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HEINZ C. PRECHTER BIPOLAR RESEARCH PROGRAM
MICHIGAN MEDICINE

CELEBRATING 20 YEARS OF PARTNERSHIP

A Letter From Our Director
Melvin McInnis, M.D., FRCPsych

I like anniversaries! There are many reasons. First and foremost, they provide a basis for reflection and an appreciation for what we have, who we are, the journey we have traveled, and, most importantly — they prepare us for the road ahead. Anniversaries give us confidence. We see what we have accomplished and reflect on those who have made everything possible. We celebrate. We splurge a bit — enjoy delicacies. Anniversaries and birthdays are forever associated with cake. And a birthday cake is so much more than the details of the recipe.

This is a year of celebration! **It has been 20 years since the establishment of the Heinz C. Prechter Bipolar Research Program at the University of Michigan,** which includes, among its many research projects, the Longitudinal Study of Bipolar Disorder, the longest running study of bipolar disorder in its class. Our Program has, however, become so much more than scientific protocols and papers. The Prechter Program celebrates the individual and engages those living with bipolar disorder in a partnership to advance scientific knowledge about this condition. We engage with research teams worldwide to develop strategies and implement methods to get closer to the core of this condition — asking continuously: How can we enhance and improve the lives of countless people and families whose lives are affected daily by bipolar disorder?

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Melvin G. McInnis, M.D., FRCPsych
Thomas B. and Nancy Upjohn Woodworth Professor of Bipolar Disorder and Depression
Professor of Psychiatry
Director, Heinz C. Prechter Bipolar Research Program

We celebrate our community that is a constant source of energy and inspiration for the mission of the Prechter Program. We celebrate the researchers and support teams throughout the University of Michigan that share our vision of a fulfilled and meaningful life for all people living with bipolar disorder. I truly delight in engaging with the rainbow of administrative teams that are behind us, as prior to getting to the issues at hand, they often ask me: "How is the project going?" They love hearing the updates and are very much a part of a dedicated team that feels ownership of our collective mission.

The Prechter Program celebrates the legacy of Heinz Prechter, a community visionary dedicated to humanity whose energy and creative insight changed the world.

We celebrate the dedication and determination of Waltraud (Wally) Prechter, founder of the Heinz C. Prechter Bipolar Research Program, who quickly recognized the power of combining community engagement with the energy of the University of Michigan to support clinical research in bipolar disorder. Heinz and Wally's daughter, Stephanie, is bringing her insights and creative talent to the community leadership of the program — another reason to celebrate!

Most importantly, we celebrate you! You are reading this because you are interested, engaged, and you care. There is no greater reason for celebration than an engaged community that has shown interest in the Prechter Program and our mission over the past 20 years.

2024 Prechter Program By the Numbers

8 million
Approximate number of people in the U.S. living with bipolar disorder.
(U.S. population: 336,569,834)

40 million
Approximate number of people in the world with a bipolar diagnosis.

15-25
Approximate age of onset of bipolar disorder.

15-20%
Of individuals with bipolar disorder die by suicide.*

1871
Lithium first used to treat mania.

2024
Lithium remains first line treatment.

27%
Of lithium users require no other treatment.

66%
Of lithium users experience a 50% reduction in baseline manic and depressive symptoms.**

228
Distributions of Prechter data in the past 4.5 years.

20
Years since the Prechter Program was established.

1,580
Participants enrolled in the Longitudinal Study of Bipolar Disorder to date.

18
Years our longest participants have been in the Longitudinal Study of Bipolar Disorder.

*Diagnosis and Treatment of Bipolar Disorder A Review; Andrew A. Nierenberg, MD1,2; Bruno Agustini, MD, PhD3; Ole Köhler-Forsberg, MD, PhD1,4,5,6; et al.

**Comparing measurements of lithium treatment efficacy in people with bipolar disorder: systematic review and meta-analysis; Andrea Ulrichsen, Elliot Hampsey, Rosie H. Taylor, Romayne Gadelrab, Rebecca Strawbridge,* and Allan H. Young

BD² Prechter Program team

A study of this size and scope is truly unprecedented in bipolar disorder. This study brings together so many expert clinicians and researchers across multiple institutions to tackle one mission. We are also energized to work in partnership with patient participants to fuel the research on a much larger scale and build a new clinical care network."

-Kelly Ryan, Ph.D.
Associate Director of the Prechter Program

Driving Discovery and Improving Care

The University of Michigan is one of six institutions to launch the BD² Integrated Network (michmed.org/GqZjk), a study sponsored by BD²: Breakthrough Discoveries for Thriving with Bipolar Disorder (michmed.org/eWMxw). This study forms a unique partnership with clinicians, researchers, and individuals with lived experience, and aims to accelerate scientific understanding of bipolar disorder and improve clinical care. With real-time data collection and analysis, this study explores the relationship between biological, physical, psychological, and social factors, and the impact they have on the course of bipolar disorder, treatment choices, and outcomes.

BD² Integrated Network is a longitudinal study that will follow individuals for five years. The goal is for the University of Michigan and the other sites to engage and follow a total of 4,000 people living with bipolar disorder. Researchers will collect clinical and biological measures — including self-reported symptoms, cognitive functioning, data on movement and sleep from Fitbit, brain scans, and other health metrics — over a five-year time span. The purpose of this extensive data collection is to learn from each other and analyze data in real time so that the knowledge can be translated into clinical practice at a much quicker pace.

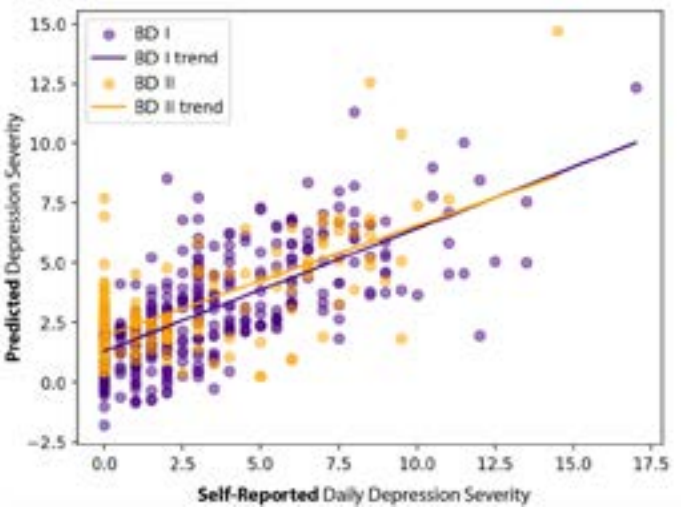
The BD² Integrated Network works to improve the health and well-being of people living with bipolar disorder. Our goal is that everyone living with bipolar disorder will thrive.

Prechter Program associate director and clinical neuropsychologist in the Department of Psychiatry **Kelly Ryan, Ph.D.,** is the site lead for the University of Michigan. Other investigators involved with the study are **Sagar Parikh, M.D., Sarah Sperry, Ph.D., Alexandra Vinson, Ph.D., David Marshall, Ph.D., and Anastasia Yocum, Ph.D.** The Prechter Program is actively recruiting participants living with bipolar disorder who are mostly receiving their psychiatric care through University of Michigan clinics.

BD² Breakthrough Discoveries for thriving with Bipolar Disorder

Excuse Me, What Did You Say?

Monitoring fluctuations in emotion, mood, and functioning through changes in speech



We're working on making it easier to tell how severe someone's mood symptoms are by listening to how they talk, especially for people with bipolar disorder (BD). BD involves shifts in mood from normal to either really high (mania) or really low (depression), which can significantly affect someone's life. Our goal is to find ways to spot these changes in mood as they happen, without making people do anything extra or different. **We're inspired by the idea that you can often detect changes in someone's mood through the way they sound, so we're developing technology that listens to people's voices and picks up on emotional changes.**

Thanks to funding from the National Institutes of Health (NIH), we're planning to study how 160 people talk in their daily lives over the next five years using smartphones equipped with an app called **PRIORI**. The participants will also tell us how they're feeling and we'll have clinical information about their mental health. We're using advanced AI to analyze the emotions in their voices. We're trying to figure out how these emotional clues, along with the participants' own reports of their feelings, can help us understand the severity of their mood swings, whether they're feeling manic or depressed.

The study we're doing with the NIH is built on what we learned from an earlier, smaller, research project, which was funded through generous philanthropic support from Patricia and Jerry Wagner, Jan and David Baszucki, and The Richard Tam Foundation. In that study, we used the PRIORI app to collect voice data and discovered that we could predict how severe a person's mood symptoms might be. For instance, our predictions matched very closely with how the participants said they were feeling each day in terms of depression. Additionally, the information we got from analyzing their speech and the emotions they reported feeling contributed to our prediction model in similar ways.

The long-term goal of this project is to provide innovative AI tools that people with bipolar disorder can use to help manage their illness and improve outcomes.

A New Way to Measure Wellness

People with bipolar diagnoses fill out numerous surveys to help themselves, their clinicians, and researchers understand their health status. These surveys explore engagement in life activities and symptom control that include levels of depression and mania. **But few of these surveys explore well-being in ways that consider what people actually do to help themselves live well.**

Over the past year, the Prechter Program's Bipolar Disorder Learning Community (BDLC) has developed an innovative approach to understand well-being. The BDLC launched in August 2022 as a multi-stakeholder team dedicated to improving care for people with bipolar disorder diagnoses. We are a group of about 15 researchers, clinicians, people with lived experience, family members, data scientists, and program managers that is co-led by **Alexandra Vinson, Ph.D., and Claudia Diaz-Byrd, MSc.**

Together we work to build a Learning Health System — a way of learning from research studies and everyday clinical care that helps us identify areas for improvement and make positive changes to the health care system. To build our Learning Health System, we use cycles of testing new ideas and analyzing their effectiveness to promote learning within the Prechter Program to improve care for people with bipolar disorder. Combining the strengths of our different backgrounds and life experiences is called **"co-production."** We have seen co-production in action as we developed our new Wellness Measure, a survey completed by research participants and patients.

Our Learning Community used the power of co-production to develop better ways to measure well-being. As a team, we developed a measure that is strengths-based and individually-tailored. **The Wellness Measure is strengths-based because it emphasizes things that people are doing that help them to live well, rather than focusing mainly on things that people with bipolar disorder have trouble doing, or ways that their symptoms are affecting them.** It is individually-tailored because people who fill it out list their own priorities, activities, hobbies, and wellness behaviors, rather than selecting from a pre-set list decided by researchers. **This is a powerful advantage because it helps people tap into their own insights about what it takes for them as unique individuals to live well.** We hypothesize that over time this could help people track their own progress, raise their awareness about areas in which they are doing well or less well, and work with their therapist, psychiatrist, and support system to course-correct if needed.

HOW DO WE KNOW THAT THIS NEW MEASURE IS ACTUALLY EFFECTIVE FOR MEASURING WELL-BEING?

We tapped into the power of our multi-stakeholder BDLC Core Team and our Prechter Longitudinal Study participants to scientifically validate the measure. Thanks to the 195 participants who filled out the Wellness Measure, we have been able to use statistics and analysis of open-ended responses to understand if and how the Wellness Measure works. The statistical analysis has been conducted by BDLC members **Dr. Sarah Sperry,** assistant professor of psychiatry and associate director of the Prechter Program, and her graduate student **Audrey Stromberg,** and the results were discussed at our BDLC meetings. The analysis of the open responses has been conducted by the whole BDLC using an innovative workshop format and consensus discussions led by **Dr. Vinson** and **Ms. Diaz-Byrd**. During the workshop, we categorized responses to questions that asked people what activities helped them live well or what they would need to change about their lives in order to live well. The workshop format allowed BDLC members to receive training in how to conduct the analysis and to contribute to developing the results and interpretation during the consensus discussions.

Overall, our approach to designing and analyzing the Wellness Measure has allowed us to combine rigorous methods of measure development and validation with the innovative multi-stakeholder approach of co-production. Our preliminary findings are encouraging — the initial results indicate that the Wellness Measure gives us scientifically valid insight into a person's well-being and helps us understand what well-being looks like through the eyes of people with bipolar disorder. **We would like to sincerely thank the participants in the Prechter Longitudinal Study who helped our efforts by participating in the Wellness Measure!**

As we move forward, the BDLC Core Team will continue to work together to analyze, interpret, and report the results of this investigation of the Wellness Measure. We also hope to publish our results so that colleagues at other institutions can try it out in their own clinics.

Keto Diet for Bipolar Disorder?

Research interest in ketogenic interventions to support mental health has skyrocketed in recent years — ironically, for an intervention that is over 100 years old. Although the ketogenic diet has gained increasing popularity (and scrutiny) in recent years, it is often misunderstood. Invented in 1921, the ketogenic diet was originally intended to mimic the fasting state as a treatment for epilepsy. In the decades that followed, a multitude of pharmacological treatments for seizures were introduced to clinical practice, but the diet remains a cornerstone in the management of pediatric epilepsy, particularly for treatment-resistant cases.

The observation that many of the same treatments for seizures are considered standard of care for the treatment of bipolar disorder — for example, many 'mood stabilizers' are rebranded seizure medications, and lithium was initially used for seizures — led to an intriguing possibility: **could the oldest treatment for seizures, ketosis, also have an effect for bipolar disorder?**

A multitude of studies in recent years sought to answer this question, with preliminary evidence suggesting that the ketogenic diet may be beneficial for some individuals with bipolar disorder. A pilot clinical trial conducted by Dr. Shebani Sethi at Stanford University demonstrated remarkable metabolic and clinical improvements associated with a ketogenic diet among individuals with bipolar disorder

The following is one individual's experience with the keto diet. Individual experiences will vary and research is currently underway to validate the usefulness of the diet in moderating mood symptoms. The keto diet is not a replacement for seeing your doctor or therapist.

Rediscovering My Mind — A Happy Accident

The keto diet and lived experience — written by Prechter Program research participant Nanette Snider.

I am 65 years old and have struggled with bipolar disorder since I was 19. My depressions are crushing, dark, and leave me tearful, listless, and paranoid for months. My manias are impulsive, destructive, and exhausting. As I've gotten older, my moods have become more extreme — so I have kept more and more to myself. An isolated life is not healthy for anyone, especially for someone dealing with bipolar disorder.

For 30 years, lithium tempered my bipolar symptoms, but it upset my stomach and left me exhausted and struggling in the day-to-day.

Two years ago, a doctor I was seeing announced that I needed to start statins and metformin for my physical health — that this medication regimen was the only option, there were no lifestyle solutions. While I waited for an appointment with another doctor for a second opinion, I figured I'd better get busy and make lifestyle changes, or I'd be told the same thing! I knew I needed to lower my blood glucose to address my type 2 diabetes and hypertension, so I decided I would remove sugar from my diet.

I did everything wrong. Decades of dieting had me eating low fat dairy and lean meat. I was eating many small meals a day, and sugar

Jeff Bohnen
U-M Medical Student Researcher on the Keto and Bipolar Disorder study

and schizophrenia, including an average improvement of 31% in clinical global impression (CGI), a measure of mental illness severity, and an average improvement of 23% in high-sensitivity C-reactive protein (hs-CRP) levels, a marker of systemic inflammation.*

A critical question, however, is to what extent potential benefits of ketosis may be accessible through less restrictive diets. Many people may struggle to adhere to the strict degree of carbohydrate restriction necessary for classic ketogenic diets, which is typically less than 20-50 grams of carbohydrates per day — for context, one apple contains about 25 g of carbohydrates. What other options might those people have? A new study at the University of Michigan, made possible by the oversight and support of **Dr. Melvin McInnis** and an impact grant generously provided by the Eisenberg Family Depression Center, seeks to answer that question.

Complex, therapeutic ketosis involves two foundational components: **high levels of ketones** and **minimal spiking of glucose/insulin.**

By combining a ketone supplement (exogenous ketones) with a low-sugar diet (glycemic index dietary changes), researchers hope to emulate some of the conditions of the ketogenic diet with a less restrictive approach. **Exogenous ketones are synthesized ketone molecules** — the molecules our body naturally makes while fasting or when eating a ketogenic diet — which are commonly taken as an over-the-counter sports supplement. **The low glycemic index dietary changes** — intended to reduce blood sugar spiking — were designed with the intention of being as simple and straightforward to implement as possible. Specifically, participants will not consume candy or sweets, not drink soda, replace simple carbs — for example, white pasta or white rice — with complex carbs — for example, brown rice or quinoa — and, if eating fruit, eat it at the end of a meal to minimize blood sugar spikes.

The pilot study will also utilize cutting-edge neuroimaging techniques to assess how diet changes impact brain functioning via functional magnetic resonance imaging (fMRI) and an optional positron emission tomography (PET) scan. Metabolic and inflammatory markers will be measured before and after the 90-day intervention.

*Sethi, Shebani et al. "Ketogenic Diet Intervention on Metabolic and Psychiatric Health in Bipolar and Schizophrenia: A Pilot Trial." Psychiatry Research vol. 335 (2024): 115866. doi:10.1016/j.psychres.2024.115866

was still present in my diet with fruit. After a month, I was ravenous, exhausted, confused, and I had discovered that sugar is in ***everything***.

After three months of being on the keto diet, I had more energy, clarity, and calm. I felt steady and safe enough to start making plans with friends and family again. I looked forward to walking in my neighborhood since I no longer had crippling pain in my joints. My sleep also improved. After five months, my doctor saw improvements in my bloodwork, weight, and blood pressure. Nine months later, my therapist and psychiatrist had noticed newfound clarity, stability, and calm. They saw that I was much more present, and suggested we reduce my lithium dose. My crippling stomach problems stopped and have never returned.

After a year, I had my brain back! I could sew, read, play cards, and I was a much better friend.

I had been free of all my bipolar disorder symptoms for over a year when I discovered that others with bipolar disorder had also experienced drastic reductions in their symptoms after they switched to using ketones as a fuel source instead of glucose.

Two years later, I'm on a 150 milligram maintenance dose of lithium and am finally sleeping through the night for the first time in decades. My A1C is 5.2 and I am no longer pre-diabetic, my blood pressure and glucose levels are down, I've lost over 100 pounds, and I feel great. I know I will need to stay in medical ketosis for life, but being free of bipolar disorder symptoms is more than worth it. Good metabolic health has provided me with good mental health, and I'm so grateful.

Now that I've figured this out, it's really not that difficult — and for me it is totally worth it.

I want to be a part of the solution — to let others suffering with bipolar disorder know that this could be an option for them if they choose. And I want to do whatever I can to hurry along the research so that others will be able to do this, and so the necessary tools, expertise, and monitoring to do it safely can be covered by insurance.

Nanette Snider

Nanette and her son have been in the Prechter Longitudinal Study of Bipolar Disorder for 17 years. We thank them for their commitment to our research mission.

A New Study of Light Sensitivity in Prechter Participants

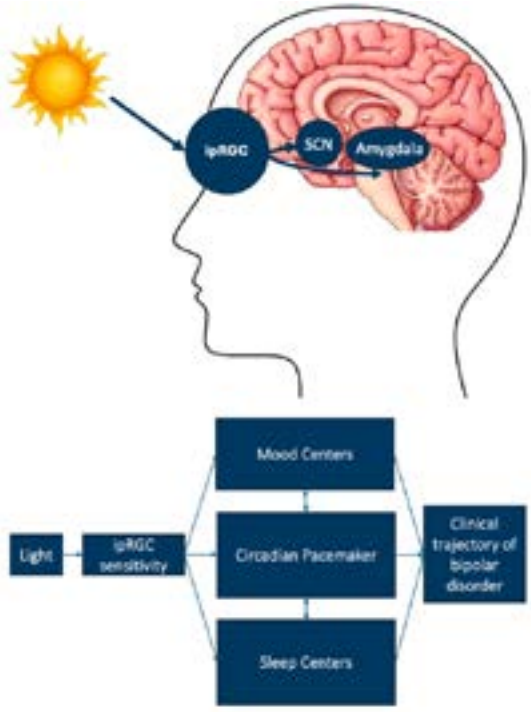


Figure 1. A conceptual model illustrating the pathways by which ipRGC sensitivity to light can impact mood, sleep, and circadian rhythms, all with the potential to ultimately impact the clinical trajectory of bipolar disorder.

There is some evidence that people with bipolar disorder, particularly those with bipolar I disorder, are more sensitive to light. For example, it is generally recognized that mania is more likely to occur in spring when the days become longer. In some rarer cases, morning light therapy, which is sometimes used as an antidepressant, can elicit mania. Since the 1980s, 10 studies have examined light sensitivity in people with bipolar disorder by monitoring how much their melatonin secretion at night is suppressed by nighttime light exposure. Seven out of the 10 studies found that people with bipolar I disorder are more sensitive to light, regardless of the medications they're taking.

Since these earlier studies were conducted, our understanding of the circadian photoreceptor in the eyes and how to best measure its sensitivity has markedly improved. In the early 2000s, specialized cells in the retina, **called intrinsically photosensitive retinal ganglion cells, or ipRGCs,** were discovered. Later research showed that separately from **rods** and **cones** — the photoreceptors in the eye used for vision — the ipRGCs transmit the light signal to many different areas of the brain, including to circadian, sleep, and mood centers *(see Figure 1)*.

In addition, a newer measure called the **post-illumination pupil response (PIPR)** is now considered a more direct measure of ipRGC sensitivity to light. This measure looks at how much the pupil constricts after a brief flash of light. No study to date has measured PIPR in people with bipolar disorder in the time period around usual nighttime sleep. Light exposure, and thus light sensitivity just before and just after the nighttime sleep period, has an impact on circadian rhythms, sleep, and mood — all important factors in bipolar disorder. As such, there is a need to assess PIPR in bipolar disorder and determine whether it impacts sleep, mood, and energy.

Special appreciation to Karen Glorio, Bill Zirinsky, and Ruth Schekter who provided generous gifts to expand the grant-funded research in bipolar disorder and circadian rhythms.

Sleep and Circadian Research Laboratory bedroom

Drs. Helen Burgess and Sarah Sperry were recently awarded a research grant from the National Institute of Mental Health for a study titled Light Sensitivity in Bipolar Disorder: A Potential Driver of Variability in Sleep, Mood and Energy. The researchers aim to measure PIPR in Prechter participants, and they are **specifically looking for people with bipolar I disorder and unaffected controls — people who do not have bipolar disorder — to participate.** They determine if light sensitivity is higher in people with bipolar I disorder versus unaffected controls, and examine how light sensitivity affects subsequent variability in sleep, mood, and energy — key clinical targets in the treatment of bipolar disorder *(see Figure 1)*.

This study takes three weeks and includes four visits to the Sleep and Circadian Research Laboratory at the Rachel Upjohn Building.

- Visit 1: Eligibility check and tour of lab
- Visit 2: Receive Fitbit and start daily logs
- Visit 3: Overnight in the sleep lab (no wires or sleep recording), start daily surveys
- Visit 4: Return equipment, review data

Staying overnight in the Sleep and Circadian Research Laboratory is necessary for measurement of light sensitivity just before and after participants' usual sleep times. The lab bedrooms are designed to be welcoming and comfortable in order to provide participants with the best possible experience.

These findings will also inform future therapeutic trials aimed at testing practical light exposure recommendations (including use of blue light blocking glasses) to shift circadian timing earlier and reduce sleep and mood variability in bipolar disorder.

Correcting Circadian Rhythms in Bipolar Disorder

Many people with bipolar disorder are **"night owls"** — their body clock runs later than the clock on the wall. This can lead to difficulty falling asleep and trouble waking up in the morning. These kinds of sleep problems can lead to a mood episode by triggering mania or worsening depression and currently, there are no effective treatments. The Prechter Program is partnering with the Sleep and Circadian Research Laboratory to bring together a team of experts in bipolar disorder and sleep and circadian rhythms. **Drs. Leslie Swanson and Sarah Sperry,** alongside their collaborators **Drs. Helen Burgess and Melvin McInnis,** received funding from the National Institutes of Health, in addition to funds from the Eisenberg Family Depression Center, to test an exciting new treatment that directly targets the body clock disruptions that are common in bipolar disorder. This treatment syncs the body clock to the clock on the wall and helps night owls fall asleep faster, wake up earlier, and sleep longer. The treatment involves taking a small dose of melatonin in late afternoon while gradually adjusting time-in-bed schedule across four weeks. Melatonin is a hormone that can help shift the body clock, is available over-the-counter, and is inexpensive and safe, with few side effects.

Researchers are testing this new treatment in a small study with 30 adults who have bipolar disorder, are night owls, and are experiencing mild depressive symptoms. Half of the participants in the study will receive the active treatment and half will receive a placebo (an inactive sugar pill). The study hopes to uncover how the active treatment affects mood (including depressive and mania symptoms), sleep, and the body clock. Side effects and safety will also be monitored. If this study shows promising results, the information will be used to plan a larger, more detailed study.

Is Any Alcohol Too Much Alcohol?

New research from U-M scientists shows that even slight increases in alcohol use can lead to problems for individuals with bipolar disorder.

Bipolar spectrum disorders are a set of complex psychiatric disorders that are characterized by fluctuations in mood, energy, and activity levels often resulting in episodes of depression, mania, and/or hypomania. More than half of individuals that have bipolar disorder will also experience problems with alcohol throughout their lifetime. Despite this, little is known regarding why bipolar disorders and alcohol use disorder co-occur at such high rates, and few interventions have been developed that focus on reducing symptoms for both.

An existing theory is that individuals with bipolar disorder use alcohol to "self-medicate" or reduce symptoms caused by bipolar disorder that are not well controlled. For example, individuals often report using alcohol to sleep. This self-medication hypothesis has been the prevailing theory explaining the increased rates of alcohol use in this population for the last 50 years.

Researchers with the Heinz C. Prechter Bipolar Research Program sought to formally test this theory leveraging 10 years of data from the Prechter Longitudinal Study of Bipolar Disorder (PLS-BD). The PLS-BD is a unique and detailed study that has engaged over 1,500 individuals with the aim of identifying biological, genetic, psychological, and environmental causes of bipolar disorder and its trajectory over time. Individuals in the PLS-BD complete measures of mood symptoms, life functioning, and alcohol use every 6 months throughout their involvement in the study. **"This is exactly the type of data needed to test how mood symptoms impact an individual's alcohol use and conversely, how changes in alcohol use impact mood symptoms,"** says Dr. Sarah Sperry.

Using sophisticated computational approaches needed for this type of intensive longitudinal data, **Dr. Sperry,** Ph.D. candidate **Audrey Stromberg** (co-first author), and their collaborators **Victoria Murphy, Carly Lasagna, Margo Menkes, Anastasia Yocum, Ph.D., Melvin McInnis, M.D., and Ivy Tso, Ph.D.,** examined the bi-directional relationships between alcohol use and mood symptoms (depression, mania, anxiety) over 10 years in 584 individuals with a bipolar disorder. **Results revealed that when an individual with bipolar disorder drinks more than typical for them (regardless of how much more), they are more likely to show an increase in depressive and/or manic symptoms over the following six months. This was true even if individuals did not have a co-occurring alcohol use disorder.** Contrary to the self-medication hypothesis, there was no evidence that having increased mood symptoms predicted lasting changes in alcohol use over the following six months. Audrey Stromberg was also

The EmoTe lab team

interested in the impact of alcohol use on functioning across domains of family, friends, work, and home life. **She found that when an individual with bipolar disorder drinks more than typical for them (regardless of how much more), they are more likely to report problems in work functioning over the following six months.** These findings were true for both individuals with bipolar I disorder and bipolar II disorder, although it was even more pronounced in individuals with bipolar II disorder.

Taken together, these findings, recently published in "JAMA Network Open," challenge the prevailing theory that changes in mood symptoms produce increases in alcohol use. The researchers conclude that individuals with bipolar disorder are at greater risk for mood instability when they use more alcohol than is typical for them, even if not using problematic levels of alcohol (e.g., binge drinking, drinking with high intensity or frequency, or experiencing impairment related to alcohol). In terms of clinical implications, the researchers highlight the importance of including measures of alcohol use such as the Alcohol Use Disorder Identification Test (AUDIT) in care for individuals with bipolar disorder to facilitate conversations with their care providers.

Dr. Sperry and her team will follow up on these exciting findings to identify psychological and neurophysiological factors that contribute to alcohol use in people with bipolar disorder and ultimately, develop new interventions that target both.

This research was supported by the Heinz C. Prechter Bipolar Research Fund, a Brain and Behavior Research Foundation Young Investigator Award (BBRF 30719), and the National Institute of Mental Health (NIMH K23MH131601, NIMH L30MH127613).

From Lab to Life: Stem Cell Research

K. Sue O'Shea, Ph.D., the Crosby-Kahn Collegiate Professor of Cell and Developmental Biology and director of the University of Michigan Center for Pluripotent Stem Cell Research, is a leader in research using induced pluripotent stem cells (iPSCs) to model bipolar disorder at the cellular level. Our community's generous philanthropy has helped Dr. O'Shea recruit some of the best and brightest in the field for this work. These experts changed how we see bipolar disorder.

GROUNDBREAKING RESEARCH

The O'Shea lab sampled skin tissue from adults living with bipolar disorder and those without. **Then, after turning the skin cells to stem cells (iPSCs) in the lab, the team became the first in the world to grow brain cells from these stem cells. This allowed researchers to examine, for the first time, how brain cells derived from people with and without bipolar disorder look and behave when analyzed under a microscope.**

With donor support, the team was able to dig even deeper and use this "brain in a dish" model to study inhibitory and excitatory neurons and astrocytes, vital support cells in the brain. A long-held theory is that when neurons malfunction, it can contribute to bipolar disorder. In an effort to examine the differences between control neurons and bipolar neurons, the team identified a difference in the respective content of small particles called exosomes, which appear to influence the development and function of neurons.

Dr. O'Shea led experiments that introduced bipolar exosomes into the medium populated with iPSC-derived brain cells from control groups. Researchers in O'Shea's lab demonstrated that the introduced bipolar exosomes caused a reduction of the electrical activity of neurons, indicating that these particles have the potential to be a site of medical intervention, possibly leading to new treatments and a testable biomarker of bipolar disorder.

Dr. O'Shea is a pioneer in the fields of psychiatry and neuroscience. Bipolar disorder is a largely misunderstood disease that is historically difficult to treat with current medications, even when coupled with ongoing psychotherapy. **By precisely answering the question of how bipolar cells and control cells differ, Dr. O'Shea has begun the process of educating the scientific field on the basics of this disease.** Members of the O'Shea lab have won prestigious awards, including the Clyde Bartter Bipolar Research Scholar Award, and others have gone on to lead their own labs within U-M and at other prestigious medical institutions.

Dr. O'Shea's lab has laid the foundation for critical knowledge of bipolar disorder and trained a new generation of thoughtful medical scientists who are tackling some of the most important questions in bipolar and mood disorder research. Dr. O'Shea will retire this year, but her research has set the stage for work on the next frontier of bipolar cell biology.

LOOKING TO THE FUTURE

Paul Jenkins, Ph.D., University of Michigan graduate and assistant professor of pharmacology and psychiatry, and associate director of the Prechter Program, is well suited to build on the O'Shea lab research. The Jenkins laboratory focuses on psychiatric and neurodevelopmental disorders on the cellular level, using animal models to study how genetic variations affect behavior. This work will be an important extension of Dr. O'Shea's research to ensure that what has been found in the "brain in a dish" translates to realistic models and furthers understanding.

The goal for bipolar cell biology is to ultimately change how we treat bipolar disorder. "We are treating the symptoms of bipolar disorder with drugs but not treating the cause, because we are still finding out what the cause is," says Dr. Jenkins. "Once we find out the cause, we need to ask, 'Can we design therapies to alter this disease and change lives?'"

K. Sue O'Shea, Ph.D.

WITH GRATITUDE

Dr. O'Shea and the Prechter Program would like to thank our researchers, participants, and donors for their support of this work and for ensuring the longevity of our research and success. Together, we will change the lives of thousands of patients and their families.

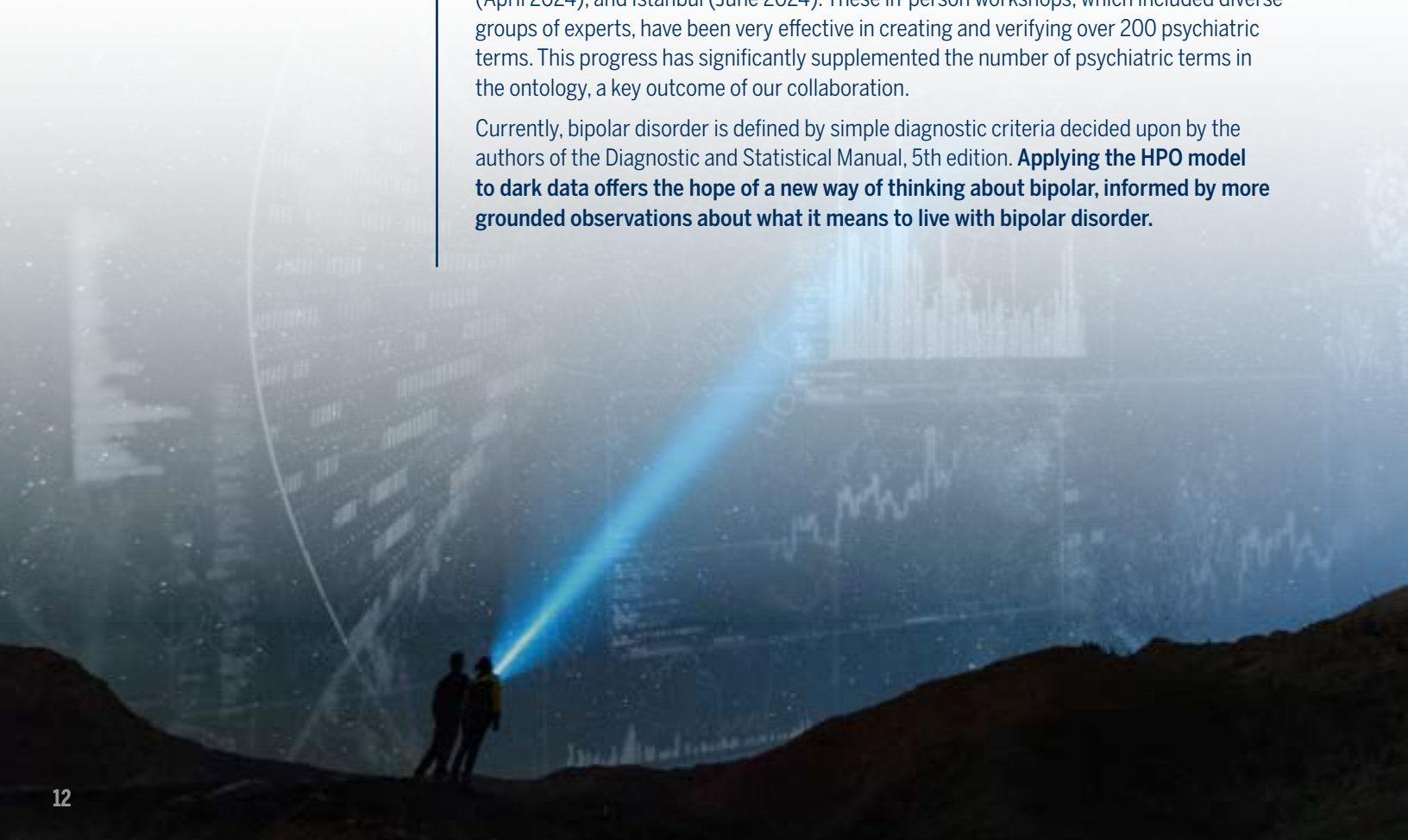
Bringing Dark Data to Light

"**Dark data"** may sound mysterious, but it describes data collected as part of a study beyond the data used in publications. **Dark data** is collected as part of the study protocol using methods like surveys, interviews, experiments, and wearable technology, to name a few. However, some of these methods generate large volumes of data, not all of which may be relevant to or used in publication. This year, the Global Bipolar Cohort (GBC) members have discussed 1) the usefulness of sharing datasets, 2) methods to help researchers and clinicians share data, and 3) how to integrate multiple datasets. The advantage of dark data is that it already exists. **The challenge is, how do we organize it so it's easily accessible to researchers and clinicians who want to use it?**

This was a key question and starting point for the GBC's partnership with **Peter Robinson, M.D.,** an expert in computational biology and bioinformatics and a founder of the **Human Phenotype Ontology (HPO).** The HPO is an international group of investigators focusing on identifying a standardized terminology for characterizing disease-gene relationships. Dr. Robinson's team challenged the GBC to think about what terms are used to describe bipolar disorder and other mood disorders. He also challenged the group to consider how each term relates to another. This GBC-HPO partnership has provided much food for thought for both programs. **Originally developed to standardize descriptions of physical and genetic disorders, the HPO has expanded its scope to include psychiatric and behavioral disorders,** making it a comprehensive resource for phenotypic annotations. **Phenotypic annotation** is the process of systematically documenting an organism's observable traits or characteristics, which typically involves describing clinical symptoms and physical features associated with medical conditions and diseases. These annotations serve as a standardized method to capture and communicate complex information.

Since the first GBC-HPO conference in Chicago in June 2023, **Drs. McInnis and Robinson** have successfully led three additional workshops in Montreal (October 2023), Budapest (April 2024), and Istanbul (June 2024). These in-person workshops, which included diverse groups of experts, have been very effective in creating and verifying over 200 psychiatric terms. This progress has significantly supplemented the number of psychiatric terms in the ontology, a key outcome of our collaboration.

Currently, bipolar disorder is defined by simple diagnostic criteria decided upon by the authors of the Diagnostic and Statistical Manual, 5th edition. **Applying the HPO model to dark data offers the hope of a new way of thinking about bipolar, informed by more grounded observations about what it means to live with bipolar disorder.**



Participant Perspectives: An Interview with Kiersten

The inclusion of lived experiences is crucial to well-informed health care and research. The participation of people with real-world knowledge gained from their experiences with mental health conditions drives the Heinz C. Prechter Bipolar Research Program and others like it. The Prechter Program studies individuals with bipolar disorder through the course of their lifetimes in the Longitudinal Study of Bipolar Disorder. With 18 years of data and over 1,500 research participants, the Prechter Program could not study bipolar disorder without the help of those participants — including Kiersten.

When asked about her motivation for getting involved with bipolar disorder research, Kiersten talks about her drive to help others. She recalls the mental health challenges she experienced while obtaining her master's degree and wanting to pursue a Ph.D. program to conduct research. "I really wanted to get my Ph.D. and do research but I know that I can't participate in research the way I want to," Kiersten says. "So, if I can be a research participant, that's still being involved." Participating in research is a way that Kiersten can share her journey with others. "I want other people to know that they're not alone, because that was something that helped me so much. Researchers might learn connections that they didn't know about before that might help guide treatments."

Kiersten fiercely defends the need for lived experiences to be central in mental health research. She is a social worker currently working in suicide prevention, with a focus on education and training, including dispelling myths that exist within the field of suicide prevention and research. She currently has a grant that requires her to plan and run an annual community-based event. Kiersten's event in 2023 centered on how lived experience with suicide should influence suicide care. "Research is so often led by people with Ph.D.s — but who doesn't have Ph.D.s? Poor people, and people whose mental health has tanked them so they couldn't survive a Ph.D. program. There are so many reasons why the people doing the research are not the people who have lived experience. The wisdom that you've learned from what you've gone through is just as important as clinical or distanced research."

The need is great for people who have lived experience when it comes to mental illness research. Research programs and studies across Michigan Medicine (umhealthresearch.org) are always seeking participants to help inform treatment and care.

Unsure about taking the dive into research participation? Kiersten offers some advice for the wary. First, she says, remember that participating in research is confidential and can't impact insurance, a job, etc. Second, what you share while participating has an impact on the world's understanding of bipolar disorder. Lastly, she emphasizes that everything you share has an impact on the lives of others and can give you a sense of meaning. "Yes, you are a data point, but every single point on that graph is a person. Within that data point is how you've survived, how you've found wellness, how you're still going. You're a data point in this average, but they couldn't make that average without you."

"The wisdom that you've learned from what you've gone through is just as important as clinical or distanced research."

Celebrating Our Friends Leslye and Lisa

I will be retiring in the spring of 2025, at which time Brad and I will be moving to Florida. This has been a life-changing decision for us, just like coming to work as Wally's personal assistant 21 years ago was life-changing for me.

Wally Prechter, founder of the Heinz C. Prechter Bipolar Research Program, is an extraordinary woman with great courage and determination. She established the Prechter Program at U-M to bring awareness to bipolar disorder, with the ultimate goal of achieving personalized treatments for the patient and to become the number one place in the nation regarding all research into bipolar.

It has been my distinct honor to work for Wally and to be involved with the Heinz C. Prechter Bipolar Research Program at the University of Michigan for more than 20 years. It has been inspiring and encouraging to observe the hard work, dedication, and enthusiasm of the research team and their many significant accomplishments: the opening of the Depression Center at U-M, the largest longitudinal study in the nation, the bipolar genetics repository, the stem cell study, the Prechter Lecture Series — to name just a few.

It was also my pleasure to be part of the numerous fundraising efforts for the Prechter Program — gala dinners, luncheons, fashion shows — and to become acquainted with so many of the wonderful donors who have ensured the future of this valuable research program.

There is a famous quote that states "Find a job you love and you will never have to work a day in your life." That sums up my 21 years working for Mrs. Prechter. Thank you, Wally, and all at the Prechter Bipolar Research Program, for everything. I will miss you so very much.

Leslye Martin
Assistant to Mrs. Prechter, 2004-2025

It has been my honor and pleasure to spend close to eight years immersed in this growing, vibrant community. My days have been filled with meaningful conversations — with researchers, colleagues, study participants, and family members who want answers for loved ones experiencing serious mood episodes. Perhaps those who have touched me the most are those who are desperate to give to our bipolar research so that others might be spared the sorrows they have known. The entire community works together with that common purpose — finding new answers and better treatment options. You are my heroes and have given me a master class in strength, resilience, and selfless generosity.

This September I am retiring but I won't be leaving the Prechter Program community. Between road trips to national parks and other adventures, I intend to follow the progress of this amazing community and continue donating to the Prechter Fund.

It is an exciting time for the Heinz C. Prechter Bipolar Research Program and I am more optimistic than ever for the coming years.

With appreciation,

Lisa Fabian
Development Officer for the Prechter Program, 2017-2024

LETTERS FROM THE PRECHTERS

The Heinz C. Prechter Bipolar Research Program Celebrates 20 Years!

As I reflect on the past 20 years, I can't help but share with you how this all started. In the aftermath of my husband's tragic suicide, I established a fund focused on the genetic basis of bipolar disorder. The strategy was to collect and distribute funding among eight universities and institutions. I soon realized that the task was too enormous for me to take on alone. In the spring of 2004, I was fortunate enough to meet with Dr. Robert Kelch, the head of University of Michigan Health System.

The fund was moved over to U-M and we subsequently renamed it the Heinz C. Prechter Bipolar Research Fund with an expanded mission and vision. In 2005, Dr. Melvin McInnis joined us as director. With the help of Dr. McInnis and his incredible commitment to this work, we established the Prechter Bipolar Genetics Repository and the Prechter Longitudinal Study of Bipolar Disorder.

As the founder, I remain engaged with our team. I meet with the fundraising and marketing staff frequently and I stay connected with Dr. McInnis and other team members to assist with strategic planning. It's remarkable to think about the number of people impacted by our ongoing efforts.

Thinking about the progress of our Program prompts me to share about Heinz. In many ways, he was a genius. He was caring, compassionate, optimistic, forward thinking, and motivated to make a difference. It's clear to me that the Heinz C. Prechter Bipolar Research Program is a part of his legacy. His spirit lives on.

Waltraud "Wally" Prechter
Founder, Heinz C. Prechter Bipolar Research Program
Prechter Advisory Board Chair

Transforming pain into purpose is true alchemy. In the months following my dad's passing in July 2001, my family navigated shock, disbelief, and grief. My mom will often describe that time as surreal. She felt called by her faith to bring attention to the condition that took my dad's life. What you see in place 20 years later is a result of her steadfast devotion coupled with a team of dedicated researchers and clinicians, and a community of compassionate stakeholders.

In that first year, in addition to absorbing the sheer devastation of a husband dying by suicide, my mom was faced with her daughter's bipolar diagnosis. Shortly after 9/11, I responded with a manic episode. Prior to this instance, I understood the throes of depression, but I never glimpsed the disruptive energy of mania. Throughout the past two decades, my mom was there to care for me and love me unconditionally. She became a force, not only in my personal recovery, but also in the bigger picture space of research and care.

Looking ahead, I see a promising future for the Prechter Program! I am filled with gratitude for the foundation we have in place, for the emphasis being on those with lived experience, for the introduction of wellness measures, for the ability to share tools with individuals, for the empowerment of those with bipolar and their families, for innovative collaboration across various disciplines, and the list goes on.

Stephanie Prechter
Prechter Advisory Board Member

We've come a long way, but we can't lose sight of the fact that we have more to do. The Prechter family wants to extend our heartfelt thank you for your support. This work, this alchemy, could not be done without you.

18TH ANNUAL PRECHTER LECTURE

Wednesday, October 16, 2024, 6-9 p.m.

BIPOLAR GENERAL: Ya Gotta OWN Your Condition

FEATURED KEYNOTE SPEAKER:	**Gregg F. Martin, Ph.D.** Author of "Bipolar General: My Forever War with Mental Illness"
FREE EVENT:	**RSVP at PrechterProgram.org/lecture**
PANEL DISCUSSION:	Bipolar disorder research and Q&A with mental health experts
RECEPTION:	Refreshments and community resources
LOCATION:	**University of Michigan** A. Alfred Taubman Biomedical Science Research Building Kahn Auditorium 109 Zina Pitcher Place Ann Arbor, MI, 48109

HEINZ C. PRECHTER BIPOLAR RESEARCH PROGRAM
MICHIGAN MEDICINE

If you are interested in discussing a donation or a bequest to support the Prechter Bipolar Research Program, please email teammentalhealth@umich.edu.

If you would like to talk with a lab specialist about taking part in research, please email BPResearch@med.umich.edu.

OUR MISSION

The mission of the Heinz C. Prechter Bipolar Research Program is to discover the mechanisms that contribute to bipolar disorder, predict and improve outcomes, and develop effective, innovative treatments.

OUR VISION

We are building a future where personalized and evidence-based treatments for bipolar disorder will enable every individual with the illness to lead a healthy and productive life.

HEINZ C. PRECHTER BIPOLAR RESEARCH PROGRAM

877-UM-GENES
PrechterProgram.org

To sign up to receive our yearly printed newsletter or our quarterly e-newsletter, please contact: Rachel Bresnahan at **bresnahr@umich.edu** or **734-232-0456**.

HELP IS AVAILABLE

In a mental health or substance use emergency, call or text 988 to reach the national suicide and crisis lifeline.