of your group assignment. If you are assigned to the IPSRT group, you will be asked to attend a virtual one-hour therapy session once a week for 12 weeks and then every other week up to 8 weeks postpartum. During these sessions, you will interact one-on-one with a therapist using a secure telehealth platform (Yale Zoom). You can participate in these sessions at home or in any location that is most convenient for you. If you are in this group, you will also be asked to fill out the Client Satisfaction Questionnaire at the end of the study period (16 weeks postpartum). This will ask you questions regarding your experience and satisfaction with the therapy.

At the start of the study, all participants will meet in-person with trained study personnel who will conduct a structured mental health history interview and assess your current level of depressive or hypomanic symptoms using several clinical scoring measures (Edinburgh Postnatal Depression Scale, Young Mania Rating Scale, Hamilton Depression Rating Scale). At this time, you will also receive an actigraph, a watch-like device which you wear 24/7 (including during showering) on your nondominant wrist. An actigraph is similar to a fitbit and tracks your patterns of rest and activity based on movement. You will be also be trained in how to fill out the brief Social Rhythm Metric (SRM-5) which records patterns of activity throughout the day. It will ask you questions such as what time you went to bed, what time you woke up, when you ate dinner, and when you started work or childcare, etc. You will be asked to wear the actigraph and complete the SRM-5 for the first week of the study. You will also be asked to fill out the Pittsburg Sleep Quality Index and Brief Social Rhythm Scale at the end of this week. They will ask you questions about your sleep and the regularity of your daily activities.

At postpartum weeks 2, 9, and 16, you will again be asked to participate in a structured mental health interview (which will include assessment of depressive and hypomanic/manic symptoms). This will take place virtually over Yale Zoom and can be completed in a location of your choosing. Prior to these weeks you will be also be sent a new actigraph in the mail along with instructions and a prepaid return shipping label. You will be asked to wear the actigraph and complete the SRM-5 each day for these weeks and then return the actigraph in the mail to our office at 60 Temple Street, Suite 6B, New Haven, CT 06510. You will also complete the questionnaires about your sleep and daily rhythms.

Throughout the study, you will also be asked to fill out weekly self-report symptom assessments including the Edinburgh Postnatal Depression Scale, Altman Self Rating Mania Scale, Psychosis Prodromal Questionnaire-16, and Columbia Suicide Severity Rating Scale. These surveys will ask you questions about things you may have thought, felt, or experienced recently. They will be delivered virtually over Qualtrics and will be used for symptoms and safety monitoring. Additional contact with study personnel outside of pre-scheduled timepoints will be guided based on these scores. You will receive a reminder text or email to complete the questionnaires. An example of some of the questions you might be asked is included below:

				If TRUE: how much distress did you experience?			
				None	Mild	Moderate	Severe
1.	I feel uninterested in the things I used to enjoy.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
2.	I often seem to live through events exactly as they happened before (déjà vu).	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
3.	I sometimes smell or taste things that other people can't smell or taste.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**



A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

Risks and Inconveniences

IPSRT has been thoroughly explored in individuals with bipolar disorder and has also been studied in youth at risk for bipolar disorder. Interpersonal therapy (a subcomponent of IPSRT) has been well studied in pregnant women and has been found to be both safe and effective. There are no physical risks associated with this study to either you (the participant) or to the fetus/infant. However, some questions may make you feel uncomfortable. For the group receiving IPSRT, you may feel emotionally uncomfortable at times because therapy sessions may cause you to explore painful feelings, emotions, and experiences. However, your therapist is trained to guide you through this experience.

Questionnaire contents and clinical assessments may include personal information relating to psychological symptoms, so there is a risk of breach of confidentiality about your health status and participation in this study. While this is unlikely to occur and every effort will be made to keep your information confidential, this cannot be guaranteed.

There is also a possibility that you may experience worsening of mood symptoms and/or thoughts of suicide. This is not expected to be a direct result of study participation but is rather due to the complex social, emotional, and biological changes that occur during pregnancy and the postpartum. We will closely monitor your mood and risk for suicide throughout the study and will inform your provider if you develop symptoms requiring a higher level of care. If you desire a psychiatrist and do not currently have one, a referral will be placed. If study personnel determine that you are a risk to yourself or others, EMS/Police will be notified in order to connect you with emergency care.

Benefits

Benefits of participation in this study may include improvements in managing mental illness, preventing new onset of mental health symptoms, learning techniques to manage stressful situations or situations of transition, and identifying ways to manage emotions. Participation in this study could additionally benefit your infant as untreated or poorly managed maternal mental illness is associated with poor maternal-infant bonding, reduced family cohesion, and increased risk of mental illness in offspring.

Economic Considerations

There are no costs directly associated with this study. All interventions that are a part of this study are provided to you free of charge. Note, that you will still be responsible for any co-pays required by your insurance company for standard treatment with your obstetrician and/or community mental health provider. If we refer you to an outside provider for additional treatment, you will be responsible for all costs of care with that provider including any co-pays or prescription costs required by your insurance company. If you have any questions regarding your insurance coverage, please contact your insurance company directly. Note that all referrals for additional outpatient care are optional. If it is determined that emergency care is necessary, you will be responsible for all associated EMS and hospital costs.

There is no direct compensation associated with this study. IPSRT and mental health interviews will be conducted online using Zoom as the video-based platform. This requires access to a computer, tablet, or smartphone device that is sufficient for video conferencing. You will also receive weekly text or email reminders and online surveys that must be completed on one of the above devices. Standard messaging and data rates for your service carrier may apply and will not be covered by this study.

Your first appointment will be in-person at 60 Temple Street, Suite 6B, New Haven, CT 06510. Parking will be reimbursed for this appointment. All associated shipping costs for the actigraph devices will additionally be covered by this study. There will be no financial penalty for withdrawing from the study.

Treatment Alternatives/Alternatives

The alternative to participating in this study is to decline participation. If you do not wish to participate, you will receive standard monitoring and mental health treatment at the discretion of your obstetrician or other healthcare provider.

Confidentiality

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. In the event that you are deemed to be a risk to yourself or others, we are legally required to seek outside assistance and may share your personal health information and any study data that is required to facilitate treatment.

During the intake screening interview, you will be assigned a unique identification number which will replace all identifying personal health information. Information will be kept confidential by using only identification numbers on study forms and storing all signed forms in locked cabinets available only to select study staff. All data will be deidentified, and the record used to relate your personal health information to your unique identifier will be stored within password-protected, encrypted servers that comply with HIPAA (Health Insurance Portability and Accountability Act) standards and are accessible only to select study staff. All deidentified study data will likewise be stored in password-protected and HIPAA compliant encrypted servers accessible only to research staff. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Videotelecommunication will only be performed using secure methods approved by the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects). Therapy sessions will be completed over HIPAA compliant video/audio software (Yale Zoom). Computer monitors will be away from the view of anyone but the study treater, listened to in soundproofed rooms or by headphones, and the treaters will not leave the computer while the

participants are engaged. All therapy sessions will be recorded and stored in a secure password-protected, encrypted server. You will not be able to review or edit these tapes. These recordings will be viewable only by the study investigator and select study staff who are responsible for rating sessions to ensure that the therapy you receive is of high quality. Neither these videos, your voice, or your likeness will be used for any other purpose. All data, videos, and records used in the study will be kept for 10 years after data analysis has concluded and then will be securely deleted or disposed of.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

The researchers may also withdraw you from participating in the research if necessary. If it is determined that your symptoms require a higher level of care, then at the discretion of the study investigator, you will be immediately withdrawn from the study. Your primary health care provider will be informed and every effort will be made to connect you with appropriate care up to and including inpatient treatment. If you do not have an outpatient psychiatrist, a referral will be placed. In the event that you are determined to be an imminent risk to yourself or others, EMS/Police will be notified in order to facilitate emergency treatment. You will also be withdrawn from the study in the event of complications of pregnancy or childbirth that necessitate prolonged absence from study sessions.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors, with Yale School of Medicine, or with the Yale-New Haven Health System. You will still be able to acquire standard treatment in the community, or, at your request, we can refer you to a clinic or doctor who can offer this treatment.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Note, you do not give up any of your legal rights by signing this form.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization

I have read (or someone has read to me) this form, and I have decided to participate in the project described above. Its general purposes, the particulars of my involvement, and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject: _____

Signature: _____

Relationship: _____

Date: _____

_____ _____

Signature of Principal Investigator Date

or

_____ _____

Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the co-Investigator, Aubrey Presnell, PA-SII at (203) 000-0000.

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Appendix B: Calculation of Sample Size

Calculation of Effect Size for Average Weeks Well[1]

$$SD = \sqrt{N} * \frac{Upper\ limit\ of\ CI - Lower\ limit\ of\ CI}{2 * t_{\alpha;df}}$$

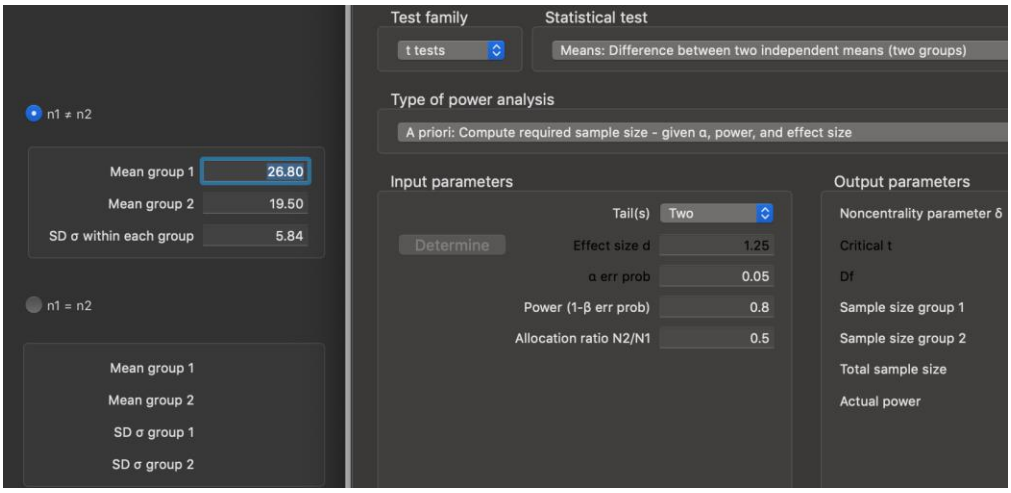
$$\boldsymbol{SD_{weeks\ well;FFT} = \sqrt{21} * \frac{29.89 - 24.03}{2 * 2.09} = 6.44}$$

$$SD_{weeks\ well;Control} = \sqrt{19} * \frac{22.11 - 17.19}{2 * 2.10} = 5.10$$

$$SD^*_{pooled} = \sqrt{\frac{(N_{FFT} - 1) * SD^2_{FFT} + (N_{Control} - 1) * SD^2_{Control}}{N_{FFT} + N_{Control} - 2}}$$

$$SD^*_{pooled} = 5.84$$

From G*Power, Cohen's d = 1.25 (see below)



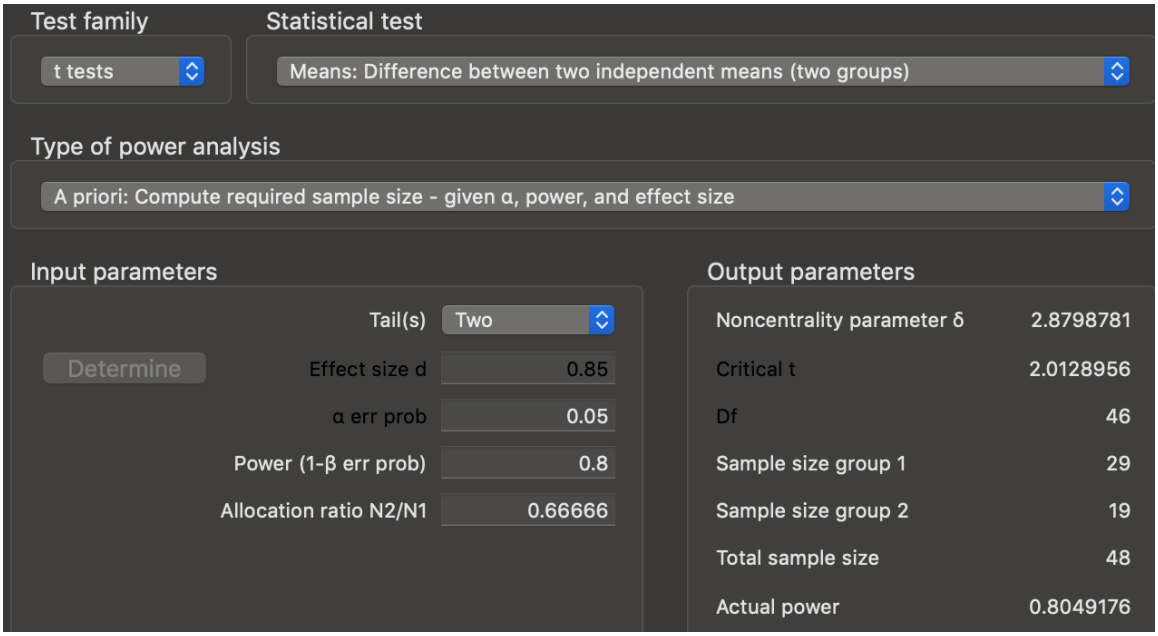
1. Miklowitz DJ, Schneck CD, Singh MK, et al. Early intervention for symptomatic youth at risk for bipolar disorder: a randomized trial of family-focused therapy. *J Am Acad Child Adolesc Psychiatry.* 2013;52(2):121-131.

Calculation of Final Sample Size for Average Weeks Well

From G*Power, assuming a two-tailed α=0.05 and β=0.80 with a Cohen's d effect size of 0.85 and 3:2 allocation between intervention and control, the sample size is as follows:

N_{IPSRT} = 29

$N_{E\text{-}TAU}$ = 19



Assuming 15% attrition, final sample size is as follows:

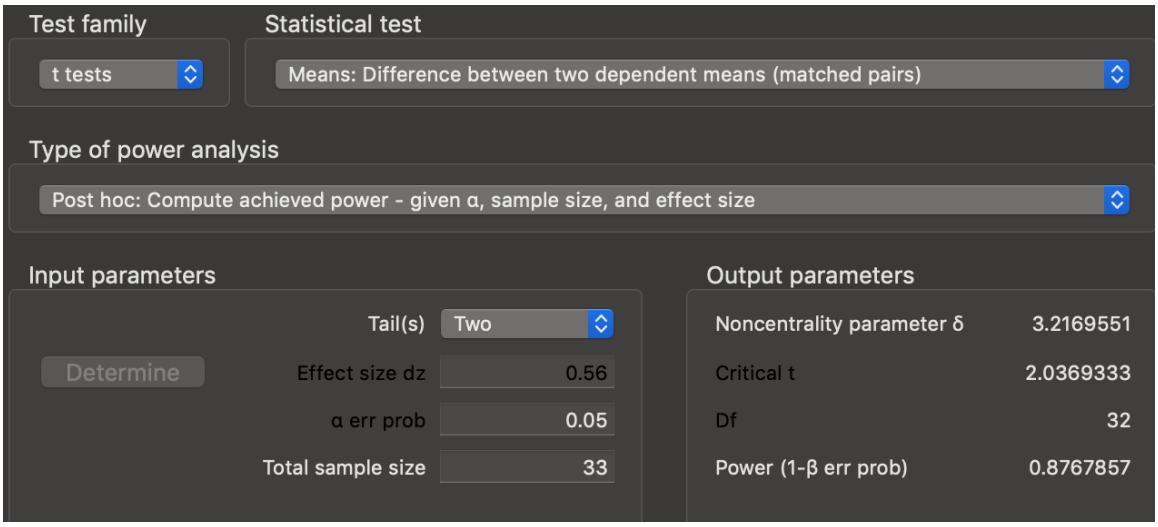
N_{IPSRT} = 33

$N_{E\text{-}TAU}$ = 22

Assessment of Power for Pre-/Post-Intervention Changes in Mood Symptoms Given Known Sample Size

Cohen's d = 0.56;

From G*Power, assuming two-tailed α=0.05 power will be >80% to detect medium effect sizes (d≥0.56) with a sample size of 33 in the intervention group.



Appendix C: Actigraphy Measures of Daily Rhythms

	Variable name	Description
Sleep	TST	Total sleep time. The time between sleep onset and offset/final wake time, minus any periods of wakefulness in between (WASO).
	WASO	Wake after sleep onset. The total number of nocturnal waking minutes.
	Sleep efficiency (SE)	Percentage of time asleep between sleep onset and offset/final wake time.
	Sleep onset latency	The number of minutes between bedtime and sleep onset.
	L_5 onset	Onset of the lowest five hours of activity in a 24-hour period. A proxy marker for sleep/rest onset.
	L_5 activity	Activity levels over the lowest five hours of activity in a 24-hour period, after L_5 onset. A proxy marker for sleep/rest activity.
Daytime activity	M_{10} onset	Onset of the most active ten hours in a 24-hour period. A proxy marker for day/activity onset.
	M_{10} activity	Activity levels over the greatest ten hours of activity in a 24-hour period, after M_{10} onset. A proxy marker for day/diurnal activity.
Rest-activity rhythms	Relative Amplitude (RA)	Differentiation score of activity during the ten most active hours in a 24-hour period (M_{10} activity) compared to activity during the five least active hours in a 24-hour period (L_5 activity). Therefore, differentiation in activity during active and rest states. Scored between 0-1, with a lower RA representing lower differentiation.
	Intradaily Variability (IV)	A variability marker of the difference in patterns within a day. Greater values represent greater rhythm fragmentation. Greater fragmentation indicates more transitions between rest and active states.
	Interdaily Stability (IS)	A stability marker of the difference in patterns across days. Greater values represent greater stability of rhythm. Greater stability indicates more consistency of rest-activity patterns between days.

Appendix D: DSM-5 Criteria for Bipolar I and Bipolar II Disorder[1]

BIPOLAR I DISORDER:

For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.

Manic Episode:

- A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

- During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
    - Inflated self-esteem or grandiosity
    - Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
    - More talkative than usual or pressure to keep talking
    - Flight of ideas or subjective experience that thoughts are racing
    - Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
    - Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless, non-goal-directed activity)
    - Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

- The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

- The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or to another medical condition.

Note: A full manic episode that emerges during antidepressant treatment [e.g., medication, electroconvulsive therapy (ECT)], but persists at a fully syndromal level beyond the physiological effect of treatment is sufficient evidence for a manic episode, and therefore, a bipolar I diagnosis.

BIPOLAR II DISORDER:

- Criteria have been met for at least one hypomanic episode and at least one major depressive episode
- There has never been a manic episode
- The occurrence of the hypomanic episode(s) and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
- The symptoms of depression or the unpredictability caused by frequent alternation between periods of depression and hypomania causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Hypomanic Episode:

- A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.

- During the period of mood disturbance and increased energy and activity, 3 (or more) of the above symptoms (4 if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree.

- The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

- The disturbance in mood and the change in functioning are observable by others.

- The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

- The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment).

Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, ECT) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess or agitation following antidepressant use) are not taken as sufficient for a diagnosis of a hypomanic episode nor necessarily indicative of a bipolar diathesis.

Note: The above DSM-5 criteria were reproduced from the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults and is in the public domain.

Reference:

1. 2019–2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults In. *The University of South Florida, Florida Medicaid Drug Therapy Management Program sponsored by the Florida Agency for Health Care Administration*2020.

Appendix E: Sample SRM-5 Form[1]

SRM — Short Form

DIRECTIONS: Please complete this form at the end of each day for the period of two consecutive weeks**.** *Write day of the week (Su, M, T, W, H, F, Sa) and write date (mm/dd/yy)* for which the form was completed**.** For each activity, *indicate the time* you started it**.** *circle 'AM' or 'PM'* so we know whether the time you entered is in the morning or evening**.** If you did not do a particular activity, *check the 'Did Not Do' box.*

Day of week	Date	Out of bed	First contact (in person or by phone) with another person	Start work, school, housework, volunteer activities, child or family care	Have dinner	Go to bed
	___ / ___ / ___	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do
	___ / ___ / ___	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do
	___ / ___ / ___	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do	Time ___:___ AM PM ☐ Did Not Do
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Reference:

1. Monk TH, Frank E, Potts JM, Kupfer DJ. A simple way to measure daily lifestyle regularity. *Journal of sleep research.* 2002;11(3):183-190.

Appendix F: Brief Social Rhythm Scale (BSRS)[1]

The following statements are related to your life rhythm. You will find a series of statements about various every day activities. Please indicate how regularly you perform each of these activities.

	Very regularly	*Quite regularly*	*Somewhat regularly*	*Somewhat irregularly*	*Quite irregularly*	*Very irregularly*
1. Going to bed Mondays through Fridays	□	□	□	□	□	□
2. Going to bed on the weekend	□	□	□	□	□	□
3. Getting out of bed Mondays through Fridays	□	□	□	□	□	□
4. Getting out of bed on the weekend	□	□	□	□	□	□
5. Meeting other people at school or work Mondays through Fridays	□	□	□	□	□	□
6. Meeting other people at school or work on the weekend	□	□	□	□	□	□
7. Meeting other people in my free time Mondays through Fridays	□	□	□	□	□	□
8. Meeting other people in my free time on the weekend	□	□	□	□	□	□
9. Taking meals regularly Mondays through Fridays	□	□	□	□	□	□
10. Taking meals on the weekends	□	□	□	□	□	□

Reference:

1. Margraf J, Lavallee K, Zhang X, Schneider S. Social rhythm and mental health: a cross-cultural comparison. *PloS one.* 2016;11(3):e0150312.

Appendix G: Pittsburgh Sleep Quality Index (PSQI)[1]

Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. **Please answer all questions.**

1. During the past month, what time have you usually gone to bed at night? _____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? _____
3. During the past month, what time have you usually gotten up in the morning? _____
4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				

	No bed partner or room mate	Partner/room mate in other room	Partner in same room but not same bed	Partner in same bed
10. Do you have a bed partner or room mate?				
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
If you have a room mate or bed partner, ask him/her how often in the past month you have had:				
a. Loud snoring				
b. Long pauses between breaths while asleep				
c. Legs twitching or jerking while you sleep				
d. Episodes of disorientation or confusion during sleep				
e. Other restlessness while you sleep, please describe:				

Reference:

1. Buysse DJ, Reynolds Iii CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research.* 1989;28(2):193-213.

Appendix H: Hamilton Depression Rating Scale (HAM-D)[1]

Hamilton Depression Rating Scale (HDRS)

PLEASE COMPLETE THE SCALE BASED ON A STRUCTURED INTERVIEW

Instructions: for each item select the one "cue" which best characterizes the patient. Be sure to record the answers in the appropriate spaces (positions 0 through 4).

1 DEPRESSED MOOD *(sadness, hopeless, helpless, worthless)*
- 0 |__| Absent.
- 1 |__| These feeling states indicated only on questioning.
- 2 |__| These feeling states spontaneously reported verbally.
- 3 |__| Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.
- 4 |__| Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2 FEELINGS OF GUILT
- 0 |__| Absent.
- 1 |__| Self reproach, feels he/she has let people down.
- 2 |__| Ideas of guilt or rumination over past errors or sinful deeds.
- 3 |__| Present illness is a punishment. Delusions of guilt.
- 4 |__| Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

3 SUICIDE
- 0 |__| Absent.
- 1 |__| Feels life is not worth living.
- 2 |__| Wishes he/she were dead or any thoughts of possible death to self.
- 3 |__| Ideas or gestures of suicide.
- 4 |__| Attempts at suicide (any serious attempt rate 4).

4 INSOMNIA: EARLY IN THE NIGHT
- 0 |__| No difficulty falling asleep.
- 1 |__| Complains of occasional difficulty falling asleep, i.e. more than ½ hour.
- 2 |__| Complains of nightly difficulty falling asleep.

5 INSOMNIA: MIDDLE OF THE NIGHT
- 0 |__| No difficulty.
- 1 |__| Patient complains of being restless and disturbed during the night.
- 2 |__| Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).

6 INSOMNIA: EARLY HOURS OF THE MORNING
- 0 |__| No difficulty.
- 1 |__| Waking in early hours of the morning but goes back to sleep.
- 2 |__| Unable to fall asleep again if he/she gets out of bed.

7 WORK AND ACTIVITIES
- 0 |__| No difficulty.
- 1 |__| Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.
- 2 |__| Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).
- 3 |__| Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
- 4 |__| Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

8 RETARDATION (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)
- 0 |__| Normal speech and thought.
- 1 |__| Slight retardation during the interview.
- 2 |__| Obvious retardation during the interview.
- 3 |__| Interview difficult.
- 4 |__| Complete stupor.

9 AGITATION
- 0 |__| None.
- 1 |__| Fidgetiness.
- 2 |__| Playing with hands, hair, etc.
- 3 |__| Moving about, can't sit still.
- 4 |__| Hand wringing, nail biting, hair-pulling, biting of lips.

10 ANXIETY PSYCHIC
- 0 |__| No difficulty.
- 1 |__| Subjective tension and irritability.
- 2 |__| Worrying about minor matters.
- 3 |__| Apprehensive attitude apparent in face or speech.
- 4 |__| Fears expressed without questioning.

11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as:
gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching
cardio-vascular – palpitations, headaches
respiratory – hyperventilation, sighing
urinary frequency
sweating
- 0 |__| Absent.
- 1 |__| Mild.
- 2 |__| Moderate.
- 3 |__| Severe.
- 4 |__| Incapacitating.

12 SOMATIC SYMPTOMS GASTRO-INTESTINAL
- 0 |__| None.
- 1 |__| Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
- 2 |__| Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

13 GENERAL SOMATIC SYMPTOMS
- 0 |__| None.
- 1 |__| Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
- 2 |__| Any clear-cut symptom rates 2.

14 GENITAL SYMPTOMS (symptoms such as loss of libido, menstrual disturbances)
- 0 |__| Absent.
- 1 |__| Mild.
- 2 |__| Severe.

15 HYPOCHONDRIASIS
- 0 |__| Not present.
- 1 |__| Self-absorption (bodily).
- 2 |__| Preoccupation with health.
- 3 |__| Frequent complaints, requests for help, etc.
- 4 |__| Hypochondriacal delusions.

16 LOSS OF WEIGHT ***(RATE EITHER a OR b)***

a) According to the patient:	**b) According to weekly measurements:**
0 |__| No weight loss.	0 |__| Less than 1 lb weight loss in week.
1 |__| Probable weight loss associated with present illness.	1 |__| Greater than 1 lb weight loss in week.
2 |__| Definite (according to patient) weight loss.	2 |__| Greater than 2 lb weight loss in week.
3 |__| Not assessed.	3 |__| Not assessed.

17 INSIGHT
- 0 |__| Acknowledges being depressed and ill.
- 1 |__| Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
- 2 |__| Denies being ill at all.

Total score: |__|__|

This scale is in the public domain.

Reference:

1. Hamilton MAX. Development of a rating scale for primary depressive illness. *British journal of social and clinical psychology*. 1967;6(4):278-296.

Appendix I: Young Mania Rating Scale (YMRS)[1]

Young Mania Rating Scale (YMRS)

Guide for Scoring Items – The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be the exception rather than the rule.

Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired. This is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys.

1. *Elevated Mood*
   - 0 Absent
   - 1 Mildly or possibly increased on questioning
   - 2 Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
   - 3 Elevated, inappropriate to content; humorous
   - 4 Euphoric; inappropriate to content; singing

2. *Increased Motor Activity – Energy*
   - 0 Absent
   - 1 Subjectively increased
   - 2 Animated; gestures increased
   - 3 Excessive energy; hyperactive at times; restless (can be calmed)
   - 4 Motor excitement; continuous hyperactivity (cannot be calmed)

3. *Sexual Interest*
   - 0 Normal; not increased
   - 1 Mildly or possibly increased
   - 2 Definitive subjective increase on questioning
   - 3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
   - 4 Overt sexual acts (towards patients, staff, or interviewer)

4. *Sleep*
   - 0 Reports no decrease in sleep
   - 1 Sleeping less than normal amount by up to one hour
   - 2 Sleeping less than normal by more than one hour
   - 3 Reports decreased need for sleep
   - 4 Denies need for sleep

5. *Irritability*
   - 0 Absent
   - 2 Subjectively increased
   - 4 Irritable at times during interview; recent episodes of anger or annoyance on ward
   - 6 Frequently irritable during interview; short, curt throughout
   - 8 Hostile, uncooperative; interview impossible

6. *Speech (Rate and Amount)*
   - 0 No increase
   - 2 Feels talkative
   - 4 Increased rate or amount at times, verbose at times
   - 6 Push; consistently increased rate and amount; difficult to interrupt
   - 8 Pressured; uninterruptible, continuous speech

7. *Language – Thought Disorder*
   - 0 Absent
   - 1 Circumstantial; mild distractibility; quick thoughts
   - 2 Distractible; loses goal of thought; changes topics frequently; racing thoughts
   - 3 Flight of ideas; tangentiality; difficult to follow; rhyming; echolalia
   - 4 Incoherent; communication impossible

8. *Content*
   - 0 Normal
   - 2 Questionable plans, new interests
   - 4 Special project(s); hyperreligious
   - 6 Grandiose or paranoid ideas; ideas of reference
   - 8 Delusions; hallucinations

9. *Disruptive – Aggressive Behavior*
   - 0 Absent; cooperative
   - 2 Sarcastic; loud at times; guarded
   - 4 Demanding; threats on ward
   - 6 Threatens interviewer; shouting; interview difficult
   - 8 Assaultive; destructive; interview impossible

10. *Appearance*
    - 0 Appropriate dress and grooming
    - 1 Minimally unkempt
    - 2 Poorly groomed; moderately disheveled; overdressed
    - 3 Disheveled; partly clothed; garish makeup
    - 4 Completely unkempt; decorated; bizarre garb

11. *Insight*
    - 0 Present; admits illness; agrees with need for treatment
    - 1 Possibly ill
    - 2 Admits behavior change, but denies illness
    - 3 Admits possible change in behavior, but denies illness
    - 4 Denies any behavior changes

Name: _____

Rater: _____

Date: _____

Score: _____

Reference:

1. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *The British journal of psychiatry.* 1978;133(5):429-435.

Appendix J: Edinburgh Postnatal Depression Scale (EPDS)[1]

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
- ☐ Yes, all the time
- ☒ Yes, most of the time — This would mean: "I have felt happy most of the time" during the past week.
- ☐ No, not very often — Please complete the other questions in the same way.
- ☐ No, not at all

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   - ☐ As much as I always could
   - ☐ Not quite so much now
   - ☐ Definitely not so much now
   - ☐ Not at all

2. I have looked forward with enjoyment to things
   - ☐ As much as I ever did
   - ☐ Rather less than I used to
   - ☐ Definitely less than I used to
   - ☐ Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
   - ☐ Yes, most of the time
   - ☐ Yes, some of the time
   - ☐ Not very often
   - ☐ No, never

4. I have been anxious or worried for no good reason
   - ☐ No, not at all
   - ☐ Hardly ever
   - ☐ Yes, sometimes
   - ☐ Yes, very often

*5 I have felt scared or panicky for no very good reason
   - ☐ Yes, quite a lot
   - ☐ Yes, sometimes
   - ☐ No, not much
   - ☐ No, not at all

*6. Things have been getting on top of me
   - ☐ Yes, most of the time I haven't been able to cope at all
   - ☐ Yes, sometimes I haven't been coping as well as usual
   - ☐ No, most of the time I have coped quite well
   - ☐ No, I have been coping as well as ever

*7 I have been so unhappy that I have had difficulty sleeping
   - ☐ Yes, most of the time
   - ☐ Yes, sometimes
   - ☐ Not very often
   - ☐ No, not at all

*8 I have felt sad or miserable
   - ☐ Yes, most of the time
   - ☐ Yes, quite often
   - ☐ Not very often
   - ☐ No, not at all

*9 I have been so unhappy that I have been crying
   - ☐ Yes, most of the time
   - ☐ Yes, quite often
   - ☐ Only occasionally
   - ☐ No, never

*10 The thought of harming myself has occurred to me
   - ☐ Yes, quite often
   - ☐ Sometimes
   - ☐ Hardly ever
   - ☐ Never

Administered/Reviewed by _____ Date _____

[1]Source: Cox, J.L., Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786 .

[2]Source: K. L. Wisner, B. L. Parry, C. M. Piontek, Postpartum Depression N Engl J Med vol. 347, No 3, July 18, 2002, 194-199

Reference:

1. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. *The British journal of psychiatry*. 1987;150(6):782-786.

Appendix K: Altman Self-Rating Mania Scale (ASRM)[1]

Altman Self-Rating Mania Scale (ASRM)

Name _____ Date _____

Instructions:

1. There are 5 statements groups on this questionnaire: read each group of statements carefully.
2. Choose the one statement in each group that best describes the way you have been feeling for the past week.
3. Check the box next to the number/statement selected.
4. Please note: The word "occasionally" when used here means once or twice; "often" means several times or more and "frequently" means most of the time.

Question 1

- ☐ 0 I do not feel happier or more cheerful than usual.
- ☐ 1 I occasionally feel happier or more cheerful than usual.
- ☐ 2 I often feel happier or more cheerful than usual.
- ☐ 3 I feel happier or more cheerful than usual most of the time.
- ☐ 4 I feel happier or more cheerful than usual all of the time.

Question 2

- ☐ 0 I do not feel more self-confident than usual.
- ☐ 1 I occasionally feel more self-confident than usual.
- ☐ 2 I often feel more self-confident than usual.
- ☐ 3 I feel more self-confident than usual.
- ☐ 4 I feel extremely self-confident all of the time.

Question 3

- ☐ 0 I do not need less sleep than usual.
- ☐ 1 I occasionally need less sleep than usual.
- ☐ 2 I often need less sleep than usual.
- ☐ 3 I frequently need less sleep than usual.
- ☐ 4 I can go all day and night without any sleep and still not feel tired.

Question 4

- ☐ 0 I do not talk more than usual
- ☐ 1 I occasionally talk more than usual.
- ☐ 2 I often talk more than usual.
- ☐ 3 I frequently talk more than usual.
- ☐ 4 I talk constantly and cannot be interrupted

Question 5

- ☐ 0 I have not been more active (either socially, sexually, at work, home or school) than usual.
- ☐ 1 I have occasionally been more active than usual.
- ☐ 2 I have often been more active than usual
- ☐ 3 I have frequently been more active than usual.
- ☐ 4 I am constantly active or on the go all the time.

Permission for use granted by EG Altman, MD

Reference:

1. Altman EG, Hedeker D Fau - Peterson JL, Peterson Jl Fau - Davis JM, Davis JM. The Altman Self-Rating Mania Scale. (0006-3223 (Print)).

Appendix L: Psychosis Prodromal Questionnaire-16 (PQ-16)[1]

The 16-item Version of the Prodromal Questionnaire (PQ-16)

				If TRUE: how much distress did you experience?			
				None	Mild	Moderate	Severe
1.	I feel uninterested in the things I used to enjoy.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
2.	I often seem to live through events exactly as they happened before (déjà vu).	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
3.	I sometimes smell or taste things that other people can't smell or taste.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
4.	I often hear unusual sounds like banging, clicking, hissing, clapping or ringing in my ears.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
5.	I have been confused at times whether something I experienced was real or imaginary.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
6.	When I look at a person, or look at myself in a mirror, I have seen the face change right before my eyes.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
7.	I get extremely anxious when meeting people for the first time.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
8.	I have seen things that other people apparently can't see.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
9.	My thoughts are sometimes so strong that I can almost hear them.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
10.	I sometimes see special meanings in advertisements, shop windows, or in the way things are arranged around me.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
11.	Sometimes I have felt that I'm not in control of my own ideas or thoughts.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
12.	Sometimes I feel suddenly distracted by distant sounds that I am not normally aware of.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
13.	I have heard things other people can't hear like voices of people whispering or talking.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
14.	I often feel that others have it in for me.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
15.	I have had the sense that some person or force is around me, even though I could not see anyone.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**
16.	I feel that parts of my body have changed in some way, or that parts of my body are working differently than before.	□ True	□ False	□**0**	□ **1**	□ **2**	□ **3**

Reference:

1. Ising HK, Veling W, Loewy RL, et al. The validity of the 16-item version of the Prodromal Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-seeking population. *Schizophrenia bulletin.* 2012;38(6):1288-1296.

Appendix M: Columbia Suicide Severity Rating Scale (C-SSRS)[1] with Suicide Assessment Five-Step Evaluation and Triage (SAFE-T) Protocol

SAFE-T Protocol with C-SSRS, Safety Planning and Telephone Follow-up

Step 1: Identify Risk Factors

C-SSCS Suicidal Ideation Severity	48 hr	Month	Lifetime (Worst)
1) Wish to be dead *Have you wished you were dead or wished you could go to sleep and not wake up?*			
2) Current suicidal thoughts *Have you actually had any thoughts of killing yourself?*			
3) Suicidal thoughts w/ Method (w/no specific Plan or Intent or act) *Have you been thinking about how you might kill yourself?*			
4) Suicidal Intent without Specific Plan *Have you had these thoughts and had some intention of acting on them?*			
5) Intent with Plan *Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*			

C-SSRS Suicidal Behavior: *"Have you ever done anything, started to do anything, or prepared to do anything to end your life?"* Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc.	48 hr	3 Months	Lifetime

Current and Past Psychiatric Dx:
- □ Mood Disorder
- □ Psychotic disorder
- □ Alcohol/substance abuse disorders
- □ PTSD
- □ ADHD
- □ TBI
- □ Cluster B Personality disorders or traits (i.e., Borderline, Antisocial, Histrionic & Narcissistic)
- □ Conduct problems (antisocial behavior, aggression, impulsivity)
- □ Recent onset

Presenting Symptoms:
- □ Anhedonia
- □ Impulsivity
- □ Hopelessness or despair
- □ Anxiety and/or panic
- □ Insomnia
- □ Command hallucinations
- □ Psychosis

Family History:
- □ Suicide
- □ Suicidal behavior
- □ Axis I psychiatric diagnoses requiring hospitalization

Precipitants/Stressors:
- □ Triggering events leading to humiliation, shame, and/or despair (e.g. Loss of relationship, financial or health status) (real or anticipated)
- □ Chronic physical pain or other acute medical problem (e.g. CNS disorders)
- □ Sexual/physical abuse
- □ Substance intoxication or withdrawal
- □ Pending incarceration or homelessness
- □ Legal problems
- □ Inadequate social supports
- □ Social isolation
- □ Perceived burden on others

Change in treatment:
- □ Recent inpatient discharge
- □ Change in provider or treatment (i.e., medications, psychotherapy, milieu)
- □ Hopeless or dissatisfied with provider or treatment
- □ Non-compliant or not receiving treatment

□ **Access to lethal methods:** Ask specifically about presence or absence of a firearm in the home or workplace or ease of accessing

Step 2: Identify Protective Factors (Protective factors may not counteract significant acute suicide risk factors)

Internal:	**External:**
□ Ability to cope with stress	□ Cultural, spiritual and/or moral attitudes against suicide
□ Frustration tolerance	□ Responsibility to children
□ Religious beliefs	□ Beloved pets
□ Fear of death or the actual act of killing self	□ Supportive social network of family or friends
□ Identifies reasons for living	□ Positive therapeutic relationships
	□ Engaged in work or school

Step 3: Specific questioning about Thoughts, Plans, and Suicidal Intent – (see Step 1 for Ideation Severity and Behavior)

If semi-structured interview is preferred to complete this section, clinicians may opt to complete C-SSRS Lifetime/Recent and Since Last Visit versions for comprehensive behavior/lethality assessment.

C-SSRS Suicidal Ideation Intensity (with respect to the most severe ideation identified above)	**48 hr**	**Month**	**Lifetime (Worst)**
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day			
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous			
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts			
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply			
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply			
Total Score			

Notes:

Behaviors:

- □ Preparatory Acts (e.g., buying pills, purchasing a gun, giving things away, writing a suicide note)
- □ Aborted/self-interrupted attempts,
- □ Interrupted attempts and
- □ Actual attempts

□ **Assess for the presence of non-suicidal self-injurious behavior** (e.g. cutting, hair pulling, cuticle biting, skin picking) particularly among adolescents and young adults, and especially among those with a history of mood or externalizing disorders

□ **For Youths:** ask parents/guardian about evidence of suicidal thoughts, plans or behaviors and changes in mood, behaviors or disposition

□ **Assess for homicidal ideation, plan behavior and intent** particularly in:

- □ character disordered males dealing with separation, especially if paranoid, or impulsivity disorders

Step 4: Guidelines to Determine Level of Risk and Develop Interventions to LOWER Risk Level

"The estimation of suicide risk, at the culmination of the suicide assessment, is the quintessential **clinical judgment**, since no study has identified one specific risk factor or set of risk factors as specifically predictive of suicide or other suicidal behavior."
From The American Psychiatric Association Practice Guidelines for the Assessment and Treatment of Patients with Suicidal Behaviors, page 24.

RISK STRATIFICATION	TRIAGE	POSSIBLE INTERVENTIONS
High Risk □ Suicidal ideation with intent or intent with plan **in past month** (C-SSRS Suicidal Ideation #4 or #5) **Or** □ Suicidal behavior **within past 3 months** (C-SSRS Suicidal Behavior)	**Refer to Psychologist or Psychiatrist to evaluate for hospitalization** **Place on Facility High Risk List**	□ Assessment of patient's medical stability □ Observation Status □ Elopement precautions □ Body/belongings search □ Pharmacological treatment □ Family/significant-other engagement □ Psychotherapy (CBT, DBT) □ Psychoeducation (coping skills, stress management, symptom management, etc.) □ Safety Plan □ Telephone Follow-up upon discharge **Safety needs to consider in the physical environment:** □ Assess the physical environment, focusing on limiting access to methods. The most common methods of suicide in hospitals are hanging, suffocation and jumping. **If risk assessment is conducted in outpatient setting:** □ Place individual in a room that is away from exits but close to staff where patient is observed at all times □ Beware of elopement risk if patient is against admission AND/OR wanting to be alone to follow through with plans of suicide
Moderate Risk □ Suicidal ideation **WITHOUT plan, intent or behavior in past month** (C-SSRS screen #2 or #3) **Or** □ Suicidal behavior more than 3 months ago (C-SSRS Suicidal Behavior) **Or** □ Multiple risk factors and few protective factors	**Refer to mental health professional to evaluate risk factors and determine appropriate treatment setting**	□ Pharmacological treatment □ Psychotherapy (CBT, DBT) □ Psychoeducation (coping skills, stress management, symptom management, etc.) □ Engagement with family-member or significant-other □ Safety Plan □ Provide National Suicide Prevention Lifeline card and local emergency contacts
Low Risk □ Wish to die (C-SSRS Suicidal Ideation #1) **no plan, intent or behavior** **Or** □ Suicidal ideation more than 1 month ago **WITHOUT plan, intent or behavior** (C-SSRS screen #2 or #3) **Or** □ Modifiable risk factors and strong protective factors **Or** □ No reported history of Suicidal Ideation or Behavior	**Outpatient**	□ Provide information about warning signs. □ Provide National Suicide Prevention Lifeline card and local emergency contacts □ Wellness Recovery Action Planning (WRAP) □ Re-assess at treatment plan review

Step 5: Document Level of Risk, Rationale for Risk Assignment, Intervention and Structured Follow Up Plan (to be developed)

Risk Level :

[ ] High Risk [ ] Moderate Risk [ ] Low Risk Suicidal

Clinical Formulation:

1- Specify findings from Steps 1-3 (including risk and protective factors).
2- State clinical rationale for selected risk level and treatment setting.

Treatment Plan for Reducing Risk Level:

☐ **If Suicidal:**
1- Discuss risk-linked interventions (see Step 4 for possible interventions)
2- Identify risk and protective factors that can be modified through treatment and intervention
3- If Access to Means is present, document instructions to patient and significant others
4- Develop *Risk Reduction Plan* with specific interventions to reduce risk factors and enhance protective factors.
5- Develop *Safety needs* for individual's physical environment and *Special Observations*, if warranted.
6- Create a Safety Plan
7- Create a Follow-up plan

☐ **If not suicidal:**
1- Discuss warning signs
2- Provide National Lifeline information
3- Re-assess at treatment plan review

Suicide-Risk Following Discharge from INPATIENT Setting:

The highest risk of suicide is within the **first three days of discharge** from inpatient setting.
The next highest risk of suicide is during the **first 30 days** post discharge.

Community Prevention Practices

☐ ***3 & 30 Follow-up:*** Outpatient appointment **MUST** be scheduled within the **first 3 days of discharge** with **close follow up** and support **during the first 30 days** of inpatient discharge.

☐ ***Warm-hand off*** and ***Peer Bridger***: Outpatient staff and/or Peer Bridger meet with individual as an inpatient. Same Bridger and outpatient staff continues shared collaboration and connection with individual until outpatient connection and follow-up services are in place.

☐ **Safety Plan** must be developed during the inpatient stay and shared with the individual's outpatient provider.

Guidelines for When to Document Suicide Risk Assessments:

☐ At the time of inpatient and/or outpatient admission
☐ With occurrence of any suicidal behavior or ideation
☐ Whenever there is clinical change
☐ Before increasing privileges or giving passes (if individual is in an inpatient setting for moderate /high risk individuals)
☐ At regular intervals (i.e., treatment plan review) or as clinically indicated
☐ At the time of inpatient or outpatient discharge

Collaborative Accountability:

A team-based, collaborative, shared responsibility approach to enhance individual's safety and foster on-going communication among team-members.

C-SSRS Categories

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide

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