Bipolar Disorder Research

NIMH
National Institute of Mental Health

At the National Institute of Mental Health

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Bipolar disorder, also called manic-depressive illness, is a serious disorder of the brain. More than 2.3 million American adults, or about one percent of the population in a given year, have bipolar disorder. Abnormalities in brain biochemistry and in the structure and/or activity of certain brain circuits are responsible for the extreme shifts in mood, energy, and functioning that characterize bipolar disorder. Fortunately, the intense and disabling symptoms of bipolar disorder often can be relieved through treatment involving combinations of medications and psychotherapy.

Bipolar disorder typically emerges in late adolescence or early adulthood but in some cases begins earlier. Episodes of depression and mania flare up across the life course, often disrupting work, school, family, and social life. Despite the fact that an episode may remit on its own due to the cyclic nature of the illness, treatment to achieve and maintain a balanced state is extremely important. Without effective treatment, the illness can lead to suicide in nearly 20 percent of cases.[1]

Research is the key to understanding bipolar disorder. The National Institute of Mental Health (NIMH), the world's leading mental health biomedical research organization, conducts and supports studies on the causes, diagnosis, and treatment of bipolar disorder. A variety of research approaches are being used, including neuroscience studies, basic science approaches to brain and behavior, genetic investigations, epidemiological studies, and clinical research. Clinical treatment research is underway to determine the best use of available treatments and treatment combinations. Better treatments and, eventually, ways to prevent and cure the illness will be found only through careful scientific study.

> *"Manic-depression distorts moods and thoughts, incites dreadful behaviors, destroys the basis of rational thought, and too often erodes the desire and will to live. It is an illness that is biological in its origins, yet one that feels psychological in the experience of it; an illness that is unique in conferring advantage and pleasure, yet one that brings in its wake almost unendurable suffering and, not infrequently, suicide.*
>
> *I am fortunate that I have not died from my illness, fortunate in having received the best medical care available, and fortunate in having the friends, colleagues, and family that I do."*
>
> Kay Redfield Jamison, Ph.D.
> *An Unquiet Mind*, 1995, p. 6.
> Reprinted with permission from Alfred A. Knopf, a division of Random House, Inc.

Symptoms and Types of Bipolar Disorder

Bipolar disorder is characterized by episodes of depression, mania, or mixed state that typically recur and become more frequent across the life span.[1] In most patients, these episodes, especially early in the course of illness, are separated by well periods during which there are few to no symptoms. A small percentage of people experience chronic, unremitting symptoms despite treatment.

Depression

Symptoms include a persistent sad mood; loss of interest or pleasure in activities that were once enjoyed; significant change in appetite or body weight; difficulty sleeping or oversleeping; physical slowing or agitation; loss of energy; feelings of worthlessness or inappropriate guilt; difficulty thinking or concentrating; and recurrent thoughts of death or suicide. The depressive episodes of people with bipolar disorder are often indistinguishable from those of patients with unipolar major depressive disorder.

Mania

Symptoms include abnormally and persistently elevated (high) mood or irritability occurring with at least three of the following: overly-inflated self-esteem; decreased need for sleep; increased talkativeness; racing thoughts; distractibility; increased goal-directed activity or physical agitation; and excessive involvement in risky behaviors or activities (e.g., unwise spending sprees, reckless driving, sexual affairs).

"Mixed" state

Symptoms of mania and depression are present at the same time. The symptom picture frequently includes agitation, trouble sleeping, significant change in appetite, psychosis, and suicidal thinking. Depressed mood accompanies manic activation.

Sometimes severe mania or depression is accompanied by periods of ***psychosis***. Psychotic symptoms include hallucinations (hearing, seeing, or otherwise sensing the presence of stimuli that are not actually there) and delusions (false fixed beliefs that are not subject to reason or contradictory evidence and are not explained by a person's usual cultural concepts). Psychotic symptoms associated with bipolar disorder typically reflect the extreme mood state at the time (e.g., grandiosity during mania, worthlessness during depression).

Bipolar disorder with ***rapid cycling*** is defined as four or more episodes of illness within a 12-month period. This form of the illness tends to be more resistant

An NIMH Snapshot

The National Institute of Mental Health (NIMH) is one of 25 components of the National Institutes of Health (NIH), the Government's principal biomedical and behavioral research agency. NIH is part of the U.S. Department of Health and Human Services. The actual total fiscal year 1999 NIMH budget was $859 million.

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NIMH Mission

To reduce the burden of mental illness through research on mind, brain, and behavior.

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How Does the Institute Carry Out Its Mission?

- NIMH conducts research on mental disorders and the underlying basic science of brain and behavior.
- NIMH supports research on these topics at universities and hospitals around the United States.
- NIMH collects, analyzes, and disseminates information on the causes, occurrence, and treatment of mental illnesses.
- NIMH supports the training of more than 1,000 scientists to carry out basic and clinical research.
- NIMH communicates information to scientists, the public, the news media, and primary care and mental health professionals about mental illnesses, the brain, mental health, and research in these areas.

to treatment than non-rapid-cycling bipolar disorder.

The particular combinations and severity of symptoms vary among people with bipolar disorder. Some people experience very severe manic episodes, during which they may feel "out of control," have major impairment in functioning, and suffer psychotic symptoms. Other people have milder ***hypomanic*** episodes, characterized by low-level, non-psychotic symptoms of mania such as increased energy, euphoria, irritability, and intrusiveness, that may cause little impairment in functioning but are noticeable to others. Some people suffer severe, incapacitating depressions, with or without psychosis, that prevent them from working, going to school, or interacting with family or friends. Others experience more moderate depressive episodes, which may feel just as painful but impair functioning to a lesser degree. Inpatient hospitalization is often necessary to treat severe episodes of mania and depression.

A diagnosis of ***bipolar I disorder*** is made when a person has experienced at least one episode of severe mania; a diagnosis of ***bipolar II disorder*** is made when a person has experienced at least one hypomanic episode but has not met the criteria for a full manic episode. ***Cyclothymic disorder***, a milder illness, is diagnosed when a person experiences, over the course of at least two years (one year for adolescents and children), numerous periods with hypomanic symptoms and numerous periods with depressive symptoms that are not severe enough to meet criteria for major manic or depressive episodes. People who meet criteria for bipolar disorder or unipolar depression and who experience chronic psychotic symptoms, *which persist even with clearing of the mood symptoms,* suffer from ***schizoaffective disorder***. The diagnostic criteria for all mental disorders are described in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (*DSM-IV*).[2]

Many patients with bipolar disorder are initially misdiagnosed.[3] This occurs most often either when a person with bipolar II disorder, whose hypomania is not recognized, is diagnosed with unipolar depression, or when a patient with severe psychotic mania is misjudged to have schizophrenia. However, since bipolar disorder, like other mental illnesses, cannot yet be identified physiologically (for example, by a blood test or a brain scan), diagnosis must be made on the basis of symptoms, course of illness, and, when available, family history.

Genetics Research

Data from family, twin, and adoption studies unequivocally demonstrate the involvement of genetic factors in the transmission of bipolar disorder.[4] Research to date leads to the conclusion that in most families the etiology of bipolar disorder is complex, with vulnerability being produced by the interaction of multiple genes and nongenetic factors. Scientists expect that identification of genes conferring vulnerability to bipolar disorder, and the brain proteins they code for, will make it possible to develop better diagnostic procedures, treatments, and preventive interventions targeted at the underlying illness process.

The NIMH Bipolar Disorder Genetics Initiative, launched in 1989, continues to gather genetic material and state-of-the-art diagnostic and clinical data from families with two or more members affected by bipolar disorder. The primary goal of this initiative is to establish a national resource that makes DNA and clinical information widely available to qualified investigators in the scientific community. The genetic and clinical information is distributed in a way that keeps the research volunteers anonymous. Ten

major research groups worldwide are currently studying DNA and clinical data from over 650 individuals with bipolar disorder and related conditions in an effort to find genes that confer vulnerability to bipolar disorder. Further information on the Initiative is available at http://www-grb.nimh.nih.gov/gi.html.

Successful genetic studies of complex disorders like bipolar disorder will require very large samples drawn from diverse populations, and/or samples drawn from genetically isolated populations. In order to facilitate such research, NIMH recently funded three major collaborative projects to collect data that will significantly augment the information already available in the NIMH Bipolar Genetics Initiative. In one study, scientists at nine research institutions across the United States will gather clinical and genetic data from at least 500 families in which two or more siblings suffer from bipolar disorder.[5] In another, American and Israeli researchers will use shared methods of data collection, diagnosis, and clinical assessment to study 300 additional families.[6] A third project will study over 300 families collected from the population of the Azores, a nine-island archipelago off the coast of Portugal.[7] NIMH also recently issued a Program Announcement (http://grants.nih.gov/grants/guide/pa-files/PA-99-120.html) to encourage collaborations among genetic research groups worldwide, by which multiple samples of bipolar disorder pedigrees can be assembled into one large data set for combined analysis. New genetic analytic methods and technologies like gene chips offer great potential for identifying specific gene sites responsible for vulnerability to bipolar disorder in such large samples of families.

Brain Imaging

Brain imaging technologies are helping scientists learn what goes wrong in the brain to produce mental illness. NIMH researchers are using advanced imaging techniques to examine brain function and structure in people with bipolar disorder.

An important area of imaging research focuses on identifying and characterizing neural circuits—networks of interconnected nerve cells in the brain, interactions among which form the basis for normal and abnormal behaviors. Researchers hypothesize that abnormalities in the structure and/or function of certain brain circuits could underlie bipolar and other mood disorders. Better understanding of the neural circuits involved in regulating mood states will influence the development of new and better treatments, and will ultimately aid in diagnosis.

Structural Imaging

NIMH has supported considerable research with the new technology of magnetic resonance imaging (MRI) to examine the structure of brain tissue in various mental disorders, including bipolar disorder. The first such studies have appeared only within the past ten years, with the pace of progress accelerating steadily since that time. The goal of this research is to discover the ways in which specific areas of the brain in people with bipolar disorder may differ from healthy individuals.

One of the most consistent findings to date has been the appearance of specific abnormalities, or lesions, in the white matter of the brain in patients with bipolar disorder.[8] White matter consists of groups of nerve cell fibers surrounded by fatty sheaths that appear white in color. These sheaths help the transmission of electrical signals within the brain. While the white matter abnormalities appear in many parts of the brain in indi-

viduals with bipolar disorder, they tend to be concentrated in areas that are responsible for emotional processing. These brain changes increase in frequency with age both in people with bipolar disorder and individuals with no mental illness, but they appear more often than expected in young patients with bipolar disorder. This finding suggests that the white matter abnormalities seen with MRI are related to the presence of the disorder. However, some patients with bipolar disorder do not show the white matter changes, and conversely, some entirely healthy individuals have the lesions. Also, it is not yet clear whether these changes contribute to the onset of the disorder, or are in some way a result of becoming ill. While these MRI abnormalities likely indicate one type of malfunction in the brain circuits involved in bipolar disorder, more research is clearly needed to understand their significance and their utility for early diagnosis and treatment.

Functional Imaging

Functional neuroimaging is an important tool for NIMH-supported researchers studying bipolar and other mood disorders. Studies using positron emission tomography (PET), a technique that measures brain function in terms of blood flow or glucose metabolism, have found abnormal activity in specific brain regions including the prefrontal cortex, basal ganglia, and temporal lobes during manic and depressive episodes.[9] It is not yet known whether these functional abnormalities are a cause or consequence of mood disorders.

When neurons become more active, their demand for oxygen, delivered via the blood supply, increases. Using a special measurement technique called functional magnetic resonance imaging (fMRI), scientists can measure these changes in blood oxygen levels in different brain areas in healthy people and those with specific brain disorders, including unipolar and bipolar disorder and schizophrenia. This technique provides a powerful tool for understanding how the brains of individuals with mental disorders process information differently from healthy individuals, and for understanding and even predicting how people with these diseases might respond to different types of drug therapy. For example, NIMH supported researchers have studied how brain regions of healthy people and of people with depression respond differently when emotionally evocative pictures are viewed, and how drug treatment changes the response to these pictures in individuals with depression.[10] Modified versions of both the fMRI and PET techniques, which allow scientists to directly study changes in brain chemistry and the activity of specific signaling molecules (neurotransmitters) in both healthy individuals and people with mood disorders, are enabling researchers to better understand the fundamental characteristics of bipolar disorder.

Treatment Research

NIMH is dedicated to improving treatments for bipolar disorder and is investing considerable research effort in pursuit of this goal. Although many people with bipolar disorder can be helped by currently available treatments, significant challenges remain. Rapid cycling is a form of the illness that is difficult to manage. Medication side effects are often troublesome and can lead to reduced treatment adherence. Some regimens work well for years and then gradually lose their effectiveness. NIMH researchers are working at multiple levels—from molecular genetics, to neuroimaging, to behavioral science, to clinical trials—to learn what underlies these and other treatment-related problems and to apply this knowledge toward the development

of better treatments and enhanced treatment strategies.

Medication

For years, lithium has been the "gold standard" pharmacological treatment for bipolar disorder. When taken regularly, lithium can effectively control mania and depression in many patients and can reduce the likelihood of episode recurrence.[1] However, scientists still do not know exactly how it works, nor do they understand why it works well for some people but not others. In attempt to answer these questions, NIMH researchers are investigating the biochemical mechanisms of action of lithium.[11, 12] This and future work will inform the development of new and better treatments.

For patients who either do not respond to lithium or cannot tolerate its side effects, which can include weight gain, tremor, and excessive urination, there are several anticonvulsant medications that may serve as alternative mood stabilizers. Valproate and carbamazepine have been used for the past two decades for treatment of acute mania and prevention of cycling. However, valproate is the only anticonvulsant approved by the U.S. Food and Drug Administration (FDA) for use with bipolar disorder—specifically, for the acute treatment of mania. NIMH researchers are currently investigating the efficacy of newer anticonvulsant drugs, including lamotrigine and gabapentin, as mood stabilizers for treatment refractory bipolar disorder.[13] Topiramate is also receiving attention in clinical studies.

NIMH-funded research has evaluated the efficacy of atypical antipsychotic medications in the treatment of bipolar disorder. One recent NIMH study demonstrated mood stabilizing and antimanic effects of clozapine in patients with treatment-resistant bipolar disorder.[14] Another NIMH study found olanzapine to help relieve psychotic depression in patients with a diagnosis of major depression or bipolar I disorder.[15] Other research has supported the efficacy of olanzapine for acute mania,[16] an indication that has recently received FDA approval. The efficacy of risperidone is also under study.

A nutritional approach under investigation for maintenance treatment of bipolar disorder involves omega-3 fatty acids found in fish oil. Preliminary research has found a combination of the two main omega-3 fatty acids to be better than placebo, when added to ongoing conventional medications, in avoiding an acute illness episode and in improving a variety of symptoms over four months.[17] However, due to several limitations in this preliminary study, more definitive research is required to validate the appeal of a naturally occurring, apparently safe substance in the treatment of bipolar disorder.

Treatment of Bipolar Depression

Antidepressant medications have long been used to treat the depressive phase of bipolar disorder. However, research has shown that antidepressants, when taken without a mood-stabilizing medication, can increase the risk of switching into mania or hypomania, or of developing rapid cycling, in people with bipolar disorder. Therefore, *mood-stabilizing medications are generally required, alone or in combination with antidepressants, to protect patients with bipolar disorder from this switch*. Lithium and valproate are the most commonly used mood stabilizing drugs today. Research studies are evaluating the potential mood stabilizing properties of newer medications.

Psychotherapy

Interest in using psychotherapy in combination with medication for bipolar disorder has grown in recent years with the recognition of the continuing high rate of relapse, some of which appears preventable, during pharmacological maintenance treatment.[18] NIMH researchers are conducting studies to evaluate the benefits of specific types of adjunctive psychotherapy in the long-term management of bipolar disorder. These psychotherapies include Psychoeducation (PE), Cognitive-Behavioral Therapy (CBT), Family Focused Therapy (FFT), and Interpersonal and Social Rhythm Therapy (IPSRT). PE involves teaching patients with bipolar disorder about their illness and its treatment. Emphasis is placed on recognizing early signs of relapse so that patients can seek medical care before a full-blown illness episode develops. CBT helps patients modify detrimental or inappropriate thought patterns and behaviors associated with bipolar disorder. FFT employs strategies to reduce the level of distress within the family that may either contribute to or result from the ill person's symptoms. IPSRT uses techniques aimed at regularizing daily routines and improving interpersonal relationships. Research indicates that regular daily routines and sleep schedules may protect against manic episodes.[19] A large-scale NIMH study (called STEP-BD, described below) will compare the effectiveness of intensive CBT, FFT, and IPSRT, each in combination with medication, for treatment of acute depressive episodes and for prevention of recurrent episodes in people with bipolar disorder.

Efficacy vs. Effectiveness Research

In recent years there has been an increasing emphasis on extending clinical trials research—research that examines how well treatments work in patients—from tightly controlled, inpatient hospital settings to settings in the "real world." Many past studies have established the safety and efficacy of various treatments for bipolar disorder—that is, how well they work in very specific groups of patients under ideal conditions. However, few studies have adequately tested the effectiveness of particular treatments or treatment strategies—how well they work, for example, in patients who live in the community, come from diverse backgrounds, have co-occurring illnesses, or experience atypical patterns of manic and depressive episodes. In addition, quality of life, ability to work, social functioning, treatment adherence, and treatment cost-effectiveness are among the important, real world issues that only effectiveness research can adequately assess. In contrast to efficacy research, effectiveness studies have very few exclusionary criteria and enroll very large numbers of participants—several hundred to thousands—so that the findings will be representative of and broadly applicable to an entire population group.

To improve the standards of treatment for bipolar disorder, NIMH has taken the lead in treatment effectiveness research on this illness. Major goals are:

- to establish treatment effectiveness both in the short and long term;
- to develop guidelines for treating patients who do not respond to standard single therapies;
- to evaluate combinations of pharmacological and psychosocial treatments;
- to define a core set of outcome measures to make findings across studies comparable; and
- to translate research findings more quickly into routine clinical practice.

NIMH recently awarded a multi-million dollar contract for a bipolar disorder research study designed to achieve these goals. The study is called the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

STEP-BD is a large-scale, 5-8 year clinical study being conducted at 20 sites across the U.S. to determine the most effective treatment strategies for people with bipolar disorder. The study will evaluate both individual and combined pharmacological and psychosocial treatments.

Because STEP-BD is an *effectiveness* study, there are very few exclusionary criteria. Anyone who is age 15 or older and formally diagnosed with bipolar disorder is eligible. (Individuals younger than 18 need parental consent to participate.) In addition, individuals may join the study during any phase of their illness, whether or not they are currently in treatment, and whether or not their symptoms are controlled.

STEP-BD offers all the standard treatment options used for bipolar disorder. The aim is to examine existing, efficacious treatments to come up with the best set of strategies for tackling this very complex illness. Participants may choose their own preferred treatment plan with their study doctor or may decide to have treatments chosen for them through a randomization process. Randomized treatment "pathways" were built into the study to compare competing treatment strategies where existing guidelines and expert recommendations offer no clear treatment of choice. Either way, *all participants will always receive active treatment with one or more mood stabilizing medications*. Placebos (inactive pills) will never be used alone in any part of the study but may be used in combination with a mood stabilizer for limited periods during the randomized treatment pathways. The investigators will track participants for up to 8 years to document and evaluate long-term treatment outcome. More information about NIMH clinical trials can be obtained by accessing the NIMH home page at www.nimh.nih.gov/studies/index.cfm or the National Library of Medicine clinical trials database at www.clinicaltrials.gov.

Sleep Loss and Social Rhythms

Findings from NIMH-supported research indicate that sleep deprivation can trigger a manic episode in some people with rapid-cycling bipolar disorder.[19] For reasons that are still unknown, people with bipolar disorder appear to have very delicate "internal clock" mechanisms, and disruption of these mechanisms by losing even a single night's sleep often results in mania. Developing and adhering to a structured daily routine and sleep schedule may help protect against mood disturbances. NIMH researchers are investigating the independent effects of the internal clock and the sleep-wake cycle on mood in patients with rapid-cycling bipolar disorder.[20]

Based on the clinical observation that episodes are often precipitated by disruptions of sleep or other daily routines, a group of NIMH-funded researchers developed interpersonal and social rhythm therapy (IPSRT) to help stabilize the course of bipolar disorder. IPSRT teaches patients techniques to regularize their daily routines and improve their interpersonal relationships. In preliminary studies, IPSRT, in combination with ongoing medication maintenance, reduced depressive symptoms and improved the quality of remission from active bipolar disorder.[21] Patients who received IPSRT as a preventive intervention spent more time in a balanced state and less time in a subclinical depressive condition.

Stress, Life Events, and Social Support

NIMH researchers are currently investigating the influence of stress, life events, and social support on the course of bipolar disorder. These relationships can be determined most accurately by studies that follow patients forward through time—that is, by *prospective* research. One prospective, NIMH-funded study is examining the impact of life events and social support on the time to recovery and relapse in people with bipolar disorder.[22]

Another prospective study supported by NIMH is investigating the influence of psychosocial factors—life events, stress, cognitive processes, and personality factors—on the onset and course of cyclothymia (periods of mild hypomanic symptoms alternating with periods of mild depressive symptoms), and on the onset and course of bipolar disorder among people with cyclothymia.[23] Cyclothymia is a known risk factor for developing bipolar disorder. However, little is known about what factors determine which people with cyclothymia will develop bipolar disorder, or about the mechanisms involved in the change from cyclothymia to the more severe illness. Findings from this study will help clarify the role of various psychosocial factors in the course of cyclothymia and in the initial onset and subsequent course of full-blown bipolar disorder; help explain the relationship between unipolar major depression and the depressive phases of bipolar disorder; and suggest new methods for treating and preventing bipolar disorder.

Co-occurring Illnesses

The most common co-occurring illnesses among people with bipolar disorder are substance abuse disorders. Approximately 60 percent of people with bipolar disorder have drug and/or alcohol abuse or dependence problems—the highest rate across all patients with major psychiatric illnesses.[24] Research suggests that many factors likely contribute to these substance abuse problems, including self-medication of symptoms, mood symptoms either initiated or perpetuated by substance abuse, and risk factors that may influence the occurrence of both disorders.[25]

A review of multiple research studies revealed several factors that increase the risk for co-occurring substance use among individuals with bipolar disorder, including early age of illness onset, family history of substance use disorders, and presence of mixed symptoms.[26] A current NIMH-funded study is investigating how substance abuse affects the frequency, duration, and severity of episodes in people with bipolar disorder.[27] Better understanding of the relationship between substance use and bipolar disorder will help improve both treatment and preventive interventions for co-occurring substance use, leading to better mental health outcome.

Other research has indicated that certain anxiety disorders may co-occur with bipolar disorder. In one recent NIMH-supported study of post-traumatic stress disorder (PTSD) in people with bipolar disorder or schizophrenia, almost all patients reported having experienced at least one traumatic event in their lifetime.[28] While 43 percent of study participants met criteria for PTSD, only two percent had the diagnosis listed in their medical charts. The results suggest that PTSD commonly co-occurs with severe mental disorders. Routine screening for PTSD during medical visits would lead to improved diagnosis and treatment of this anxiety disorder, thus allowing the other co-occurring illness—bipolar disorder, schizophrenia, etc.—to be more effectively treated.

Another NIMH-funded study found a high co-occurrence of both PTSD and obsessive-compulsive disorder (OCD) among patients with bipolar disorder

across a 12-month period.[29] While the course of PTSD was independent of the mood disorder, the course of OCD frequently waxed and waned along with mood episodes. More research is needed to determine the nature of this apparent connection between OCD and bipolar disorder in some patients.

Children and Adolescents

Both children and adolescents can develop bipolar disorder. NIMH research efforts are attempting to clarify the diagnosis, course, and treatment of bipolar disorder in youth. Evidence suggests that bipolar disorder beginning in childhood or early adolescence may be a different, possibly more severe form of the illness than older adolescent- and adult-onset bipolar disorder.[30] When the illness begins before or soon after puberty, it is often characterized by a continuous, rapid-cycling, irritable, and mixed symptom state that may co-occur with disruptive behavior disorders, particularly attention deficit hyperactivity disorder (ADHD) or conduct disorder (CD), or may have features of these disorders as initial symptoms. In contrast, later adolescent- or adult-onset bipolar disorder tends to begin suddenly, often with a classic manic episode, and to have a more episodic pattern with relatively stable periods between episodes. There is also less co-occurring ADHD or CD among those with later onset illness.

Findings from one NIMH-supported study suggest that the illness may be at least as common among youth as among adults. In this study, one percent of adolescents ages 14 to18 were found to have met criteria for bipolar disorder or cyclothymia in their lifetime.[31] In addition, close to six percent of adolescents in the study had experienced a distinct period of abnormally and persistently elevated, expansive, or irritable mood even though they never met full criteria for bipolar disorder or cyclothymia. Compared to adolescents with a history of major depressive disorder and to a never-mentally-ill group, both the teens with bipolar disorder and those with subclinical symptoms had greater functional impairment and higher rates of co-occurring illnesses (especially anxiety and disruptive behavior disorders), suicide attempts, and mental health services utilization. The study highlights the need for improved recognition, treatment, and prevention of even the milder and subclinical cases of bipolar disorder in adolescence.

Bipolar disorder in children and adolescents has been difficult to recognize and diagnose because it does not fit precisely the symptom criteria established for adults, and because its symptoms can resemble or co-occur with those of ADHD and CD. In addition, symptoms of bipolar disorder may be initially mistaken for normal emotions and behaviors of children and adolescents. But unlike normal mood changes, bipolar disorder significantly impairs functioning in school, with peers, and at home with family.

Although research in adults indicates that the essential treatment for bipolar disorder is the use of appropriate doses of mood stabilizing medications, few studies of the safety and efficacy of these drugs have been conducted in children and adolescents. NIMH is attempting to fill the current gaps in treatment knowledge with carefully designed studies. Data from adults do not necessarily apply to younger patients, because the differences in development may have implications for treatment efficacy and safety. Thus, research in children and adolescents is needed to properly guide clinicians, patients, and families.

Current multi-site studies funded by NIMH are investigating the value of long-term treatment with lithium and other mood stabilizers in preventing recurrence of bipolar disorder in adolescents.[32, 33, 34] Specifically, these studies aim to determine

how well lithium and other mood stabilizers prevent recurrences of mania or depression and control subclinical symptoms in adolescents; to identify factors that predict outcome; and to assess side effects and overall adherence to treatment. Another NIMH-funded study is evaluating the safety and efficacy of valproate for treatment of acute mania in children and adolescents, and also is investigating the biological correlates of treatment response.[35] Other NIMH-supported investigators are studying the effects of antidepressant medications in the treatment of the depressive phase of bipolar disorder in youth.[36]

Women

Although bipolar disorder is equally common in women and men, research indicates that approximately three times as many women as men experience rapid cycling.[37] NIMH researchers and others are investigating possible causes for this gender difference, including greater use of antidepressant medication among women (antidepressants may induce mania or hypomania if not used in combination with a mood stabilizing drug, such as lithium or valproate), differences in thyroid activity (see below), and effects of sex hormones. Other research findings have indicated that women with bipolar disorder may have more depressive episodes and more mixed episodes than men with the illness.[37]

A number of studies have found that among people with bipolar disorder, women are more likely than men to have a thyroid disorder.[1] In addition, lithium treatment may cause low thyroid levels in some patients, particularly women, which may account for some depressive episodes that occur during treatment. Low thyroid levels also have been associated with rapid-cycling bipolar disorder. Thyroid hormone supplementation may be needed to restore normal thyroid levels. However, since too much or too little thyroid hormone alone can lead to mood and energy fluctuations, it is important that thyroid levels are carefully monitored in all patients with bipolar disorder.

Older Adults

Although bipolar disorder typically appears between early and mid-life, some people develop the disorder for the first time late in life. Research indicates that the factors contributing to late-onset bipolar disorder may differ from those influencing early-onset illness.

A recent NIMH-supported study found that older adults with late-onset bipolar disorder reported less family history of psychiatric problems, more co-occurring vascular disease, and more social support than older adults with early-onset illness.[38] In addition, the study revealed that stressful life events were more frequent among individuals with earlier age of depressive symptom onset compared to individuals with later onset. The study findings suggest that while psychosocial factors may play an important role in early-onset illness, physical medical factors may be particularly important in late-onset bipolar disorder. Ongoing NIMH-funded research continues to investigate neuroanatomical and clinical features of bipolar disorder in older adults.[39] This research is likely to help scientists better understand the psychobiology of bipolar disorder in older adults and may lead to better diagnosis and management of the illness in this population.

The Broad NIMH Research Program

In addition to bipolar disorder, NIMH supports and conducts a broad based, multidisciplinary program of scientific inquiry aimed at improving the diagnosis, prevention, and treatment of other mental disor-

ders. These illnesses include schizophrenia, clinical depression, panic disorder, and obsessive-compulsive disorder.

Increasingly, the public as well as health care professionals are recognizing these disorders as real and treatable medical illnesses of the brain. Still, there is a need for more research that examines in greater depth the relationships among genetic, behavioral, developmental, social, and other factors to find the causes of these illnesses. NIMH is meeting this need through a series of research initiatives.

- **NIMH Human Genetics Initiative**

This project has compiled the world's largest registry of families affected by schizophrenia, manic-depressive illness, and Alzheimer's disease. Scientists are able to examine the genetic material of these family members with the aim of pinpointing genes involved in the diseases.

- **Human Brain Project**

This multi-agency effort is using state-of-the-art computer science technologies to organize the immense amount of data being generated through neuroscience and related disciplines, and to make this information readily accessible for simultaneous study by interested researchers.

- **Prevention Research Initiative**

Prevention efforts seek to understand the development and expression of mental illness throughout life so that appropriate interventions can be found and applied at multiple points during the course of illness. Recent advances in biomedical, behavioral, and cognitive sciences have led NIMH to formulate a new plan that marries these sciences to prevention efforts.

While the definition of prevention will broaden, the aims of research will become more precise and targeted.

More Than 2,000 Grants and Contracts

In total, NIMH supports more than 2,000 research grants and contracts at universities and other institutions across the nation and overseas. It also conducts basic research and clinical studies involving 9,000 patient visits per year at its own facilities on the National Institutes of Health campus in Bethesda, MD, and elsewhere. NIMH research projects focus on:

- basic research on behavior, emotion, and cognition to provide a knowledge base for a better understanding of mental illnesses
- basic sciences, including cellular and molecular biology, developmental neurobiology, neurochemistry, neurogenetics, and neuropharmacology, to provide essential information about the anatomical and chemical basis of brain function and brain disorders
- neuroscience and behavioral aspects of acquired immune deficiency syndrome (AIDS) and behavioral strategies to reduce the spread of HIV (human immunodeficiency virus)
- interventions to treat, prevent, and reduce the frequency of mental disorders and their disabling consequences
- mental health services research, including mental health economics and improved methods of services delivery
- co-morbidity among mental disorders and with substance abuse and other medical conditions, such as depression and heart disease
- the prevalence of mental disorders
- risk factors for mental disorders
- differences in mental health and mental illness among special populations
- children and adolescents who suffer from or who are at risk for serious mental disorders and learning disabilities
- psychotherapies and pharmacotherapies for specific disorders

At the beginning of the 21st century, NIMH stands poised to surmount the burden, loss, and tragedy of mental illnesses that afflict millions of Americans.

For More Information About NIMH

The Office of Communications and Public Liaison carries out educational activities and publishes and distributes research reports, press releases, fact sheets, and publications intended for researchers, health care providers, and the general public. A publications list may be obtained on the web at http://www.nimh.nih.gov/publist/puborder.cfm or by contacting:

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