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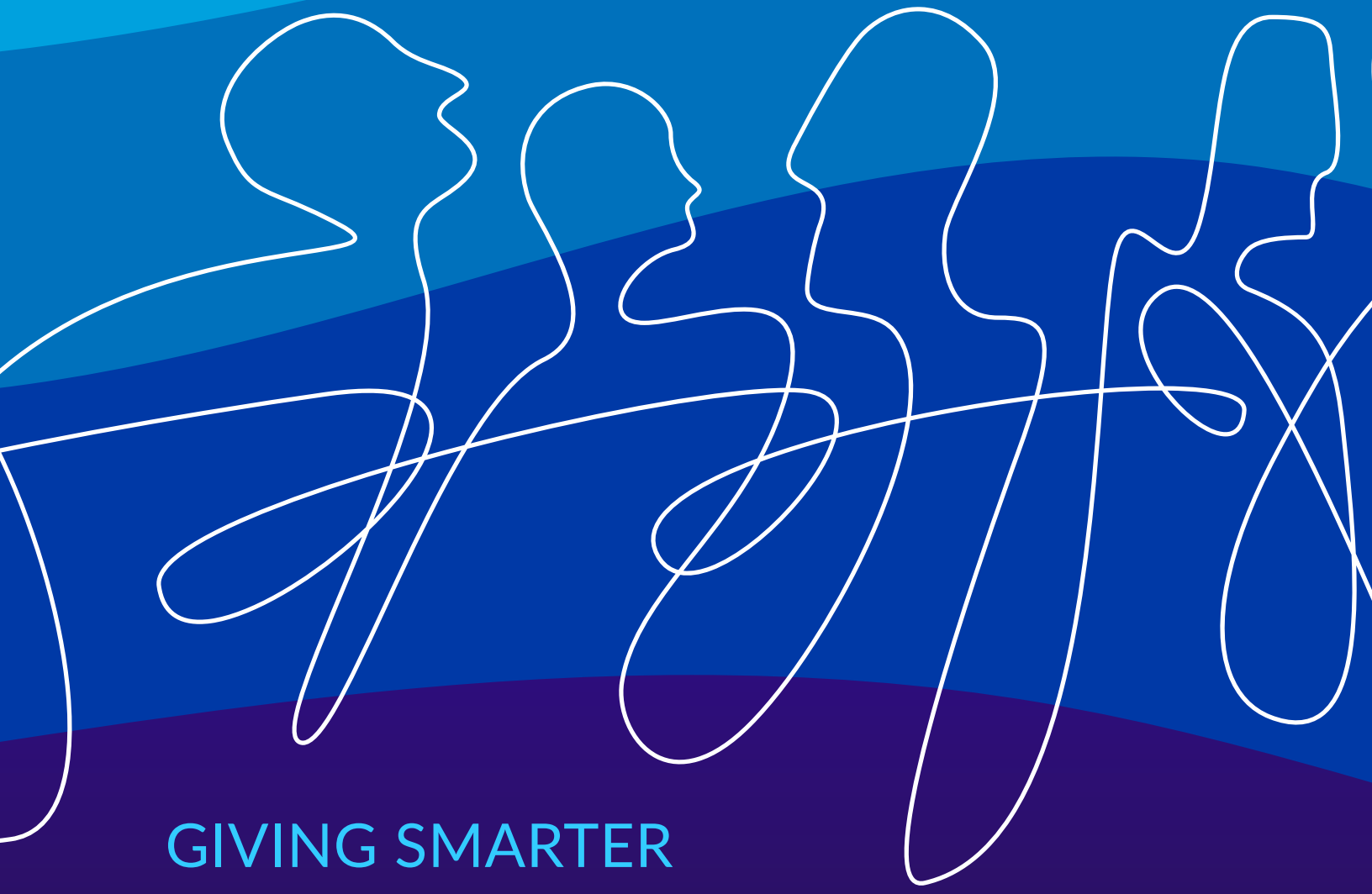

GIVING SMARTER

Philanthropic Opportunities to Advance Bipolar Disorder Research

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ABOUT US

About the Milken Institute

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For the past three decades, the Milken Institute has served as a catalyst for practical, scalable solutions to global challenges by connecting human, financial, and educational resources to those who need them. Guided by a conviction that the best ideas, under-resourced, cannot succeed, we conduct research and analysis and convene top experts, innovators, and influencers from different backgrounds and competing viewpoints. We leverage this expertise and insight to construct programs and policy initiatives.

These activities are designed to help people build meaningful lives in which they can experience health and well-being, pursue effective education and gainful employment, and access the resources required to create ever-expanding opportunities for themselves and their broader communities.

About the Center for Strategic Philanthropy

The Milken Institute Center for Strategic Philanthropy advises philanthropists and foundations seeking to develop and implement transformative giving strategies.

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EXECUTIVE SUMMARY

Bipolar disorder (BD) is a serious mental health disorder with dramatic and sometimes unpredictable shifts in mood, energy, and activity levels. Unlike other mental health conditions, BD is characterized by disruptive recurrences of mania and depression that may last for weeks. Mania causes people to experience increased energy, irritability, grandiosity, elation, and may lead them to engage in risky, unpredictable behaviors. Depressive episodes include sadness, hopelessness, lethargy, indifference, and fatigue. Other conditions such as cardiovascular disease, obesity, cognitive impairment, and asthma co-occur at higher rates in individuals with BD, suggesting an interaction in the biological mechanisms with BD and these other illnesses. These comorbidities, as well as mood episodes, may worsen if untreated.

Roughly 3 percent of the global population experiences BD, which can lead to not only loss of employment, strained relationships, and suicide but also the feeling of powerlessness over one's daily routines and behavior. When combined with comorbidities such as substance use disorder and anxiety, BD may be debilitating for people with the disorder and their caregivers and loved ones. Researchers and clinicians have shown that delayed diagnosis and treatment lead to worse long-term health outcomes. However, 70 percent of individuals with BD are misdiagnosed at least once, and, generally, the time from symptom onset to correct diagnosis and treatment is seven years. Despite its prevalence and impact, BD attracts fewer research dollars than other psychiatric conditions. In this report, we outline key areas for prioritized research funding to support transformative science that could meaningfully improve the lives of people with BD.

STATE OF THE FIELD

BD is relatively common, yet clinicians and researchers do not know its exact cause (Vieta et al., 2018). Vast differences in how a person experiences BD, including when symptoms start, severity, and comorbidities, have complicated the study of the disorder. As a result, treatments are effective for only a subset of individuals.

Despite its detrimental economic and societal impacts, funding for BD research remains low. According to our funding analysis detailed below, US federal funding for BD research overall has been stable over the past 10 years, but the disorder is increasingly studied in the context of other disorders such as schizophrenia and major depressive disorder. Our research shows that this shift has affected a 50 percent decrease in the annual federal budget for research exclusively focused on BD.

> *The economic burden of BD, including hospitalizations and loss of work productivity, is estimated to be approximately $200 billion annually in the United States alone*
>
> *(Bessonova et al., 2020).*

GLOSSARY

MANIA – A period of high energy and mood that is a hallmark of bipolar disorder.

DEPRESSION – A period of low energy, mood, loss of interest or pleasure. Depression occurs in bipolar disorder, as well as major depressive disorder and other conditions.

COMORBIDITIES – Symptoms and conditions that occur alongside symptoms of bipolar disorder.

PHILANTHROPIC OPPORTUNITIES

There are numerous barriers to the development of effective treatments and interventions for individuals with BD. Therefore, targeted philanthropic investment is needed to advance the field, drive innovation, and meet the needs of individuals with BD and their loved ones.

The Sergey Brin Family Foundation partnered with the Milken Institute Center for Strategic Philanthropy and the Brain and Behavior Research Foundation to identify and develop strategic investments to advance the BD field. This document is the result of a review of the science, funding opportunities, and key stakeholders in the field, as well as assessment of current research and discussions of the barriers and opportunities for philanthropic investment with experts within and outside of the BD field.

Philanthropy can have an outsized impact on the field by funding research that focuses on the following:

1. **Characterizing the vast range of symptoms and trajectory for disease progression**
   Research to examine the range of symptoms and disease progression, track treatment response over time, analyze comorbidities, and identify biomarkers is needed to understand the condition clearly. This research is pivotal to developing sufficient data to characterize the specific ways that BD presents and will improve diagnoses and strategies to treat individuals with BD.

2. **Expanding the understanding of the biology that underpins how BD develops**
   BD is highly heritable, and shifts in mood, energy, and cognitive abilities suggest a biological involvement of specific neural circuits. How genetics, cellular interactions, or neural circuits cause or influence BD, however, remains unclear. Discovering the biology underlying BD will improve diagnosis and interventions.

3. **Creating additional opportunities to translate basic science findings into clinical research**
   Translational science accelerates the process of turning basic science breakthroughs into health-care interventions. Our funding analysis estimates that less than one-quarter of current funding supports translational science, creating a potential bottleneck for meaningful research. Philanthropy can support programs with intentional flow between basic and translational research to facilitate faster therapy development and new methods of detecting BD.

4. **Providing better workforce training and education**
   Philanthropy can support clinician networks and programs to recruit additional researchers and clinical scientists to promote diversity of thought and skills, as well as initiatives to increase medical school training on mood disorders.

GLOSSARY

DISEASE PROGRESSION – The course of how a disease manifests over time, characterized by changes in symptom onset and severity.

NEURAL CIRCUITS – Specific connections of brain cells from one area to another that may give rise to certain behaviors.

5. Supporting collaboration and thought leadership in the field

Many barriers in BD research and clinical practice require collaboration across multiple stakeholders and disciplines. BD-focused research organizations must bring together clinicians, researchers, funders, advocates, and individuals with lived experience to catalyze the community. There is a need for philanthropy to lead the formation of an organization to centralize research funding, messaging, and advocacy in an effort to accelerate research progress.

BIPOLAR DISORDER: INTRODUCTION

What Is Bipolar Disorder (BD)?

> *"[I wish that] the feeling of doom would go away, and I can have happy days."*
>
> *2018 responder from Milken Institute and DBSA survey of lived experience*

Individuals with bipolar disorder (BD) experience considerable shifts in mood, energy, and activity levels. They live through periods of depression that include feelings of sadness, worthlessness, and fatigue, similar to individuals who experience unipolar depression. But individuals with BD also experience episodes of mania, or feelings of extreme elation, grandiosity, increased energy, and irritability. Symptoms of BD can be debilitating. According to a recent Milken Institute survey conducted in partnership with the Depression and Bipolar Support Alliance, individuals with BD cite the ability to be independent, to function, and to get through the day as top wellness priorities. Many individuals with BD also experience cognitive impairment, which can affect memory and the ability to reason and focus (Altimus, 2018). If left untreated, the severe mood swings and cognitive impairment associated with BD can progressively worsen.

What Causes BD?

Current research suggests that BD has no single cause but may develop because of several factors, including genetics. Family studies have found that children of parents who both live with BD have a 50 percent chance of also developing BD (Purse, 2020). Looking more closely, studies evaluating families with a history of BD have yielded dozens of genes that may cause increased susceptibility to BD. Many of the identified genes influence how brain cells communicate. Researchers speculate that these genetic alterations may result in a predisposition to BD, and external stressors may trigger the onset of the disorder (Stahl et al., 2019).

Individuals with BD also exhibit altered levels of brain chemicals (Mora et al., 2019), circadian rhythms (Verkooijen et al., 2017), immune responses (Rosenblat and McIntyre, 2017), and cellular energy production (Clay, Sillivan, and Konradi, 2011). However, it remains unclear whether these differences contribute to the development of BD, are symptoms of BD, or a combination of both.

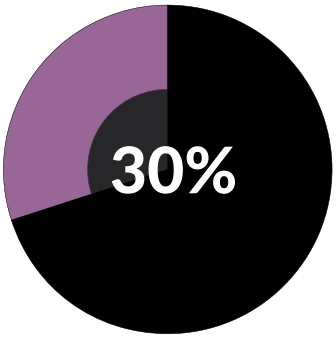
Who Experiences BD?

BD occurs in approximately 3 percent of individuals worldwide, cutting across race, gender, socioeconomic status, and geography (Rowland and Marwaha, 2018). Although most individuals with BD experience their first symptoms during adolescence, children as young as age six can display extreme mood shifts indicative of BD and other mood disorders (Frye, 2020). If left untreated, BD symptoms may worsen with age (Drancourt et al., 2013), leading experts to believe that BD is progressive (Muneer, 2016). Because BD is heritable, children with one parent with BD have up to a 25 percent chance of inheriting BD, increasing to 50 percent if both parents have BD (Purse, 2020).

FIGURE 1: BIPOLAR DISORDER BY THE NUMBERS

2-3%
Adults have BD

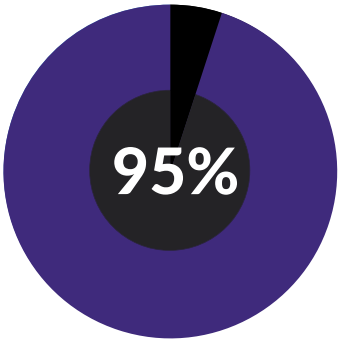
AGE 6
Earliest onset of mood episodes indicative of BD



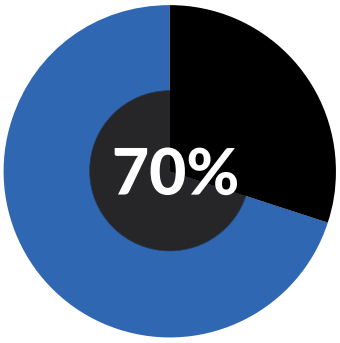
LITHIUM RESPONSE RATE

7 YEARS
Symptom onset to correct diagnosis

10-20 YEARS
Lower life expectancy



WITH 3+ OTHER PSYCHIATRIC DISORDERS



MISDIAGNOSED WITH OTHER PHYCHIATRIC CONDITIONS

$202 BILLION
Annual Impact on US Economy

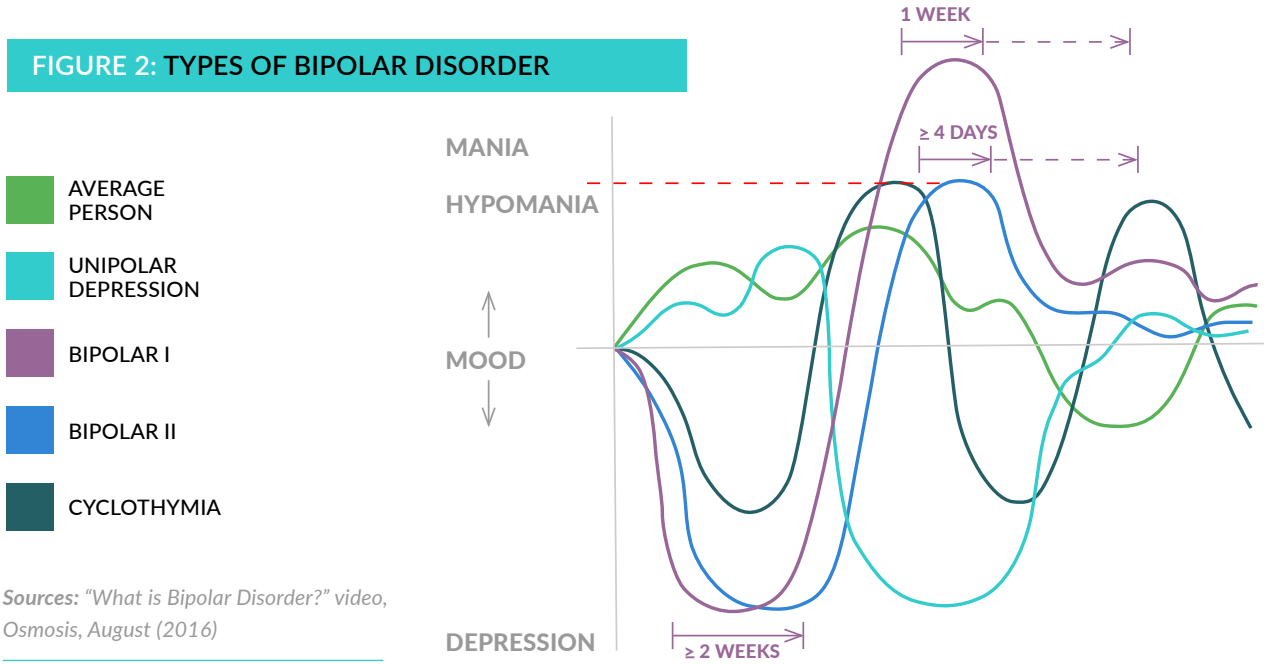
Sources: *Rowland and Marwaha, (2018); Frye, (2020); Singh and Rajput, (2006); Ghaemi et al., (1999); Yager, (2019); R. Kessler, (1999); Chesney, Goodwin, and Fazel, (2014); Bessonova et al., (2020)*

What Are the Different Types of BD?

Physicians generally classify BD into two categories: bipolar disorder type I and bipolar disorder type II. Individuals with bipolar I have experienced at least one major depressive episode and one manic episode. To be classified as BD, the major depressive episode must span at least two weeks and includes depressed mood, decreased interest, insomnia, fatigue, feelings of worthlessness, or recurrent thoughts of death or suicide. The manic episode must last at least one week and includes grandiosity, decreased sleep, intensified speech, or increased distractibility. Individuals with BD II experience periods of major depression and hypomania, a less intense manic episode that lasts four days or more (Truschel, 2020).

Although this broad distinction informs treatment approaches, individuals with BD experience a wide range of symptoms. The disorder is not so easily classified into two subtypes but likely exists on a spectrum and includes a myriad of underlying pathologies. Some individuals with BD experience rapid cycling, which includes at least four episodes of mania, hypomania, or depression in one given year. Others may also experience mixed episodes, during which symptoms of both mania and depression occur simultaneously. Some experience the classic depressive and manic episodes interspersed with periods of relative stability, or euthymia, while others experience mood instability that never reaches euthymia (Müller and Leweke, 2016). Researchers do not fully understand the mechanisms that cause the switch between depression and mania, the full spectrum of BD presentations, or the progression of BD, all of which would help to identify a personalized treatment approach.

FIGURE 2: TYPES OF BIPOLAR DISORDER



Sources: "What is Bipolar Disorder?" video, Osmosis, August (2016)

GLOSSARY

RAPID CYCLING – An experience of at least four episodes of mania, hypomania, or depression in one year.

MIXED EPISODES – A period when both manic and depressive symptoms occur closely together.

HYPOMANIA – A less intense manic episode that lasts 4 or more days.

EUTHYMIA – A period of time when an individual is not experiencing mania, hypomania, or depression.

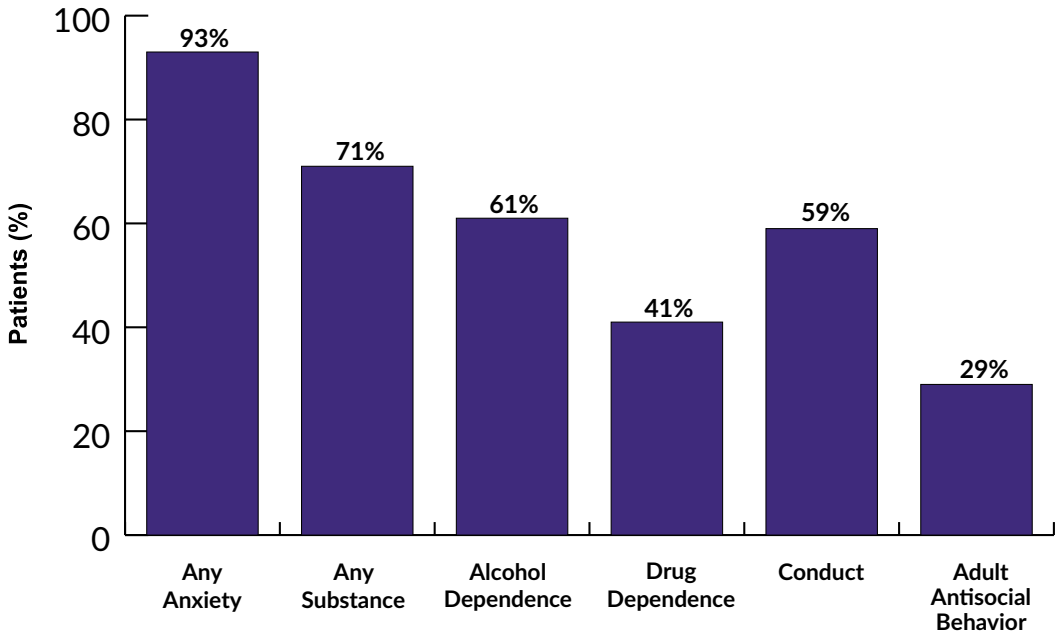
A majority of individuals with BD also experience cognitive impairment, even when not clinically manic or depressed. Age of onset, duration of the disorder, number of episodes, and comorbidities may contribute to cognitive deficits in BD (Solé et al., 2017). Many individuals with BD also live with other disorders, such as migraines, asthma, cardiovascular disease, obesity, and diabetes. Co-occurring metabolic disorders may interact with BD to worsen long-term prognosis and cognitive impairment, suggesting that the management of physical health may be critical to managing BD (R. Kessler, 1999).

FIGURE 3: COMORBIDITIES OF INDIVIDUALS WITH BIPOLAR DISORDER

ANXIETY DISORDERS	SUBSTANCE ABUSE	CHILDHOOD MENTAL HEALTH	SOMATIC DISORDERS
Panic Disorder	Alcohol Misuse	Childhood Bipolar	Cardiovascular Disease
Simple Phobia	Substance Misuse	Conduct Disorder	Obesity
Social Phobia	PERSONALITY DISORDERS	ADHD	Diabetes
Generalized Anxiety Disorder		EATING DISORDERS	Thyroid Disease
OCD	Cluster B		Autoimmune Disorder
Sleep Disorder	Borderline	SUICIDALITY	MIGRAINE DISORDERS
PTSD	Emotionally Unstable		

Sources: Adapted from Stafford, (2012)

FIGURE 4: PERCENT OF INDIVIDUALS WITH BIPOLAR DISORDER WHO EXPERIENCE COMORBIDITIES



Sources: R. C. Kessler, Davis, and Kendler, (1997)

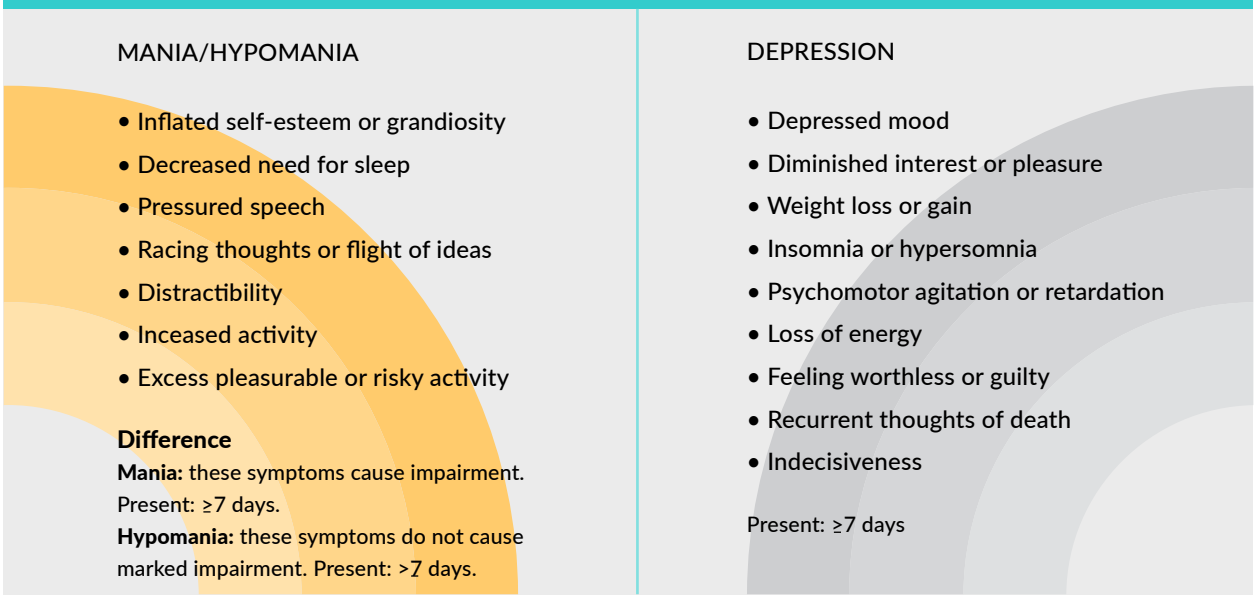
How Is BD Diagnosed?

The Diagnostic and Statistical Manual of Mental Disorders (DSM) from the American Psychiatric Association guides clinicians in diagnosing psychiatric disorders, including BD. Individuals must experience a specific number of symptoms in a given time period to be diagnosed with BD. A diagnosis of BD, and other mood disorders, relies mainly on the reporting of symptoms by individuals who have experienced a manic and depressive episode (Truschel, 2020). Unfortunately, BD is often first misdiagnosed as depression or schizophrenia, resulting in incorrect treatment to manage symptoms (Singh and Rajput, 2006). Mania is also less likely to be self-reported, which also contributes to an incorrect diagnosis of depression (Miller et al., 2011).

CURRENT TOOLS

Clinicians typically use several surveys that measure depression and mania to diagnose BD, including the Hamilton Depression Rating Scale, the Montgomery-Asberg Depression Rating Scale, and the Young Mania Rating Scale. These measures are generally completed with a clinician's guidance and can be used in clinical trials to demonstrate an intervention's efficacy (Miller, Johnson, and Eisner, 2009). Although the surveys effectively diagnose certain aspects of BD, the field has not standardized how, when, and what combination of surveys should be used to assess risk, diagnose, and gauge progression of the disorder.

FIGURE 5: BIPOLAR DISORDER SYMPTOMS



Source: *Barends Psychology Practice*

UTILITY OF BIOMARKERS

Biomarkers are the biological markers of illness and disease progression. Biomarkers can increase the accuracy of diagnosis, thereby increasing the confidence of physicians and individuals in a treatment plan. Although researchers have seen interesting signals, they have not been able to develop validated biomarkers to diagnose BD. Currently, they are pursuing several avenues for biomarker development, including altered brain activity and inflammatory markers (Frey et al., 2013). In addition, scientists analyzing natural environment data, such as speech and sleep patterns collected with cell phone apps, have noticed a possible correlation between patterns of activity and the onset of mood episodes (De Crescenzo et al., 2017). Because other disease areas have greatly benefited from biomarkers, this research area is ripe for philanthropic investment.

How Is BD Treated?

Psychotherapy and medication are key components of comprehensive treatment and are currently recommended for BD. Brain stimulation strategies have also been increasingly used for drug-resistant BD. Education of individuals with BD and their loved ones and support groups are also important strategies for effective symptom management (Geddes and Miklowitz, 2013).

THERAPY

Clinicians often prescribe some form of therapy in parallel with pharmacological intervention. Recent studies have shown that psychotherapy alone can alleviate certain symptoms as effectively as medication for individuals with BD II, demonstrating the value of therapy for individuals with BD (Swartz et al., 2018). Several types of therapy help with different aspects of living with BD:

- **Cognitive behavioral therapy** provides the tools to shift negative thoughts to positive thoughts.
- **Family-focused therapy** educates loved ones and encourages increased communication to strengthen the support network of individuals with BD.
- **Dialectical behavioral therapy** promotes the regulation of negative emotions and self-acceptance and is used to treat individuals with suicidal ideation.
- **Social rhythm therapy** focuses on stabilizing daily routines and regulating responses to external events that may trigger mood episodes.

MEDICATION

Because there is no gold standard for medication to treat BD, finding the right balance of medications can be challenging. Most individuals with BD take a combination of several medications with differing mechanisms of action. The lack of insight into which medications work for certain individuals is likely due to BD's complexity and heterogeneity. The medications generally used by individuals with BD include the following:

- **Lithium**, which is used as a mood stabilizer, has been shown to protect against further cognitive degeneration. Although lithium is widely used as the first line of treatment, its exact mechanism of action remains unknown, and only about one-third of individuals with BD respond to the medication in isolation. Lithium's side effects can also be harmful, especially at higher doses, and may require regular blood work to manage its side effects (Yager, 2019).
- Newer generations of **antipsychotics** impact brain chemicals such as serotonin and dopamine, which play a major role in mood regulation. Most antipsychotics effectively treat and prevent acute manic episodes, while a few are used to treat bipolar depression (Jauhar and Young, 2019).

> *"Why aren't there more options in treating depression? Trial and error of creating the right cocktail of drugs should not be commonplace."*
>
> *2018 responder from Milken Institute and DBSA survey of lived experience*

- **Anticonvulsants** affect GABA and glutamate, neurotransmitters that impact brain cell activity level, and control aspects of mania. Anticonvulsants have a modest effect in treating acute mania and are also used to treat acute bipolar depressive episodes in combination with anti-manic medication (Pichler et al., 2015).
- **Psychedelics**, such as ketamine, have been shown to effectively mediate anhedonia, or the inability to feel pleasure. However, damaging side effects of ketamine may limit the use of it and other psychedelic drugs (Kraus et al., 2017).
- **Antidepressants**, even when taken during depressive states, may increase the presentation of mania and therefore are not recommended for individuals with BD. However, many individuals with BD are prescribed antidepressants because they are often misdiagnosed as having a depressive disorder (Gitlin, 2018).

BRAIN STIMULATION

Stimulating specific areas of the brain with electrical or magnetic pulses can help to improve depression and other symptoms of BD. Although more studies are needed to fully illustrate the impact of brain stimulation in BD, this approach generally alleviates BD depression symptoms, even in people who are resistant to other types of treatment.

- **Electroconvulsive therapy (ECT)** has been used to treat individuals with severe symptoms, suicidal ideation, or lack of response to medication. ECT introduces an electric current into the scalp, inducing a brief brain seizure. ECT has been shown to be highly effective, and individuals with BD experience a rapid improvement in mood after treatment (Anand, 2016).
- **Transcranial magnetic stimulation (TMS)** is a non-invasive strategy to stimulate specific areas of the brain via magnetic pulses. TMS is effective for individuals with BD and is often used in conjunction with other treatment paradigms (Gold et al., 2019).

Potential New Therapeutic Approaches

The field is developing a number of new pharmacological and nonpharmacological therapies to treat BD and adapting current treatments used to treat other disorders. Several pharmaceuticals under consideration are used to treat other disorders.

- **Transcranial direct current stimulation (tDCS)** sends direct electrical currents to increase or inhibit cellular activity in specific parts of the brain. Although it is not approved by the US Food and Drug Administration, studies have shown that tDCS may treat bipolar depression, mania, and anxiety (Dondé, Neufeld, and Geoffroy, 2018).
- **Deep brain stimulation (DBS)** is being considered as another possible treatment for individuals who experience severe symptoms or do not respond to medication. DBS, which has been used to treat movement disorders such as Parkinson's disease, delivers electrical pulses to specific brain areas through a device implanted in the brain. Clinical trials using DBS to treat individuals with BD have been promising (Gippert et al., 2017).
- **Psilocybin** is a hallucinogen, which has been recently shown to have long-lasting effects on reducing unipolar depression. It has not been extensively tested on the management of depression associated with BD (Carhart-Harris et al., 2018).
- **Pimavanserin** is an antipsychotic approved to treat psychosis associated with Parkinson's disease. Pimavanserin was shown to reduce depressive symptoms in a clinical trial (Fava et al., 2019).
- **Candesartan** is used to treat high blood pressure and congestive heart failure and impacts a similar molecular pathway implicated in BD (de Souza Gomes et al., 2015).
- **GLP-1** (glucagon-like peptide-1), which is used to treat diabetes, has been shown to improve cognition in individuals with BD (McIntyre et al., 2013).

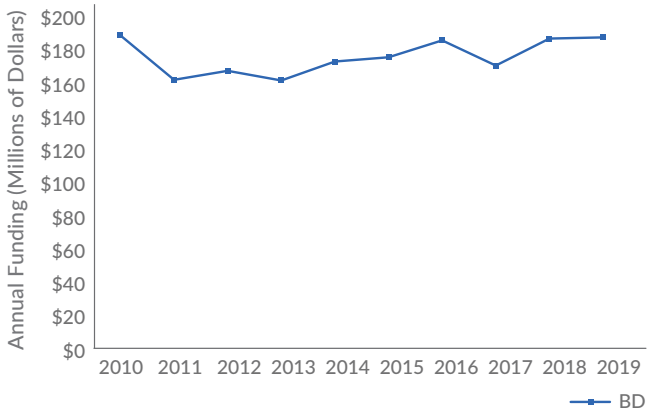
FEDERAL FUNDING ANALYSIS

Our analysis of BD research funding suggests that allocated funds have been inadequate to address the many barriers that have slowed progress in the field. In addition to being inadequate, BD funding is largely directed to studies of BD in the context of another disorder, such as schizophrenia. Further, the majority of BD research funding from the federal government is awarded to basic science research. This analysis highlights the recent trends in BD research funding.

National Institute of Mental Health Administers Majority of Federal BD Funding

The federal government funds the vast majority of BD research in the United States. From 2010 to 2019, the federal government provided $1.78 billion for BD research, of which the vast majority (98 percent) was administered by the National Institutes of Health (NIH). Other agencies, such as the Agency for Healthcare Research and Quality and the Congressionally Directed Medical Research Programs, administered less than 1 percent of the funding in this same period. Within the NIH, the National Institute of Mental Health (NIMH) administered more than three-quarters of the funding for BD ($1.39 billion during 2010-2019). In addition, 11 different NIH Institutes funded BD research at a rate of greater than $1 million/year during this time period. Although several private sources fund BD research, most limit funding to one institution.

FIGURE 6: FEDERAL FUNDING FOR BIPOLAR DISORDER BY YEAR



Source: US Federal RePORTER, (FY2010-19)

FIGURE 7: BIPOLAR DISORDER FUNDING BY NIH INSTITUTE

INSTITUTE	FUNDING FY 2010-19
National Institute of Mental Health	$1,392,474,610
National Institute of Neurological Disorders and Stroke	$52,823,638
National Institute on Aging	$49,939,023
National Institute on Drug Abuse	$48,873,645
National Institute of General Medical Sciences	$41,502,115
National Human Genome Research Institute	$35,301,169
National Institute on Alcohol Abuse and Alcoholism	$21,891,621
National Institute of Biomedical Imaging and Bioengineering	$21,243,336
National Institute of Diabetes and Digestive and Kidney Diseases	$16,843,460
Eunice Kennedy Shriver National Institute of Child Health and Human Development	$12,887,437
National Center for Research Resources	$12,763,651
Agency for Helathcare Research and Quality	$11,143,389
National Heart Lung and Blood Institute	$9,160,106
National Institute on Deafness and Other Communication Disorders	$7,388,180
National Cancer Institute	$6,834,179
NIH Office of the Director	$5,079,429
Others (under $5M)	$21,262,690
Total	**$1,767,411,678**

Note: The vast majority of federal funding for BD research comes from the National Institute of Mental Health.

Source: Federal RePORTER, (FY2010-19)

COMPARING BIPOLAR DISORDER FUNDING TO OTHER CONDITIONS

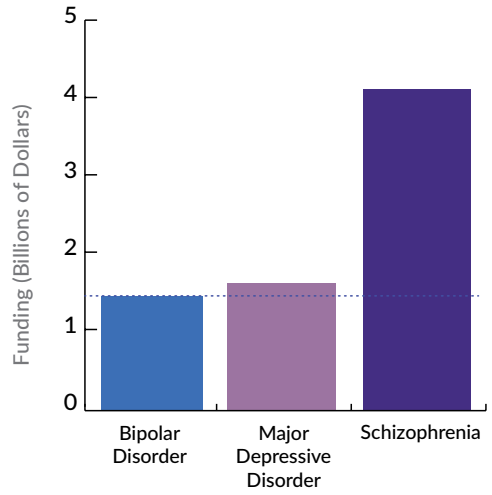
According to the US Federal RePORTER database, federal funding for BD research is lower than funding for other mental health conditions such as schizophrenia and major depressive disorder, which were funded at $4 billion and $1.6 billion, respectively, during 2010-2019.

Examination of the symptomatic characteristics associated with these disorders amplified this conclusion because the characteristics attributed to major depressive disorder and schizophrenia are substantially more representative of the NIMH funding pool than mania—a hallmark of BD. Taken together, funding for mania was substantially lower than funding for schizophrenia and psychosis, as well as major depressive disorder and depression.

A high-level analysis suggests that federal funding of BD research has remained stable during the past 10 years. However, BD researchers reported during the February 2020 Milken Institute meeting that BD funding has indeed been shrinking, driving many of them to study better-funded disorders or leave research entirely. The vast majority of BD research grants also reference the terms "schizophrenia" and "major depressive disorder," suggesting that BD research is often performed in the context of these conditions. Therefore, in a deeper dive, we examined the overlap of NIMH funding among BD, schizophrenia, and major depressive order during 2010-2019 to determine the amount of funding specific to BD.

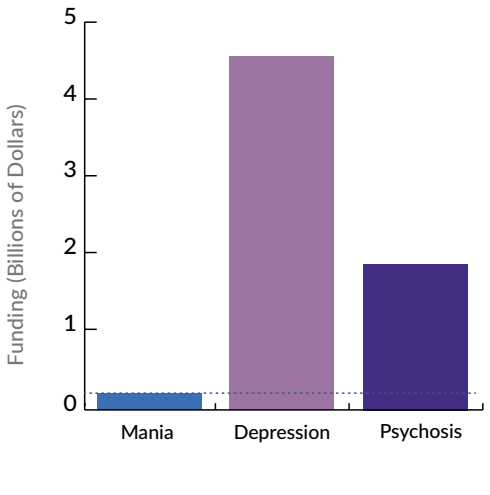
We found that NIMH funding for BD research inclusive of schizophrenia and major depressive disorder remained stable, but NIMH funding for BD research exclusive of these two terms steadily decreased. Only 24 percent ($333 million) of BD funding from the NIMH did not overlap with schizophrenia and major depressive disorder. While it is vital to study overlapping symptomologies across diagnoses because studies have shown genetic, risk factor, and neurological overlaps with BD, schizophrenia, and MDD, there is a need to understand the unique biology and challenges of BD itself.

FIGURE 8: NIMH EXTRAMURAL FUNDING BY DISORDER, FY2010-2019



Note: *NIMH funding for BD research is less than funding for MDD and schizophrenia.*
Source: *NIH RePORTER, (FY2010-19)*

FIGURE 9: NIMH EXTRAMURAL FUNDING BY SYMPTOM, FY2010-2019

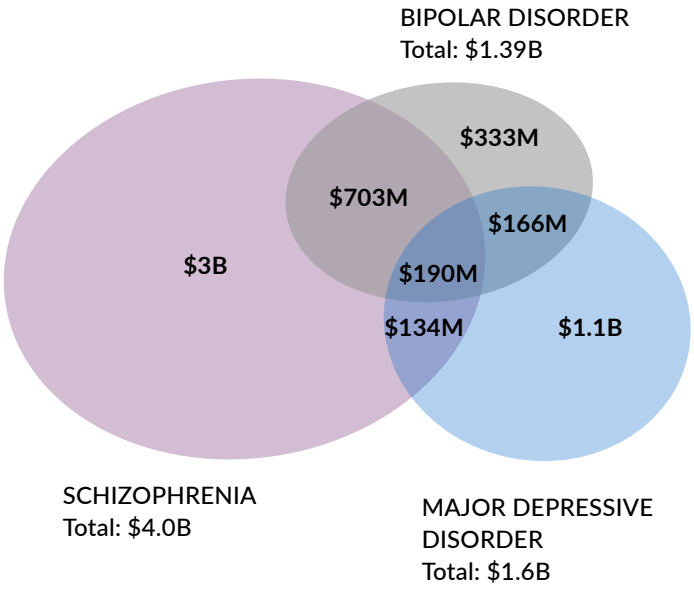


Note: *NIMH funding for research on mania is drastically less than funding for depression and psychosis research.*
Source: *NIH RePORTER, (FY2010-19)*

EXAMINING NIMH FUNDING BY CATEGORY

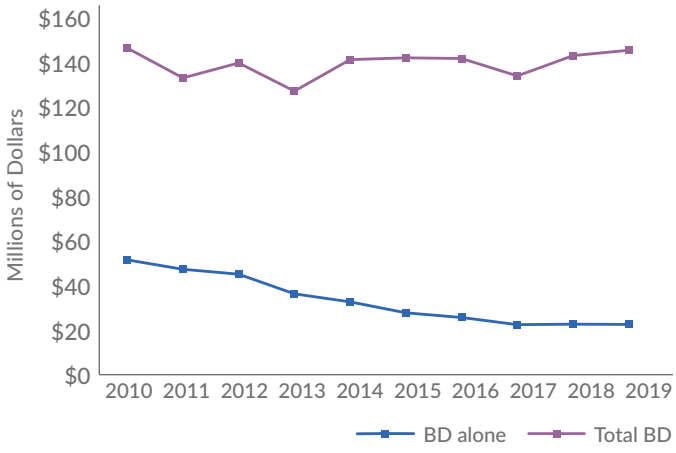
BD researchers had also reported that funding was broadly shifting toward basic science and away from translational and clinical studies. To assess this sentiment, we examined NIMH-funded grants based on keywords associated with certain scientific domains, including basic science, translational science, clinical science, and the research ecosystem. We then determined the relative NIMH funding amount for BD and five keywords per scientific domain. Our analysis shows that a majority of NIMH funding from 2010 to 2019 was directed to more basic science grants examining the genetics, circadian rhythm, biology, cognition, and circuitry of BD.

FIGURE 10: NIMH FUNDING OVERLAP BY DISORDER, FY2010-2019



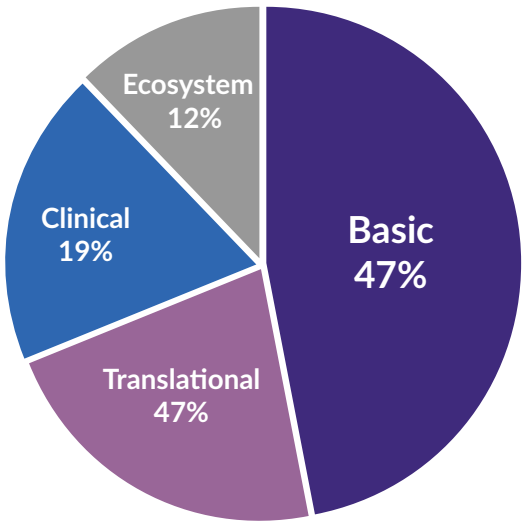
Note: A majority of BD research funding overlaps with schizophrenia and major depressive disorder research.
Source: NIH RePORTER, (FY2010-19)

FIGURE 11: NIMH FUNDING FOR BD ALONE AND TOTAL BD, FY2010-2019



Note: NIMH funding for BD outside of schizophrenia and major depressive disorder has decreased in the last ten years.
Source: NIH RePORTER, (FY2010-19)

FIGURE 12: NIMH BD FUNDING BY SCIENTIFIC DOMAIN, FY2010-2019

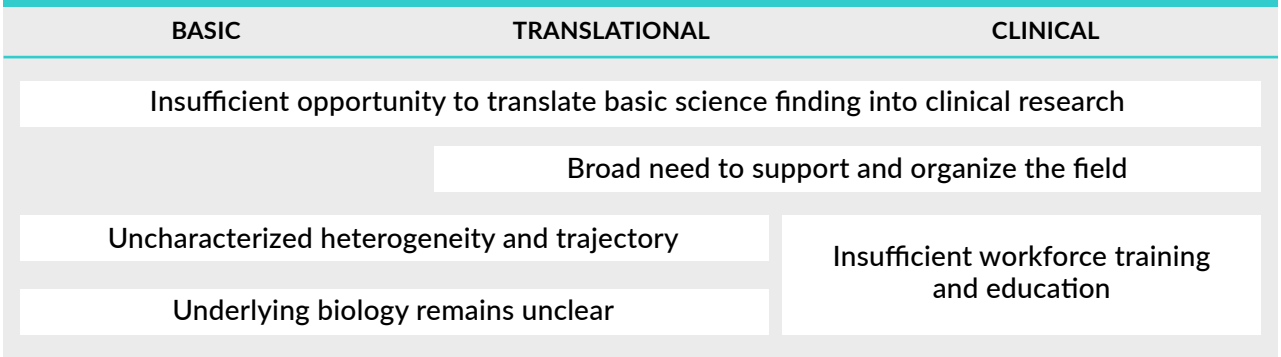


Source: NIH RePORTER, (FY2010-19)

OPPORTUNITIES FOR PHILANTHROPY

Despite the existence of several approved therapies, many individuals with BD report continued disruption from the disorder and difficulty obtaining and navigating a diagnosis (Altimus, 2018). Researchers and clinicians are developing a mechanistic understanding of the disorder so that they can develop new and more specific diagnostics and therapeutics. A deep due-diligence effort by the Milken Institute, which included a systematic review of the field, discussions with key opinion leaders, and a two-day scientific meeting in early 2020, has identified five scientific and infrastructure barriers that hinder the field from moving forward. Although not mutually exclusive, each barrier impacts the field differently.

FIGURE 13: SCIENTIFIC BARRIERS THAT IMPEDE THE BIPOLAR DISORDER FIELD



Source: Milken Institute Center for Strategic Philanthropy (developed from conversations and meetings with BD scientific community in 2020)

Barrier 1: Uncharacterized Heterogeneity and Trajectory for Disease Progression

All individuals with BD experience mania or hypomania. However, the manifestations of BD are complex, with the severity and number of symptoms, duration and frequency of mood episodes, and treatment efficacy widely ranging among individuals with BD. This complexity has made it difficult to understand and treat BD, which is further complicated by high rates of comorbidities such as anxiety, obsessive-compulsive disorders, substance use disorder, and obesity. There is a clear need to identify groups of individuals with BD who experience similar symptoms and responses to specific treatments. This effort will help to determine whether current and novel interventions are more effective in some people than others.

PHILANTHROPIC OPPORTUNITY: SUPPORT LONGITUDINAL CLINICAL RESEARCH

Philanthropy can address this barrier by supporting longitudinal clinical research that observes individuals with BD for several years while collecting various data. These types of studies have allowed scientists to understand similarly complex disorders such as Parkinson's disease and

Alzheimer's disease and to develop better treatment tools (Marek et al., 2018; Veitch et al., 2019) Philanthropy can support longitudinal studies that are:

1. **Studying the prodromal phase**
   The BD prodromal period describes the development of symptoms, such as cognitive decline and increased anxiety, that precedes the onset of a mood episode. Better characterization of this phase may allow for earlier interventions that can reduce the severity of mood episodes or prevent the development of BD.

2. **Tracking treatment responses over time**
   A majority of BD patients are treated with many therapeutics throughout their lives (Fornaro et al., 2016). Tracking the efficacy of pharmacological and nonpharmacological interventions over time in a broad sample will provide researchers with a greater ability to predict who will respond well to specific treatments.

3. **Collecting robust data on physical and mental health comorbidities**
   Researchers estimate that greater than 90 percent of individuals with BD experience a comorbid condition, which impacts treatments for certain individuals (R. Kessler, 1999). A comprehensive understanding of comorbidities may shed light on the disorder's subtypes and inform future therapy development.

Barrier 2: The Biology Underlying BD Remains Unclear

The research community continues to explore the biological underpinnings of BD. Although federal funding has shifted its focus toward the biology of BD, many questions surrounding its genetics and causes remain. That BD can be inherited is known, but the currently identified risk genes associated with BD do not predict who will develop BD, and many of these genes overlap with other psychiatric conditions such as schizophrenia (Stahl et al., 2019). In addition, scientists have identified reliable differences in the brain structures of people with BD (Collin et al., 2015; Johnston et al., 2017); however, they do not fully comprehend what causes the differences in brain structures, connections, and neural pathways. Understanding the cause of these differences and how they contribute to the control of transitions between mood states will allow the field to diagnose BD better and produce effective interventions.

REMAINING KEY QUESTIONS

Below are open questions that the research community has yet to answer. Finding answers to these questions may move the field forward and help produce better interventions for individuals with BD.

- What are the broad subtypes of BD, and how might we identify and better characterize the range of symptoms?
- How does BD progress differently between subtypes of the disorder, and what drives these differences?
- Can assessing subtypes of BD better predict individual response to certain interventions?
- How do comorbidities impact BD progression, subtypes, and treatment response?

PHILANTHROPIC OPPORTUNITY: EXPLORE THE BIOLOGICAL UNDERPINNINGS OF BD

Philanthropy can lead the way in understanding the biological underpinnings of BD by:

1. **Supporting research that expands and diversifies samples in BD genetic research**
   Too many areas of health research over sample white males of European descent. This study design leads to findings and therapies that may be unsuitable for individuals in other parts of the world. Collecting both genetic and clinical data from new large samples of individuals with BD at institutions around the world will increase the applicability of genetic results to broader populations.

2. **Supporting studies of external influences and genetics on the development of BD**
   Substance use, stressful life events, and altered circadian rhythms are examples of some factors that can impact the severity of BD (Gold et al., 2018; Cerimele et al., 2017; Melo et al., 2017). However, whether environmental factors lead to the development of BD is unclear because these factors can be affected by genetic variations. The ability to track and measure these influences over long periods and analyze how they impact BD development is essential to improving diagnostic and preventative strategies.

3. **Sponsoring research that improves characterization of neural circuits and brain structures affected in BD**
   Scientists have become increasingly able to link specific differences in brain activity to BD that may lead to the development of biomarkers to assess risk, diagnose, determine treatment strategies, or predict the onset of mood episodes (De Crescenzo et al., 2017). These studies could be leveraged to apply neural device technologies to alleviate or potentially prevent mood episodes.

4. **Supporting studies that explore the influence of altered sleep and circadian rhythms**
   Sleep and light are believed to play a role in BD onset, mood state transitions, and symptoms (Melo et al., 2017). By supporting studies to understand the role of altered sleep and circadian rhythms, philanthropists can provide a unique avenue to the development of novel interventions to regulate mood episodes in BD, which may include light therapy or other treatments to regulate sleep cycles.

Barrier 3: Insufficient Opportunities to Translate Basic Science Findings into Clinical Research

In our federal funding analysis of bipolar disorder research (see page 11), we project that less than one-quarter of current funding supports translational science—creating a bottleneck that prevents meaningful clinical research from advancing. Early translational studies are vital to testing whether potential biological mechanisms identified in foundational research studies have therapeutic potential. A lack of funding to advance treatment ideas to clinical trials has led to ineffective

treatments with detrimental side effects. In addition, more research is needed to understand and improve the impact of psychotherapy, a cornerstone of effective treatment strategy for BD (Swartz and Swanson, 2014). The development of standardized and objective tools such as biomarkers, protocols, and tests throughout the scientific spectrum will strengthen the ability to develop additional interventions for BD.

PHILANTHROPIC OPPORTUNITY: BUILD OUT THE CLINICAL TOOLBOX

Currently, there is a lack of funding opportunities to advance biological findings to develop better treatments. Philanthropy can play a key role in bridging the gap between the basic research supported by government and the treatment development supported by private industry. Donors have the opportunity to bridge this gap in the following ways:

1. **Supporting the bidirectional flow of preclinical and clinical collaborations**
   In our conversations with researchers, many expressed frustration that more animal models were not developed based on clinical population studies and that insufficient funding prevented testing of initial findings based on animal models in humans. Philanthropy can support the creation of bidirectional research systems, where animal models are iteratively improved based on human research, and human research is advanced based on updated fundamental knowledge that will accelerate therapeutic development.

2. **Creating interdisciplinary academic, clinical, and biotech networks within and outside of the field of BD**
   Advancing any field of scientific research requires multiple disciplines and a variety of expertise. Recruiting scientists and partners outside of the BD field to create novel partnerships and networks will help improve innovation by facilitating the application of different methodologies to BD. These new partnerships, especially between academia and industry, can allow academic research teams to access and test novel or shelved treatment strategies and accelerate their development.

3. **Supporting the development and application of standardized protocols and tools**
   Standardized protocols and tools are necessary to enable comparison across research studies; however, the development and adoption of such tools require the scientific community's broad engagement. Philanthropy can support the development of research tools, protocols, and analysis and help identify meaningful signs of progress, all of which could drive innovation and create a framework for collaboration.

REMAINING KEY QUESTIONS

- What are possible biomarkers that can predict treatment response, risk level, episode onset, or transitions from unipolar depression to BD?
- How might the field standardize treatments for subgroups of individuals with BD that include both pharmacological and nonpharmacological approaches?
- How can the intervention pipeline be optimized to provide improved treatments for BD?

Barrier 4: Insufficient Workforce Training and Education

In our conversations, many bipolar researchers and clinicians explained that their professional community is shrinking. Researchers describe shifting their areas of study to other psychiatry fields or neuroscience in response to funding availability, even though clinicians and caregivers report feeling poorly equipped to provide care to individuals with BD. Improving mood disorder education for medical doctors and health-care providers will decrease the delay in diagnosis and build additional trust among doctors, caregivers, and individuals with lived experience.

PHILANTHROPIC OPPORTUNITY: STRENGTHEN WORKFORCE TRAINING AND EDUCATION

A strong research community and mental health workforce are foundational to the treatment of any disease. BD is no different. Strengthening clinicians' education and training is key to early recognition of BD symptoms and the prevention of debilitating mood episodes. Philanthropy can strengthen the workforce in the following ways:

1. **Recruiting additional researchers, clinical scientists, and physicians to the community**
   The BD field needs more "solvers." A multipronged approach can educate and incentivize new minds to become part of the community. Medical and graduate program curricula can provide future clinicians and scientists with more training around mood disorders to generate interest in these disorders and the field's complexities. Philanthropy can play a key role in supporting the next generation of thoughtful, innovative, and knowledgeable clinicians for individuals with BD. Funders can target young and new researchers to engage in BD-focused research and medicine to grow the community and develop new solutions.

2. **Strengthening patient-doctor relationships**
   Building trust between health-care providers and individuals with BD is key to providing effective treatments. Funders can support programs that develop outcomes focused on lived experience, for example, wellness beyond symptom abatement, and that center care around the priorities of individuals with BD.

3. **Developing novel models of clinical care**
   Health care requires innovative thinking to improve access and quality of care, especially in the mental health field. Nearly 50 percent of Americans who seek mental health resources cannot access them. Philanthropists can play a unique role in providing pilot funding for novel strategies to improve access to care. Such strategies include programs that focus on prevention, early intervention, and resilience, as well as rethinking hospital-centric models of care that can treat acute mood episodes outside of the emergency room and hospital wards.

Barrier 5: A Broader Need to Organize and Support the Field

Philanthropy is well situated to make a meaningful impact on the field. Unlike other sectors, it is positioned to address global challenges, leverage personal experience and passion, and directly engage with research communities in flexible ways to bring necessary capital to specific challenges. However, multiple barriers to BD research can only be addressed through collaboration across funders. Although certain organizations currently bring together researchers, clinicians, funders, or advocates, no single organization consolidates and synergizes the community. Much needed is a BD-focused research organization that can drive research across the continuum and overcome silos in the field.

PHILANTHROPIC OPPORTUNITY: CREATE AN ORGANIZATION TO FUND AND SUPPORT UNMET NEEDS IN BD

The development and operation of a BD-focused organization to increase collaboration among a multitude of key stakeholders, centralize education and advocacy messaging, and standardize research and clinical techniques would propel the field forward and bring immediate attention to BD. The organization would create a philanthropic vehicle to bring private funding to research and streamline funding programs to ensure that the supported work is non-duplicative, synergistic, and impactful.

CONCLUSION

Bipolar disorder has a profound impact on individuals, society, and, because of its scale, the overall global economy. The effect on individuals with BD, their inability to function or control aspects of their lives, as well as the impact to families and loved ones of those with BD, work to create a distressing ripple effect for which there is currently little redress. Philanthropy is poised to address the remarkable dearth of funding to understand BD better and provide more treatment options. The opportunities listed in this document are intended to guide philanthropic investment to move the field in a meaningful way. Hopefully, they allow individuals with BD, along with their families and caregivers, to take back control of their lives.

These opportunities address the most critical barriers facing the field, as identified by the scientific community in combination with individuals with lived experience. BD research requires substantial investment throughout the scientific spectrum, including improving our understanding of the biological mechanisms that cause BD, developing better diagnostic and treatment tools for individuals with BD, supporting the scientific and clinical infrastructure, and creating a bipolar-focused philanthropic organization that synergizes and coordinates the field.

Now is the time for philanthropy to address the numerous barriers in the field head-on. Philanthropic investment is poised to catalyze the field and drive innovation, which can attract funding from more traditional funding sources to truly make a once-in-a-generation impact on the lives of individuals with bipolar disorder.

APPENDIX: KEY STAKEHOLDERS

Below is a list of key stakeholders in the BD field. These organizations provide funding for BD, support individuals with BD and their caregivers, and bring together scientists and clinicians studying BD. However, there is no single organizing entity that coordinates activities in the field.

Nonprofit Research Funders

These organizations provide funding for research on BD and support research for other related mental health disorders such as major depressive disorder and schizophrenia. No nonprofit funding organizations currently focuses solely on BD research.

Brain and Behavior Research Foundation

Brain and Behavior Research Foundation is the largest non-governmental funder of mental health research, awarding more than $408 million in grants, and $42 million specifically to BD research, since 1987. The foundation provides grants to scientists based on career stage and focuses on four priority areas: basic research, new technologies, diagnostic tools and early prevention, and next-generation therapies.

International Alliance of Mental Health Research Funders

The International Alliance of Mental Health Research Funders brings together funders from around the world to collaborate on mental health research investments to improve treatments and care for mental health. The alliance promotes knowledge exchange and collaboration between funders by encouraging dialogue and creating opportunities to interact to realign individual goals to make a global impact.

One Mind

Founded by Garen and Shari Staglin and Patrick Kennedy in 1995, One Mind collaborates with scientists, individuals with lived experience, and the general public to help individuals with brain illness and injury recover and succeed in life. The group funds and convenes scientists, encouraging collaboration to advance breakthroughs and translate discoveries to interventions for individuals with brain illnesses.

Professional Societies

The professional societies listed below support scientists and clinicians involved in BD research. These organizations convene scientific meetings to encourage collaboration and discourse, assemble task forces to develop community guidelines and consensus documents, and manage scientific publications of research in the field.

American College of Neuropsychopharmacology

The American College of Neuropsychopharmacology seeks to advance the scientific understanding of brain and behavioral disorders to improve prevention and treatment options. The organization hosts an annual meeting to share the latest scientific discoveries in neuropsychopharmacology.

European College of Neuropsychopharmacology

The European College of Neuropsychopharmacology supports applied and translational neuroscience research and education in Europe. Through its scientific conferences, publications, and awards, the organization supports innovative research and encourages collaboration among scientists and key stakeholders in Europe.

International Society for Bipolar Disorders

The International Society for Bipolar Disorders, a membership-driven nonprofit organization, fosters educational and research collaboration of its 700 members to advance treatment and improve quality of life for individuals with BD. Its working groups have published guidelines and consensus documents for the field and publishes a primary research journal on BD.

Community Support and Advocacy Groups

The organizations listed below support individuals with BD, as well as their families, networks, and caregivers, by providing educational tools, peer support, and more. These organizations also advocate on behalf of the BD community at the local, state, and federal levels for policies that benefit the field.

Depression and Bipolar Support Alliance

The Depression and Bipolar Support Alliance is a nonprofit that supports individuals with mood disorders, including BD. It provides educational tools, peer support, and advocacy resources for the BD community to help improve lives.

International Bipolar Foundation

The International Bipolar Foundation is a nonprofit that educates, supports, and advocates for individuals with BD and their community, striving for a world free of stigma associated with BD.

National Alliance on Mental Illness

The goal of the National Alliance on Mental Illness is to build better lives for Americans with mental illness through education and support to individuals with mental illness. The organization also advocates for increased mental health research funding for mental health, expanding services and access, and ensuring that mental illness is not criminalized.

Research Initiatives

The research initiatives listed below are collaborations that address scientific questions in BD. Some of these initiatives are supported by government funds, while others are initiatives organized by volunteers.

Canadian Network for Mood and Anxiety Treatments

The Canadian Network for Mood and Anxiety Treatments is a network of researchers addressing mood and anxiety disorders. The network publishes treatment guidelines and provides educational resources for both health professionals and individuals with mood disorders.

Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Bipolar Disorder Working Group

ENIGMA is a global network of imaging and genetic researchers that promote collaboration to further the understanding of brain structure, function, and disease. The ENIGMA Bipolar Disorder working group shares datasets and analysis methodologies to pool existing imaging and genetics data to increase statistical power.

FACE-BD

FACE-BD is managed by Fondation FondaMental, a French national network of 43 institutions that share the same clinical evaluation and identification tools for diagnosing and treating individuals with BD, autism, schizophrenia, and depression.

Global Aging and Geriatric Experiments in Bipolar Disorder Database (GAGE-BD)

Funded by the ISBD Bowden-Massey Strategic Research Initiative, GAGE-BD aims to understand the association of age to the progression of BD symptoms, cognition, and functioning. The initiative is building and harmonizing a database from existing older-age BD research studies.

International Consortium Investigating Neurocognition in Bipolar Disorder (ICONIC-BD)

Funded by the Brigham Research Institute, ICONIC-BD seeks to characterize cognition in individuals with BD, including the role comorbidities, medicines, and illness duration play on cognition and cognitive trajectories. ICONIC-BD is developing a single platform, where members will be harmonizing the data from a variety of neurocognitive tests from across centers.

National Network of Depression Centers

The National Network of Depression Centers utilizes its network to advance scientific discovery, reduce suffering, and provide evidence-based care to individuals with depression and BD. The network organizes task groups, annual meetings, and a variety of other programs to encourage collaboration and improve treatments for the field.

Psychiatric Genetics Consortium Bipolar Workgroup

The Psychiatric Genetics Consortium is a network of more than 800 investigators from 40 countries collaborating to improve the genetic understanding of several psychiatric disorders, including BD. The BD workgroup examines the role of genetics in BD and its overlap with other psychiatric disorders.

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ACKNOWLEDGMENTS

We are deeply grateful for all of the scientists, clinicians, and experts who have shared their experience and perspectives with us through in-person conversations, phone calls, and video conferences. We are especially thankful to those who attended the Milken Institute Center for Strategic Philanthropy's February 2020 scientific convening in Washington, DC. The input and expertise of those who dedicated their lives to understanding bipolar disorder and other psychiatric disorders were paramount to recognizing the most pressing gaps and barriers impeding the field, as well as identifying possible solutions that philanthropy can support to address these barriers.

Thank you to the following Center for Strategic Philanthropy staff for helping to organize and facilitate the 2020 scientific convening: Glorimar Barrios, E'Lissa Flores, PhD, Elena Helmers-Wegman, Ekemini Riley, PhD, and Erin Ross. Thank you to Mala Persaud for your guidance in developing this Giving Smarter Guide, as well as Quinton Banks, PhD, and Sylvie Raver, PhD, for their intellectual input.

Most of all, we like to thank the Sergey Brin Family Foundation for its energy and dedication to making a lasting impact on the bipolar disorder field. We also would like to thank Jeff Borenstein, MD, and the Brain and Behavior Research Foundation for being a thoughtful and supportive partner in this initiative.

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