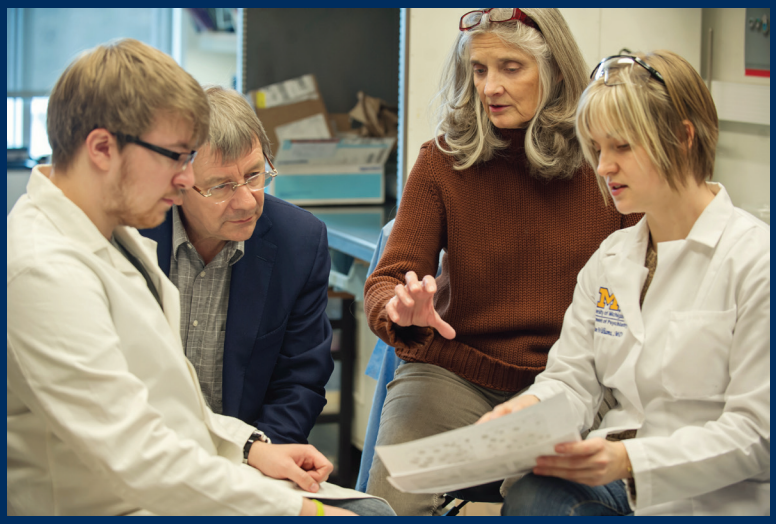

VISION › › To personalize treatment of bipolar disorder and prevent recurrences to enable those with bipolar disorder to lead healthy and productive lives.

DEPRESSION CENTER
HEINZ C. PRECHTER BIPOLAR RESEARCH FUND
UNIVERSITY OF MICHIGAN

2015 Bipolar Research Retreat Abstracts

Table of Contents

Mobile Self-Management Application for Bipolar Disorders

Background: Medications alone are insufficient at alleviating the complex set of symptoms, physical outcomes and psychosocial consequences created by bipolar illness. Despite ample knowledge of the need for innovative psychosocial programs, few interventions exist in online or mobile formats (e.g., mobile applications, or apps) that are easily accessible to patients. Apps that do exist are often simple tracking tools that do not provide active learning or skill building. In addition, many of the available mobile apps are not founded in evidence-based treatment for bipolar illness.

Hypothesis: Life Goals Collaborative Care (LG-CC), which includes self-management components, has been found to be effective in improving physical and mental health outcomes in several controlled clinical trials, including multi-site effectiveness trials sponsored by the VA Cooperative Studies Program and the NIMH. LG-CC is now recommended in national clinical practice guidelines, including the *VA-DoD Practice Guideline for Adults with Bipolar Disorder,* and is listed on Substance Abuse and Mental Health Services Administration (SAMHSA) in the National Registry of Evidenced-based Programs and Practices (NREPP). The intervention is evidence-based, flexible, and has been successfully tested via person, telephone and telehealth settings, leading us to believe that it could be translated into a mobile application for even greater dissemination.

Project: We will develop and pilot test an LG-CC mobile application for patients with bipolar disorder among individuals involved in the Prechter cohort. The purpose of the project would be to see if similar benefits in symptom reduction and improvements in mental and physical health related quality of life, or other measures, could be obtained with the use of an LG-CC mobile application. The objective is to determine whether individuals receiving the LG-CC app have reduced mood symptoms, improved quality of life, and improved social support and sleep. We will identify individuals in the Prechter cohort to participate and, using a lottery method, provide the LG-CC app to half the individuals for six months, and then provide the app to the remaining individuals.

Enhancing our ability to predict affective symptoms in bipolar illness: A comparison of technological and traditional assessment methods

Background: It is unclear what characteristics of sleep and rest/activity assessments we need to have to be useful in either research or clinical settings. Similarly, it is unclear what the "best" way is to assess affective symptoms in bipolar illness (BPI). For the measurement of affective symptoms, it is not yet known whether subjective is better than objective data or whether prospective is better than retrospective data. We hypothesized that real time technological methods (actiwatch and daily use of Mood 24/7 text messaging) would be more predictive of affective symptoms and impairment in functioning than would retrospective and traditional methods.

Project: We conducted a pilot study on 40 participants with BPI that included assessments of affective symptoms completed by participants with BPI at and during two study visits, approximately six weeks apart. This time-series design allowed us to assess change in sleep, mood, and circadian functioning as independent variables versus simply stability/instability as a dependent variable.

Results showed that changes in mood across the study period captured by Mood 24/7 texting was better at predicting depression, mania, and quality of life assessments than other traditional assessments. Subjective assessment of sleep quality was the best predictor of depression, mania and daily rhythmicity. Level of daily activity measured actigraphically was the best predictor of depression, mania, and quality of life. Finally, subjective rating of sleepiness at bedtime was better at predicting mania and daily rhythmicity than other assessments.

The next steps to this project are twofold: 1) to replicate the utility of real time technological methods and activity monitoring to predict affective symptoms. 2) To utilize the data collected from technological methods to provide personalized therapy. A therapeutic approach designed to stabilize changes in mood, sleepiness ratings will limit the transition from euthymia to a manic or depressive episode.

Gut Feelings – Targeting the Microbiome to Reduce Disease Burden

Background: The gut microbiome is emerging as an important factor in the regulation of mental and physical health, including roles in anxiety and depression. The complement of microbes that live in the human intestinal tract not only aids in digestion but also contributes to brain function throughout the lifetime by communicating directly through the gut-brain nervous system and releasing hundreds of bioactive metabolites into the blood stream. We have surveyed the composition of the gut microbiome in Prechter Study volunteers and have found many significant differences between individuals with bipolar disorder and controls.

Hypothesis: Our current studies have found associations between specific bacteria in the microbiome and self-reported depression, anxiety, mania, sleep quality and general physical health; primarily with reduced numbers of beneficial bacteria in individuals with bipolar disorder. Furthermore, diet is a known major factor in controlling microbial composition in the gut and we have found specific associations between nutrient intake and bacterial counts. We hypothesize that a pre-biotic supplement will boost beneficial bacteria and decrease burden of disease measures in bipolar individuals.

Project: We propose to (1) provide prebiotic supplements to 100 research volunteers, (2) collect baseline and follow-up stool samples for analysis, (3) collect blood samples for analysis, and (4) test for effects on improvements in depression, anxiety, mania and sleep quality.

Mood State Prediction from Speech Collected Across Multiple Phone Models

Background: Speech contains acoustic patterns that can be altered by the mood of an individual. This has motivated researchers to investigate how speech can be automatically collected and analyzed to provide insight into the wellbeing of individuals suffering from mental disorders. However, the challenge is that as speech collections become increasingly distributed, the effect of the recording devices becomes increasingly problematic.

Hypothesis: Different processing techniques can be used to account for differences in phone type, environmental noise, and speaker variations. It is critical that we understand these steps to mitigate problems in recordings in order to expand the reach of these technologies.

Project: This presentation explores speech collected from phone recordings for the analysis of mood in individuals with bipolar disorder as part of the PRIORI project. We describe the two phone models that we use and highlight their different properties. We present methodologies at three levels (preprocessing, feature extraction, data modeling) to make the phones more comparable. We find that the use of these methods results in systems that perform significantly more accurately than baseline systems that do not. The results promote the feasibility of distributed mobile mental health monitoring using speech. Future research will explore how to account for other differences including subject variations.

Using mathematical models to understand bipolar disorder

Background: Current classification in bipolar disorder (BP) reflects a common understanding of clinical observations but is not empirically based and has yet to elucidate disease etiology. Mathematics can be used to objectively classify patients based on each individual's longitudinal pattern. Such an approach can enhance similarity of outcomes within classes, thereby guiding precise care of patients, along with future research into causes of BP.

Hypothesis: We developed mathematical methods that revealed three new classes of BPI, with different clinical phenotypes defined by attempted suicide rates, disability status, and chronicity of affective symptoms. We hypothesize that patient-specific modeling of detailed outcomes can establish clear expectations for future mood episodes and offer new insights into mood variation.

Project: This project will develop models to describe patient-specific, longitudinal survey scores of mood in BP. Guided by longitudinal data, we aim to test 1) common conceptions about mood in BP, 2) whether patient-specific models can predict future mood episodes, and 3) new principles about mood variation in BP.

Giant ankyrin-G and the organization of critical neuronal domains: Link to neuropsychiatric disease?

Background: In the vertebrate nervous system, a large 480 kDa splice variant of ankyrin-G (*ANK3* gene) is responsible for the formation of the axon initial segment and nodes of Ranvier, critical sites of clustered voltage-gated sodium channels that are necessary for normal neuronal signaling. A truncating mutation in the giant exon of ankyrin-G causes autism and marked cognitive dysfunction (IQ less than 50) in humans. Importantly, ankyrin-G also has been linked to bipolar disorder in genome-wide association studies. The 480kDa splice variant of ankyrin-G is also necessary for the formation of inhibitory connections in the cortex and hippocampus. Interneurons that release aminobutyric acid (GABA) are a major source of inhibitory signaling in vertebrate nervous systems, and defects in these circuits are strongly associated with neuropsychiatric disorders.

Hypothesis: Our laboratory examines how human variants affect the formation of inhibitory circuits in mouse models and in samples derived from human patients with the hopes of identifying therapeutic pathways for the restoration of these critical neuronal connections. Our hypothesis is that human mutations in *ANK3* are affecting formation of critical circuits required for normal neuronal function.

Project: We will perform the following studies: (1) assess the *ANK3* genotype of patients participating in the Prechter study by direct Illumina sequencing; (2) work in collaboration with Dr. Sue O'Shea to generate induced pluripotent stem cell-derived neurons carrying these mutations; (3) measure the effects of these mutations on ankyrin-G protein levels and function in formation of critical circuits.

Black-White Differences in Concordance between Clinician- and Patient-Rated Measures of Depression and Mania

Background: Clinician- and patient-rated measures are being routinely used in research and practice with individuals with bipolar disorder (BD). However, the level of concordance between these measures overall, and across populations, is still unclear. Our pilot findings show consistently stronger YMRS - ASRM as well as PHQ-9 - HAM-D correlations among Blacks compared to Whites. We still do not know the exact mechanism behind higher concordance between these measures among Blacks in comparison to Whites.

Hypothesis: We hypothesize that Blacks and Whites with BD and controls are different in the agreement between the clinician- and patient-rated measures of the illness burden.

Project: We will use baseline and longitudinal data from the Prechter Longitudinal Study of Bipolar Disorder (BD). White and Black individuals with BD and controls will be enrolled. Demographic (age, gender), socio-economic (employment, education, and marital status), and clinical (comorbid disorders, rapid cycling) factors were measured. We will use data from *Young Mania Rating Scale* (YMRS), the *Altman Self-Rating Mania* (ASRM), the *Patient Health Questionnaire (*PHQ-9*)*, and the *Hamilton Depression Rating Scale* (HAM-D) among patients with BD and controls. Severity of mania (YMRS and ASRM) and depression (*PHQ-9 and* HAM-D) will be measured at baseline and over time. In the first step we will use the pooled sample of BD and controls to test correlations between YMRS*,* ASRM, PHQ-9, and HAM-D. We will then assess the same correlations across race groups.

Stem Cell Models of Bipolar Disorder

Background: Recent advances in stem cell biology now make it possible to derive stem cells from adult tissues, such as skin. This represents a significant advance in studying the causes of neuropsychiatric disorders, since living brain cells are not available. Prior to the availability of patient stem cells, scientists used "proxy" tissues including saliva, blood cells, or neurons and glia from the olfactory mucosa to study mood disorders, while others have used postmortem brain samples. Obviously, proxy tissues do not often behave like brain cells, and postmortem samples are problematic since they represent a lifetime of degenerative changes, making it hard to study the cause of diseases that affect the nervous system.

Project: Remarkably, scientists have determined how to "reset the biological clock", taking adult cells and causing them to behave as though they were derived from embryos rather from mature cells such as skin cells. This amazing new technology has allowed us to take small samples of skin from patients diagnosed with bipolar disorder and from non-diagnosed controls, and reprogram them to stem cells. The stem cells can then be coaxed to form any of the tissues in the adult body. This allows us, for the first time, to carefully study the development of a neuron in a tissue culture dish, to find out how bipolar neurons might be different from controls. A second major technological breakthrough has been the development of a microscope that can be placed in a tissue culture incubator, so that we can monitor the differentiation and behavior of these cells—sometimes over weeks. We have been very fortunate to be able to purchase an Incucyte Zoom for our stem cell studies! We will show the transformation of skin cells to stem cells, how cells differentiate into neurons and respond to different substrates. Finally, Mitchell Smith will present his work studying how the stem cells from bipolar and control individuals self-organize to form "brain organoids".