Nutrition, Exercise, and Wellness Treatment (NEW Tx) for Bipolar Disorder

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NUTRITION, EXERCISE, AND WELLNESS TREATMENT (NEW TX) FOR PATIENTS WITH BIPOLAR DISORDER: A TWO-PHASE PILOT STUDY TO TEST FEASIBILITY AND ACCEPTABILITY

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I. BACKGROUND AND SIGNIFICANCE

Cardiovascular disease is the leading cause of morbidity and mortality among individuals with bipolar disorder (BD)[1, 2]. Diabetes, hypertension, hyperlipidemia, and obesity are among the most common diseases in BD and are also the leading risk factors for cardiovascular disease[3-6] and subsequent mortality[7-9]. Individuals with BD are at high risk for medical comorbidity[3-6] which leads to high rates of morbidity and mortality[1, 2], medical visits and admissions[10] as well as complicates treatment and course of BD[11]. The medical burden for BD appears to be worsening, perhaps due to increased use of medications that are associated with cardiovascular risk factors[8, 12, 13].

To further treatment development, the National Institute of Mental Health (NIMH) held a meeting in 2005 to discuss the impact of obesity, nutrition, and physical inactivity among those with mental disorders[14]. Experts in the field stated that "obesity among those with mental disorders has not received adequate research attention, and empirically-based interventions to address the increasing prevalence of obesity and risk of cardiovascular and metabolic diseases in this population are lacking"[14]. In 2006, another meeting was convened to develop a "plan of action" in managing medical comorbidity and psychiatric illness. The committee recommended "integrated models of care" to prevent and treat medical comorbidity in psychiatric populations with outcomes focused on enhancing individuals' physical "health" and "quality of life" (p. 518[15]).

Pharmacological treatment contributes to the risk of cardiovascular disease in BD[16] and weight gain is a major cause of treatment noncompliance, completing a dangerous cycle of increased burden of illness and decreased treatment efficacy[9, 17]. This medical burden is highlighted by the fact that individuals with BD have nearly three times more medical admissions than other behavioral health care diagnoses[10]. Although the phenomenology of the medical burden associated with BD is unclear, it has been recognized as a primary concern in the treatment of this population[13, 18]. Pharmacological strategies as adjunctive treatments for psychotropic-associated weight gain have been examined in overweight or obese outpatients with BD with limited benefit[19]. Even less promising data has been observed in pediatric bipolar samples[20] and schizophrenia[21]. Thus, adjunct psychosocial interventions have become increasingly important in reversing the behavioral antecedents that lead to poor nutrition and overeating. Interventions aimed at increasing healthy, nutritious eating have produced better outcomes for both clinical[22] and non-clinical populations[23]. Reducing the medical burden requires an integrated approach given that several factors (i.e., body mass index, exercise, food choices) impact BD individuals' outcomes in a weight loss program[24].

Despite these multiple factors, very few integrated programs have been developed, and only a few have been developed for severe mental illness. The Lifestyle Challenge Program incorporated nutrition, weight-management and exercise strategies into weekly, group-based psychoeducational sessions[25]. Only 43% of participants completed the program, but of these participants, they reported improvements in health-related quality of life and depressive symptoms[25]. The Integrated Intervention Model is an individualized psychoeducational program on sleep/wake rhythms, nutrition, exercise, and time management in BD (n = 24) and improved overall functioning and reduced psychiatric hospitalizations, but did not examine risk factors for cardiovascular disease[26]. The medical care model for BD consists of four psychoeducational group-based, self-management sessions about cardiovascular disease and how to improve diet and increase exercise. The treatment group showed improvements in mental health-quality of life and may have buffered against further decline in their quality of life[18]. Other current treatments for co-morbid medical and psychiatric conditions focus on establishing co-located general medical providers or treatment teams within mental health clinics[27, 28]. Although these approaches are targeting medical burden and enhance communication between providers, they tend to be costly, rely on an abundance of resources, or do not develop an individualized, integrated treatment. Without integrated treatments, one provider is not responsible for monitoring the patient which may limit observations of interactions between treatment and conditions[15, 29].

The nutrition, exercise, and wellness treatment program (NEW Tx) is designed to reduce medical burden by targeting three areas: poor nutrition/obesity, sedentary lifestyle, and unhealthy lifestyle choices:

i. **Nutrition:** Individuals with BD have poor eating and nutritional habits[30, 31]. Moreover, obesity is more prevalent in BD than the general population, with one study finding 38% of bipolar individuals are overweight and 29% are obese[32].

ii. **Exercise:** Sedentary lifestyle is associated with increased morbidity and mortality[33] and exercise training has been demonstrated to improve a number of important risk factors of medical burden (i.e., weight, cholesterol, insulin level[34, 35]). Exercise may be dually beneficial for BD given that it has also been found to improve mood [36, 37]. In a unipolar depressed sample, exercising 3 days/week for 45-min was as effective in reducing depressive symptoms as an antidepressant (i.e., sertraline)[38, 39], with promising data for bipolar samples[40]. Given the duality of exercise benefit for mental health, interventions are needed to increase lifestyle activity.

iii. **Wellness:** Individuals with BD make poor food choices[31] and use maladaptive coping strategies for stress, such as smoking, that increase their medical burden. For example, smoking in BD populations has been shown to increase heart disease mortality[41]. Individuals with BD have dysregulated behavioral activation systems[42] which may explain why they chose rewarding activities (i.e., cigarettes, caffeine), opposed to healthier coping skills. It is essential that an intervention reinforce the importance of making healthy lifestyle choices (i.e., food choices, lifestyle activity, reducing caffeine).

II. SPECIFIC AIMS

The purpose of this research is to develop and test the feasibility and acceptance of a theoretically integrated treatment to address the impact of medical comorbidity of individuals with BD, while exploring its efficacy, whether it improves overall functioning and symptoms, as well as examine a potential moderator and mediator of treatment response. NEW Tx is a proposed solution to this problem as it builds upon previous empirical studies in healthy populations as well as the limited literature on lifestyle modification with serious mental illness. NEW Tx also integrates and modifies treatment strategies, such that it can be administered by a sole provider who is skilled in intervention and assessment of medical comorbidity and BD. NEW Tx is not intended to replace the need to collaborate with other providers, and strongly encourages such support as needed, but is a first-line, adjunct treatment to reduce the medical burden in individuals with BD.

A. Primary Aims

i. **Aim 1:** Feasibility and Acceptance of NEW Tx in the Nonrandomized Trial (N=6). *Hypothesis 1a*: A preliminary study of whether NEW Tx will be feasible with regards to recruitment, retention, blinded assessments, and therapist adherence to NEW Tx[43]. *Hypothesis 1b*: Participants will report high satisfaction with the treatment (CSQ-8) and acceptability (NEW Tx Scale) over the study duration (i.e., 20-weeks) in a nonrandomized trial (n = 6).

ii. **Aim 2:** Feasibility and Acceptance of NEW Tx and its Evaluation in the Randomized Pilot Trial (n = 40). *Hypothesis 2a*: A pilot study of whether NEW Tx will be feasible with regards to recruitment, randomization, retention, blinded assessments, and therapist adherence to NEW Tx[43]. *Hypothesis 2b*: Participants will report high expectations for the treatment (CEQ) and high satisfaction and acceptability with the treatment (CSQ-8; Post-Tx Questionnaire; NEW Tx Scale) in a 20-week nonrandomized trial (n = 6).

B. Exploratory Aims

i. **Aim 3a:** Reducing Medical Burden in the Randomized Pilot Trial. Pilot test (n = 40) the efficacy of NEW Tx in improving medical burden using the Framingham Risk Score (FRS). *Hypothesis 3a*: Over the course of 20-weeks (18 sessions) the NEW Tx group will have a lower FRS compared to treatment as usual (TAU) in the randomized pilot trial.

ii. **Aim 3b:** Symptoms and Functioning in the Randomized Pilot Trial. Examine the efficacy of NEW Tx in improving functioning and symptoms of BD. *Hypothesis 3b*: Over the course of 20-weeks (18 sessions) the NEW Tx group will improved functioning (LIFE-RIFT) and symptoms (YMRS, MADRS) compared to TAU in the randomized pilot trial.

iii. **Aim 3c:** Moderator and Mediator of NEW Tx in the Randomized Pilot Trial. Investigate a potential moderator and mediator of treatment response. *Hypothesis 3c.1*: Individuals with higher baseline BMI (>30) will moderate the between treatment effect size for medical burden (FRS) in the randomized pilot trial, such that of NEW Tx will have lower FRSs. *Hypothesis 3c.2*: Mastery of the diet (food diaries) and exercise (exercise duration from Exercise Questionnaire) modules of NEW Tx will mediate the association of NEW Tx and improvement in medical burden (FRS).

III. INTERVENTION MODULES AND OVERVIEW

NEW Tx is a flexible modular treatment such that modules are selected based on the needs of the individual to increase its generalizability across patients, settings, and providers as well as its acceptability to patients. The three modules of the intervention are as follows:

A. Nutrition/Weight Loss Module

To enhance nutrition, we review nutritious foods (e.g., high in vitamins and minerals, low in fat) in each of the food groups as well as teach participants how to calculate serving size to enhance portion control. We discuss the importance of a "balanced diet" as well as having essential vitamins and minerals, particularly ones that may be beneficial for mood disorders. Finally, we review food that may be unhealthy and why. Weight loss is tracked as needed and food diaries are used as needed (at minimum at baseline, week 10, and week 20) to monitor participants' daily foods consumed and calories. Participants, with guide from their NEW Tx therapist, will determine a daily goal for caloric intake to assist in identifying healthy and realistic weekly weight loss goal. We utilize Cognitive Behavioral Therapy (CBT) strategies to challenge negative thoughts about changing food choices[44]. We also include a session on emotional eating, or eating to cope with negative affect, by evaluating the accuracy of thoughts associated with the craving. We discuss positive coping strategies, or distraction activities, to replace food as a way to improve mood or "comfort" oneself. We also utilize the philosophy from Brownell's LEARN program[45] that there are no "forbidden foods" as evidence suggests that this may increase cravings for these foods as well as negative thoughts about the module[46]. We use psychoeducational materials to enhance adherence. We specifically discuss the impact of "psychological factors" and review research studies of diet programs that have had positive outcomes in severe mental illness. Finally, we employ behavioral strategies in NEW Tx, such as positive reinforcement, to enhance adherence through the use of reward charts. We then collaboratively set homework and weekly goals each session.

B. Exercise Module

The goal of this module is to exercise 5 days/week, for at least 30 min each day, of moderate intensity [47]. Participants complete the Exercise Questionnaire each session to track their exercise. We begin this module by discussing the importance and rationale for exercise. We review evidence that exercise is particularly important in enhancing mood. We also discuss ways of increasing *lifestyle activity* (i.e., taking the stairs, standing instead of sitting, walking to the store). In this way, we approach exercise as a task not requiring sustained or extreme energy, concentration, and motivation, but a more casual experience, which can last for a relatively short period of time and still be helpful. This paradigm shift in conceptualizing exercise as lifestyle activity is very important for individuals who have a vulnerability to think negatively about themselves, their world, and their future. We utilize CBT strategies to challenge negative thoughts about exercising, which for individuals with BD is often their most significant obstacle[44, 48]. We also set weekly exercise goals and discuss participants' obstacles to adhering to these goals. Many exercise programs encourage participants to find a "work out partner"[45]. This can be especially problematic for individuals with BD who tend to isolate when depressed or have interpersonal problems when manic[48]. Given that social support is still a very important motivator and can buffer against future episodes[49, 50], we discuss the concept of "structured, group lifestyle activities." Feedback from our pilot groups suggests that this is immensely helpful, even participants with anxiety report that they can tolerate *structured* groups as they do not feel pressure "to perform" or "to interact with others." Some participants from our pilot group have noted that exercising when manic helps them to stay focused and keep their energy level down, while others have reported the opposite effect. Similarly, some participants reported choosing to exercise in the evening as it helps them to relax and sleep, while others report needing "wind down time" after exercising. By including individuals with manic symptoms, we will learn more about the association of exercise and mania.

C. Wellness Module

This module is integrated throughout the first two modules as it reinforces the importance of making healthy decisions (e.g., food choices, exercise, increasing behavioral activation) and helps to problem solve obstacles to making these choices. This module is reflected in the use of CBT-based strategies that focus on increasing adherence to the nutrition and exercise modules as well as other healthy choices (e.g., reduction of caffeine, smoking, substance use). For example, we discuss that having 5 to 6 smaller meals throughout the day is an ideal meal plan as it is healthier and enhances their routine and energy level, opposed to using caffeine or smoking as stimulants. We focus on these other lifestyle choices as exercise reduces the craving for smoking[51] and substance use[52] as well as seems to buffer against substance abuse[53].

Similarly, we encourage participants to choose a feasible time every other day to exercise and to use positive rewards when meeting exercise and diet goals. In this module, we also discuss important aspects of behavioral activation, such as balancing mastery and pleasurable tasks and setting appropriate mood-dependent schedules. An important aspect of enhancing healthy lifestyle choices is accounting for mood-specific shifts in their activation. For example, during (hypo)manic episodes bipolar individuals tend to be impulsive and overly energetic, and thus their lifestyles often become chaotic and erratic. In contrast, during depressive episodes, bipolar individuals lose this behavioral activation and thus, tend to isolate or withdraw. In this module, we stress the importance of having two feasible choices or plans: one for elevated moods and one for depressed moods. Both plans emphasize structure and healthy coping behaviors, but the activities vary. We also use reward charts to reinforce healthy decisions and challenge self-defeating thoughts (e.g., "I can't change"). This module also incorporates motivational interviewing techniques which are effective in helping individuals gain insight into their unhealthy behaviors and the need for change[54].

IV. RESEARCH DESIGN AND METHODS

A. Overview

Currently there are no theoretically integrated treatments for the medical burden associated with BD. This is enormously problematic given the increased risk that this medical burden poses for this population's course of illness, functioning, and morbidity. Given the scope of the problem and lack of treatments, leaders in the field have called for further treatment development [14, 15]. Proposed as 18 sessions (45-60 minutes each) over 20 weeks in an individual therapy format, NEW Tx is composed of the following treatment modalities: Nutrition/weight loss, Exercise, and Wellness treatment. A blinded independent evaluator will be used to administer assessments (see Table 1) and an unblinded study coordinator will oversee recruitment and scheduling. As will be described in detail in the following sections, the research study will utilize the intervention modules in two distinct pilot samples:

i. **Phase I:** In the first phase of the study, we will test NEW Tx in a nonrandomized, open trial (n = 6). This pilot group for NEW Tx will be used to test the feasibility of the treatment as determined by participant attendance, therapist adherence to the procedures, and client feedback. All participants in this initial sample will be treated by the Principal Investigator (PI).

ii. **Phase II:** In this phase, we will pilot test the NEW Tx methods compared to TAU (n = 60) to further examine feasibility, to estimate an effect size, and to explore its efficacy for reducing medical burden. TAU will be the control group in the Phase II pilot study as it is the standard treatment in the Massachusetts General Hospital (MGH) Bipolar Clinic and Research Program. Participants randomized to TAU who complete the first 20 weeks of the study will have the option to receive NEW Tx. TAU participants who chose to receive NEW Tx (the waitlist group) will follow the same procedures as the NEW Tx group over an additional 20 weeks such that they will have assessments at Weeks 30, (mid-treatment), 40 (post-treatment), and 52 (follow-up) (see Table 2). For TAU, medication and dosage changes are allowed as needed as long as the change is recommended based on the guidelines and participants remain on a mood stabilizer. Medication changes will be monitored with the Clinical Monitoring Form Medication Module. All participants will have a three-month follow-up visit during which post-treatment measures and assessments will be repeated. Participants will be recruited with the same criteria as the nonrandomized trial, but will be randomized using a 1:1 allocation ratio with a blocking strategy. The assessments will be similar to those used in Phase I. In addition to the study staff utilized in Phase I, clinicians with training in CBT and mood disorders will be added as NEW Tx therapists.

B. Participant Selection and Recruitment

Participants (n = 6 for the open trial phase; n = 60 for the randomized phase) will be recruited from within as well as outside the MGH Bipolar Clinic and Research Program, and we plan to recruit 1 participant per month for the Phase I open trial and 2 participants per month for the Phase II randomized trial. Some subjects will be self-referred, whereas others will be referred by MGH or community clinicians. Some subjects may be obtained from media advertisements. Potential participants will not be identified through medical records, and the researchers will not contact potential participants without their permission. If a clinician feels that one of his or her patients would be potentially appropriate for this study, the patient will be encouraged to contact the PI or the research assistant directly. Alternatively, the clinician may ask the patient to give permission to be contacted over the phone by either the PI or the research assistant. Written IRB approved informed consent will be obtained from all patients before protocol-specified procedures are carried out.

Patients may be referred to the study by their treating clinicians in the MGH Bipolar Clinic and Research Program, and will be recruited according to the following criteria:

i. Inclusion Criteria

- □ Diagnosis of Bipolar Disorder (Type I or II), which is the primary focus of treatment
- □ Ability to give informed consent
- □ Currently ill (CGI-BP ≥ 3)
- □ Age > 18 years and < 65 years
- □ Overweight individuals (BMI > 25); those with BMI of 25-30 must also have high rate of percentage of body fat (greater than or equal to 32% for women and 25% for men)

ii. Exclusion Criteria

- □ Unwilling/unable to comply with study procedures
- □ Endorsed item, confirmed by patient's physician, on the PAR-Q
- □ Euthymic (CGI-BP < 3)
- □ Diagnosis of anorexia nervosa or bulimia nervosa in the past month
- □ Diagnosis of substance dependence in the past month
- □ Active suicidality (MADRS item 9 score > 4)
- □ Pregnant (as analyzed by a urine pregnancy test)
- □ Exercising regularly (i.e., 5 days per week for 30 min)
- □ Neurologic disorder or history of head trauma
- □ Contraindications to exercise or diet interventions (e.g., co-morbid nutritional and metabolic diseases, physical injuries)

An EKG will be required for participants over the age of 40, if clinically indicated, to further minimize potential risks associated with exercising. For clinical monitoring and assessment of adverse events, a fasting blood draw will be conducted at Week 0, Week 10, and Week 20. For the waitlist group (i.e., TAU participants who choose to receive NEW Tx after 20 weeks), fasting blood draws will be conducted at Weeks 30, Week 40, and Week 52, in addition to the aforementioned draws. Drug screens will not be required; however, administration of drug screening as part of ongoing treatment is at the discretion of the treating physician at any time after consultation with the participant.

C. Diagnostic and Clinical Assessments

i. **Extended Mini-International Neuropsychiatric Interview** (MINI[57]) will be used to establish DSM-IV diagnoses including BD, substance use, and eating disorders.

ii. **Demographics, Medical History,** and **Psychiatric History** forms will assess any pertinent medical or psychiatric conditions that may impact the participants' eligibility or treatment in this study.

iii. **Montgomery Asberg Depression Rating Scale** (MADRS[58]) is a 10-item clinician-rated measure of depression that assesses the presence and severity of patient's current depressive symptoms.

iv. **Young Mania Rating Scale** (YMRS[59]) is an 11-item, clinician-rated measure that assesses the presence and severity of patient's current symptoms of mania.

v. **Clinical Global Impression-Bipolar Illness** (CGI-BP[60]) is a one item illness severity score that is a widely accepted, reliable, and valid assessment of global illness in BD[61]. The CGI-BP is a modified version of the CGI designed specifically for use in assessing global illness severity in patients with BD. This version assigns ratings for mania, depression, overall severity, and side effects.

vi. **Clinical Monitoring Form** (CMF) Medication Module[62] will track medication and dosage changes and whether the subject is taking medications for blood pressure (used to calculate the FSR score).

vii. **Food Diaries** or a self-report record of foods and calories consumed will be completed by participants between study visits as needed. Selected food diaries will be reviewed by a dietician (as needed).

viii. **Exercise Questionnaire** (EQ) is a modified version of the Exercise History and Attitude Questionnaire which has been used in a wide variety of settings[63, 64]. It is typically administered to healthy populations; thus, some items were excluded that were not likely to pertain to BD. This questionnaire assesses baseline (i.e., past) exercise history as well as ongoing exercise duration and frequency at follow-up study visits[65].

ix. **LIFE- Range of Impaired Functioning Tool** (LIFE-RIFT[66, 67]) assesses the extent to which medical burden has impacted current functioning.

x. **Framingham Risk Score** (FRS) will be used to estimate medical burden as it is designed to estimate risk in adults (age > 20) to predict 10-year risk for myocardial infarction and coronary death. The FRS is calculated

based on six indices: age, gender, total cholesterol, HDL cholesterol, smoker (Y/N), systolic blood pressure, and medications to treat high blood pressure (Y/N). It is one of the most widely validated and cited clinical prediction scores, and although several modifications have been proposed, a recent review of over 1900 studies found that these studies had "flaws in their design, analyses, and reporting that cast some doubt on the reliability of the claims for improved prediction"[68]. The Medical History form will collect the patient data necessary to calculate the FRS score.

xi. **Physical Activity Readiness Questionnaire** (PAR-Q[69]) is a seven-item, self-report questionnaire to screen individuals for starting an exercise program. In addition to the PAR-Q, an EKG will be required for participants over the age of 40, if clinically indicated, to further minimize potential risks associated with exercising.

xii. **Credibility/Expectancy Questionnaire** (CEQ[70]) is a 6-item, self-report questionnaire to assess patients' perceptions of and expectations for treatment before the study begins.

xiii. **Client Satisfaction Questionnaire-8** (CSQ-8[71]) is a reliable and valid self-report of participants' acceptability of treatment. This is an assessment of client/patient satisfaction with their care and perceived quality and tolerability of NEW Tx.

xiv. **NEW Tx Scale** is a 10-item scale to assess participants' acceptability of NEW Tx. This scale also includes a comments section to solicit unstructured feedback from participants on NEW Tx.

xv. **Post-Treatment Questionnaire** is an open-ended, 3 question measure that asks participants to identify aspects of the treatment that were helpful or not helpful and that could be improved.

xvi. **Intent to Attend**[72] is a single item that measures participants' intent to attend the next study visit which will be used in part to inform the extent to which attrition is ignorable[73].

xvii. **DXA scans** measure total body composition and fat content using low-dose x-rays.

xviii. **University of Rhode Island Change Assessment Scale** (URICA) is a 32-item, self-administered measure that is a reliable and valid measure of motivation and intention to change at entrance to treatment.

xix. **Metabolic Cart Assessment**—Metabolic Cart Assessment—A metabolic cart is an electronic medical tool that is used to measure basal metabolic rate and can be used by medical professionals to determine someone's overall health condition. his test indirectly measures how much energy a person's body uses at rest by measuring the amount of oxygen a person consumes versus the amount of carbon dioxide a person expends.

Table 1. Schedule of Assessments for the NEW Tx and TAU groups

Weeks	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**16**	**18**	**20**	**32**
	Pre										Mid							Post/ ET	Follow -Up
MINI	x																		
Medical Hx	x																		
Psychiatric Hx	x																		
Demographics	x																		
PAR-Q	x																		
CGI-BP	x										x							x	x
Blood Draw**	x										x							x	x
Vitals	x										x							x	x
DXA scan	x																	x	
CMF	x										x							x	x
MADRS	x										x							x	x
YMRS	x										x							x	x
LIFE-RIFT	x										x							x	x
NEW Tx Scale																		x	x
CEQ	x																		
CSQ-8																		x	x
URICA	X																	x	x
Met Cart	X																	x	
Post-Tx Questionnaire																		x	x

EQ	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Intent-to-Attend†	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Food Diaries†	x	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x	x[1]

ET= Early Termination. Vitals = Height (at Week 0 and Week 20), weight, waist circumference, blood pressure, pulse, and Dual X-Ray Absorptiometry (i.e., body composition). ** Includes lipid profile (i.e., cholesterol, triglycerides), metabolic panel (i.e., blood urea nitrogen (BUN), creatinine (Cr), electrolytes, blood glucose level), complete blood count (CBC), and thyroid stimulating hormone (TSH). C reactive protein (CRP) and inflammatory marker panels (Human TH1/TH2 10-Plex (IFN-g, IL-1b, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, TNF-a)) will be included at pre- and post-treatment visits. A urine pregnancy test will be administered at Week 0 to determine eligibility. An EKG will be completed at Week 0 for participants ≥ 40-years-old, if clinically indicated.
[1] As needed.
†For the TAU group, will only be collected at Weeks 0, 10, and 20

Table 2. Schedule of Assessments for the Waitlist Group (TAU participants who choose to receive NEW Tx)Weeks	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**52**
										Mid-tx										Post-tx	Follow-up
CGI-BP										x										x	x
Blood Draw**										x										x	x
Vitals										x										x	
DXA scan																				x	
CMF										x										x	x
MADRS										x										x	x
YMRS										x										x	x
LIFE-RIFT										x										x	x
NEW Tx Scale																				x	x
CSQ-8																				x	x
URICA	x																			x	x
Met Cart	x																			x	
Post-Tx Questionnaire																				x	x
EQ	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Intent-to-Attend	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Food Diaries	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]

ET= Early Termination. Vitals = weight, waist circumference, blood pressure, pulse, and Dual X-Ray Absorptiometry (i.e., body composition). ** Includes lipid profile (i.e., cholesterol, triglycerides), metabolic panel (i.e., blood urea nitrogen (BUN), creatinine (Cr), electrolytes, blood glucose level), complete blood count (CBC), and thyroid stimulating hormone (TSH). C reactive protein (CRP) and inflammatory marker panels (Human TH1/TH2 10-Plex (IFN-g, IL-1b, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, TNF-a)) will be included at pre- and post-treatment visits. A urine pregnancy test will be administered at Week 0 to determine eligibility.
[1] As needed.

D. Independent Evaluator Training

The independent evaluators will receive instructions and observe the other trained independent evaluators in the BCRP, who have extensive experience in administering the study assessments.

E. Clinician Training

New therapists utilized in Phase II of the study will be trained by the PI. The therapists will be required to demonstrate understanding of the theoretical rationale for each module of NEW Tx, knowledge of BD, and proficiency in the strategies and techniques used to achieve treatment goals. Specific training components will include: (1) reviewing the procedures with PI; (2) role playing NEW Tx techniques; and (3) ongoing weekly supervision with the PI to review their sessions.

Some treatment sessions will be taped to ensure treatment integrity. The PI will review selected audio files and give feedback to the NEW Tx therapists. Audio recording is optional, so participants may opt out and still participate in the study. Audio files will be recorded with a microphone connected to a Partners computer. Files will be uploaded and saved directly to the BCRP secure network, they will not be saved as hard copies. Audio files will be labeled with the subjects' study IDs and not their names. Files will be sent to the PI through Partners Secure File Transfer (http://rc.partners.org/sFTP).

F. Targeted Enrollment

We expect to recruit a representative sample of Boston, MA, the location of our research site (see Table 3 and Table 4)[74]. We expect that our sample will resemble the general population given that current studies in the MGH Bipolar Clinic and Research Program are meeting or exceeding this minority representation.

Table 3. Minority Representation in Boston, MA

Racial/Ethnic Category	Boston, MA*
Race	
White	76.1%
Black or African American	14.4%
American Indian and Alaska Native	0.4%
Asian	7.8%
Native Hawaiian and Other Pacific Islander	0.1%
Ethnicity	
Hispanic or Latino	10.5%
White Persons, Not Hispanic/Latino	68.1%
Other	21.4%

*Suffolk & Norfolk Counties

Table 4. Expected Enrollment by Race, Ethnicity and Gender

TARGETED/PLANNED ENROLLMENT for Phase I and II Studies (*n* = 60)				
	Sex/Gender			
Ethnic Category	**Females**	**Males**	**Unknown or Not Reported**	**Total**
Hispanic or Latino	6	6		12
Not Hispanic or Latino	18	18		36
Unknown (individuals not reporting ethnicity)	6	6		12
Ethnic Category: Total of All Subjects	30	30		60
Racial Categories				
American Indian/Alaska Native	0	0		0

Asian	3	3		6
Native Hawaiian or Other Pacific Islander	0	0		0
Black or African American	4	4		8
White	23	23		46
More Than One Race				2
Unknown or Not Reported				6
Racial Categories: Total of All Subjects	30	30		60

V. POTENTIAL BENEFITS

Participants may be reimbursed for up to $20/visit for travel-related costs as needed. Additionally, at two points during the 20 week treatment (one around midway and one around the end) participants will receive $10, for a total of $20, as part of their work with NEW Tx therapists to set and achieve treatment-related goals.

The proposed research study involves an intervention that holds the potential for direct individual benefit. This research will further our knowledge about medical burden in BD and the feasibility of psychosocial treatment to reduce this burden. Risks of discomfort associated with NEW Tx should be offset by the potential physical and mental health benefits. Thus, this study has the potential to not only improve the treatment of BD patients, but also advance the field by developing a treatment that can be used in future treatment studies of BD.

VI. RISKS AND DISCOMFORT

The risks that the Phase I and II trials pose to participants are reasonable in relation to the anticipated benefits because BD is associated with a disproportionately high medical burden as well as chaotic mood swings and a high rate of functional impairment. As the NEW Tx represents an augmentation of standard treatment with an experimental psychosocial intervention, the additional risk is small, justifiable given the potential benefits, and is at least as favorable as alternative approaches.

A. Potential Risks to Subjects

There is a possibility that study patients will not improve from this treatment. During the study assessments, subjects may also experience some discomfort from discussing personal material and completing self-report questionnaires. Subjects may also experience some discomfort from the blood draw. Participants will be exposed to radiation from two DXA scans. The total amount of radiation exposure is equal to a whole body exposure of approximately 16 microSieverts. A microSievert is a unit of radiation dose. This amount of radiation is about the same as you would normally receive in 2 days from natural background sources from the earth and the sky. Participants will also participate in a metabolic cart assessment, in which a clear plastic canopy will then be fitted over the head and upper chest of the participants to collect the air the participant exhales for 15 minutes. Participants may experience some discomfort or anxiety.

There is a risk of breach of confidentiality and loss of privacy, which great care will be taken to prevent.

B. Protection Against Risks

We will take precautions to ensure that potential risks are minimized. All treatments will be provided by at least master-level mental health professionals with experience in CBT and mood disorders. NEW Tx therapists will be closely supervised by the PI. In the case of an emergency, the NEW Tx therapist will page the PI. If the PI is unavailable, the covering clinician will be paged. If immediate assistance is required, the participant will be directed to call 911 or go to the MGH Acute Psychiatric Service. The following procedures will also ensure participant safety:

i. All participants who fail to respond to treatment or withdraw prematurely will be referred for alternative treatment. If withdrawal from the study is necessary, we will provide appropriate referrals for other treatment. The PI, or the covering clinician, will be available to discuss the study, alternative treatments, or any concerns about the study with subjects if requested by the participant, therapist, or independent evaluator.

ii. Ratings on the MADRS suicide item will be monitored during the open trial (Phase I) and the randomized trial (Phase II). Participants' with a suicidality score greater than 4 at Week 0—for either trial—will be excluded from the study.

iii. Participants' NEW Tx therapists will be available to them to discuss any concerns throughout the treatment period. The PI, or a covering clinician from the MGH Bipolar Clinic and Research Program, will make every effort to be available at all times to study participants in the event of a clinical emergency. However, if immediate assistance is required, the participant will be directed call 911 or go to the MGH Acute Psychiatric Service which is open and staffed 7 days a week, 24 hours a day. Participants will be withdrawn from either the open trial (Phase I) or the pilot study (Phase II) if their clinical condition deteriorates substantially. Participants may also be withdrawn if, in the judgment of the study investigators, remaining in the study poses a substantial risk to the participant or a higher level of care is needed.

C. Ensuring Confidentiality

To ensure protection of confidential information, all data will be coded and stored in locked files in the MGH Bipolar Clinic and Research Program. Names will not be included in computerized data files or in any published reports. Case records will be reviewed only by study personnel or, if necessary, by institutional, state, or federal regulatory personnel. All research personnel will have completed the Collaborative Institutional Training Initiative (CITI) Program on-line training and final exam, be well versed in Health Insurance Portability and Accountability Act (HIPAA) regulations and procedures, and be approved as study staff by the IRB. All HIPAA guidelines will be followed and all research personnel will be educated about the importance of strictly protecting participants' rights to confidentiality.

VII. DATA COLLECTION

All data collection will adhere to HIPAA regulations. Data will be obtained specifically for research purposes and managed using the REDCap system. Data on feasibility and satisfaction of NEW Tx as well as medical burden, BD symptoms, and functioning will be collected via patient self-report, clinician- and rater-administered assessments. These data will be used to evaluate treatment feasibility and acceptability, treatment integrity, efficacy, and possible mechanisms of change. Data assessing safety and adverse events will be collected through blood analysis.

A. Safety and Monitoring

There will be a Data Safety and Monitoring Board (DSMB) for this study composed of three investigators who have experience in clinical research, clinical treatment of BD, and specifically overseeing the safety of participants in bipolar trials. This DSMB will monitor safety issues, including the review of adverse events, the PI's quarterly report of the study's progress, all IRB amendments, the adequacy and integrity of accumulating data, and the capability of the Phase I and II trials to test the hypotheses. The purpose of this process is to assess scientific integrity and patient safety issues, and ensure the ethical conduct of the trials. The DSMB will approve the initiation of the study and subject enrollment, and determine if study procedures should be altered or stopped due to evidence of benefit or harm to trial subjects that may be attributable to NEW Tx or reasons related to scientific integrity. The PI will submit quarterly reports to the DSMB detailing any study changes, adverse events, subject recruitment and retention, reasons for early termination, and ongoing data reports. The PI will also respond to all DSMB issues and queries.

B. Adverse Events

Any serious adverse events (e.g., death, suicide attempt, hospitalization) will be reported within 24 hours to the IRB and the NIMH program officer. A full written report of the event will be sent to the above entities within 10 working days of the event's occurrence. All adverse events will be assessed for the events' severity/intensity, expectedness, relatedness to NEW Tx, clinical outcome, and any action taken due to the event. Any adverse event (e.g., causing interference with usual activities or requiring treatment) and which appears definitely, probably, or possibly related to study participation will be tracked and reported to the IRB at the yearly continuing review. Any serious adverse events will be summarized in the NIMH, DSMB, and IRB annual progress reports. We will also inform the NIMH, DSMB and the IRB of actions, if any, as a result of their continuing review.

VIII. DATA ANALYSIS

Baseline demographic and clinical characteristics will be examined by the PI in collaboration with Steve Farone, Ph.D., Professor of Biostatistics. Measures of central tendency and variability will be estimated on each continuous measure; proportions estimated for categorical variables. Transformations will be used when distributional assumptions are not fulfilled for inferential tests. Dropouts and completers will be compared on baseline variables using Mann-Whitney or chi-square tests.

A. Data Management: REDCap

To ensure the quality of electronic data capture (EDC) and management, the data management team will use the REDCap EDC system. The REDCap Consortium is comprised of 135 active institutional partners and it supports two secure, web-based applications (REDCap and REDCap Survey) designed to support data capture for research studies. The REDCap application is currently in production use or development build-status for more than 2990 studies with over 9540 end-users spanning numerous research focus areas across the consortium, and the REDCap Survey application is now being adopted rapidly by consortium partners. Both REDCap and REDCap Survey provide a process for building a database or online survey, an interface for collecting data, data validation, and automated export procedures for data downloads to statistical packages (SPSS, SAS, Stata, R).

REDCap allows users to design and implement study scales to collect, store, retrieve, and manipulate data electronically. The REDCap platform for EDC that streamlines data collection and management, and the system is a study management tool used to monitor visit timing and completion in real-time, thus helping to minimize missing data. REDCap is already used at MGH for treatment studies and has proved extremely useful for conducting and managing studies. It obviates the need for data entry by staff, thus minimizing cost and human error. Furthermore, because data quality control checks can be built into the logic of the online measures, problems can be identified in real-time, thereby improving data quality and consistency.

Research staff will enter scale and assessments responses into the REDCap electronic assessment forms. Using 128 bit RSA Secure Socket Layer (SSL) encryption, approved users will be logged-in to machines using secured browsers behind the Partners Healthcare Systems IS corporate firewall or the RIH firewall. Staff will have a unique identifying key that will link them to the electronic study forms. This unique ID will be used in addition to a randomly generated secure password that only the staff person will have. Additional confidentiality procedures are detailed in the Human Subjects section.

B. Statistical Analyses Plan for Research Aims

Each of the statistical tests below will use a two-tailed alpha-level of 0.05.

i. **Aim 1: Feasibility in Nonrandomized Trial (Phase I).** *Hypothesis 1a*: Descriptive statistics will be used to report the number of intervention sessions attended (we expect > 80%), number of participants recruited per month, and therapist adherence to NEW Tx (average adherence score ≥ 6). *Hypothesis 1b*: Participants will report high satisfaction (total CSQ-8 score, M > 24[75]) with the treatment and acceptability (total NEW Tx Scale score, M<25, or at least an average score of "agree" on half of the items).

ii. **Aim 2: Feasibility in Randomized Trial (Phase II).** *Hypothesis 2a*: Descriptive statistics will be used to report the number of intervention sessions attended (we expect > 80%), number of participants recruited per month, randomization rate (number randomized/number consented), number of assessment sessions attended (we expect > 80%), and retention (number of study completers/number randomized) (we expect > 80%, which is conservative for diet and exercise interventions for severe mental illness[25, 76-78]) and therapist adherence to NEW Tx (average adherence score ≥ 6). *Hypothesis 2b*: Participants will report high expectations (CEQ score) for the treatment and high satisfaction and acceptability (CSQ-8, Post-Tx Questionnaire, NEW Tx Scale).

iii. **Aim 3: Exploratory Aims (Phase II).** *Hypotheses 3a and 3b*: Between treatment group effects sizes (and 95% CI) will be calculated. To supplement this, Mann-Whitney tests will compare treatment groups on medical burden (as measured by FRS) (*Hypothesis 3a*) and on improvement in symptoms (MADRS, YMRS) and functioning (LIFE-RIFT) (*Hypothesis 3b*) based on change from baseline. *Hypothesis 3c.1*: We will investigate baseline BMI as a potential moderator of treatment response. The focus will be on the magnitude of the effect, not on significance testing. The between treatment group effect sizes (i.e., FRS, MADRS, YMRS, LIFE-RIFT) will be compared with those who have high baseline BMI (> 30) versus low BMI (< 30). *Hypothesis 3c.2*: Mastery of the diet (Nutrition Data System score of food diaries) and exercise (weekly exercise duration from Exercise Questionnaire) modules will mediate the association of NEW Tx and improvement in medical burden (FRS). The

dependent variable will represent change in the FRS score from time of completion of respective module. The mediators will be tested separately. Differential between treatment group effect sizes for those who did and did not master the modules will provide evidence of a mediator of treatment.

C. Rate of Attrition

Some attrition (i.e., 20%) is expected and this can result in bias and reduce power, precision and generalizability[79]. Consistent with the Intent to Treat principle[80], we will continue with the assessments for the study duration, even among those who fail to comply with the treatment[81]. As one aspect of the feasibility study, we will assess the likelihood to attrite using the "Intent to Attend" measure[72].

D. Power Analysis

The sample sizes for the Phase I and II trials are based primarily on the fundamental aim of this project: feasibility. The *N* is not based on what is needed for inferential analyses as they are not a fundamental aspect of the design. Power analyses are not indicated for the proposed exploratory analyses. We acknowledge that we will not have sufficient power to detect large effects (e.g., $d = .80$).

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