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# Development and Natural History of Mood Disorders

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*To expand and accelerate research on mood disorders, the National Institute of Mental Health (NIMH) developed a project to formulate a strategic research plan for mood disorder research. One of the areas selected for review concerns the development and natural history of these disorders.*

*The NIMH convened a multidisciplinary Workgroup of scientists to review the field and the NIMH portfolio and to generate specific recommendations. To encourage a balanced and creative set of proposals, experts were included within and outside this area of research, as well as public stakeholders.*

*The Workgroup identified the need for expanded knowledge of mood disorders in children and adolescents, noting important gaps in understanding the onset, course, and recurrence of early-onset unipolar and bipolar disorder. Recommendations included the need for a multidisciplinary research initiative on the pathogenesis of unipolar depression encompassing genetic and environmental risk and protective factors. Specifically, we encourage the NIMH to convene a panel of experts and advocates to review the findings concerning children at high risk for unipolar depression. Joint analyses of existing data sets should examine specific risk factors to refine models of pathogenesis in preparation for the next era of multidisciplinary research. Other priority areas include the need to assess the long-term impact of successful treatment of juvenile depression and known precursors of depression, in particular, childhood anxiety disorders. Expanded knowledge of pediatric-onset bipolar disorder was identi-*

*fied as a particularly pressing issue because of the severity of the disorder, the controversies surrounding its diagnosis and treatment, and the possibility that widespread use of psychotropic medications in vulnerable children may precipitate the condition. The Workgroup recommends that the NIMH establish a collaborative multisite multidisciplinary Network of Research Programs on Pediatric-Onset Bipolar Disorder to achieve a better understanding of its causes, course, treatment, and prevention. The NIMH should develop a capacity-building plan to ensure the availability of trained investigators in the child and adolescent field.*

*Mood disorders are among the most prevalent, recurrent, and disabling of all illnesses. They are often disorders of early onset. Although the NIMH has made important strides in mood disorders research, more data, beginning with at-risk infants, children, and adolescents, are needed concerning the etiology and developmental course of these disorders. A diverse program of multidisciplinary research is recommended to reduce the burden on children and families affected with these conditions. Biol Psychiatry 2002;52:529–542 © 2002 Society of Biological Psychiatry*

**Key Words:** Depression, bipolar disorder, evidence-based treatments, prevention, research training

## Preamble and Charge

The current report summarizes research on the development and natural history of the major affective disorders, including unipolar and bipolar disorder. Although this report broadly examines these issues across the life span, it focuses most closely on the first three decades of life. This focus derives from a confluence of research findings over the past 20 years suggesting that the major affective disorders often begin early in life.

The report is written in response to a charge from the director of the National Institute of Mental Health (NIMH) to review current knowledge and point a course for future work. The first section summarizes what is known about the prevalence of mood disorders during the first three decades of life and changes in the rate of early depression over the past century. The next section reviews current

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knowledge about the development, natural history, treatment, and prevention of early mood disorders. The report ends by delineating the most promising and urgent directions for basic treatment and prevention research.

## The Magnitude of the Problem of Depression

### *The Global Burden of Disease Associated with Mood Disorders*

The World Health Organization/World Bank's estimates of the global burden of disease, calculated in terms of disability-adjusted life years (DALYs), found that unipolar depression was the leading cause of disability worldwide in the 15- to 44-year age group, whereas bipolar disorder was the sixth most disabling disorder (World Health Organization 1996). The DALYs associated with child and adolescent mood disorders have not been calculated, but there is growing evidence that early mood disorders are widespread, recurrent, and often chronic diseases, which increase the risk of lifelong disability.

### *Prevalence of Unipolar Depression in Late Adolescence and Adulthood*

Prevalence estimates for mood disorders vary with the time period of reference and method of assessment. The magnitude of the problem can be estimated from the National Comorbidity Survey (NCS), which assessed a representative United States population sample of over 8000 people, aged 15 through 54 years (Kessler 1994). The 30-day prevalence of a major depressive episode was 4.9%. The prevalence was highest (6.1%) in the youngest group surveyed (age 15–24 years) and lowest (3.9%) in the oldest group surveyed (45–54 years) (Blazer et al 1994). Lifetime prevalence rates also suggested more depression in younger participants; for example, the lifetime rate was scarcely higher in the oldest group (16.7%) than in the youngest (15.7%). A more detailed breakdown of the NCS data shows that the highest 12-month prevalence occurred in female adolescents during their late teens and in men during their early twenties.

### *Prevalence of Unipolar Depression in Childhood and Adolescence*

The youngest participants in the NCS were 15 years of age. There are no nationally representative studies of mood disorders in the United States in younger individuals. Moreover, because studies of children and adolescents tend to use somewhat different methods from those used among adults, estimates of the burden of disease are not directly comparable. Based on the available data from

selected geographic areas, unipolar depression seems to be more common in adolescence (1-year prevalence 4% to 7%) than in childhood (1-year prevalence around 2%).

### *Secular Change*

Some evidence from retrospective surveys of adults suggests that the lifetime prevalence of unipolar depression has increased in each age cohort born since World War II (Klerman and Weissman 1989; Lewinsohn et al 1993). Kessler and Walters (1998) reported a cohort effect in the NCS, suggesting a higher current prevalence and an earlier age at onset in its younger subjects, born in 1965 to 1975, than in the older subjects, born between 1936 and 1965. Kessler et al (1996) present evidence that the secular change was caused by an increase, not in primary or "pure" depression, but in depression secondary to, or occurring after, the onset of other conditions, particularly anxiety disorders.

Comparing studies of youth born in the two decades before or after 1975, we observed no increase between these two birth cohorts (unpublished data, NIMH Development and Natural History Workgroup—Age, Period and Cohort Effects Subcommittee).<sup>1</sup> When one considers all available data, the prevalence of unipolar depression seems to show an increase in the first two thirds of the twentieth century before leveling off in the past 35 years; however, other data provide more consistent evidence of a cohort effect for indices closely related to adolescent depression—suicide and suicidal ideation—as revealed in death certificates and population surveys (Centers for Disease Control 2001). This increase in rates may be particularly true for minority populations (Shaffer et al 1994). Although inconsistencies remain, data for changes in rates of suicide and psychopathology during the past 50 years support the presence of a possible increase before adulthood.

### *Recurrence of Unipolar Depression of Childhood and Adolescence*

Research has just begun to examine the degree to which child or adolescent unipolar depression is chronic and relapsing. Evidence (Garber et al 1988; Kovacs et al 1984; Pine et al 1998) suggests that childhood depression, although rare, entails a high risk for recurrence during adolescence. Similar rates of recurrence, between 30% and 50%, are reported in studies that observe adolescents through early adulthood (Angst et al 1990; Lewinsohn et al 1999; Rao et al 1999; Warner et al 1992). The few studies that have followed depressed children through

<sup>1</sup> This report is available upon request, see Acknowledgments for further details.

adolescence into adulthood (Fombonne et al 2001; Garber et al 1988; Harrington et al 1990; Lewinsohn et al 1999; Rao et al 1999; Weissman et al 1999a, 1999b) have all found an increased risk.

### *Age-by-Gender Differences in the Prevalence of Unipolar Depression*

An important aspect of the prevalence of unipolar depression is the marked gender-by-age change during adolescence. Until age 13 years or so, depression is equally common in boys and girls. After that age, the rate doubles or triples in females, in whom it continues to occur at a higher rate until after middle age.

### *Bipolar Disorder*

Classically defined bipolar disorder occurs infrequently in young people. The NCS estimated the lifetime prevalence of DSM-III-R bipolar I disorder in 15- to 54-year-olds to be 0.4% and the 1-year prevalence to be just under that figure. Lewinsohn et al (1995, 2000a) found a lifetime prevalence of bipolar disorders of 1% (mainly bipolar II disorder) in adolescents aged 14 to 18 years. The retrospectively recalled age at onset was around 12 years. The community-based studies that have examined recent or current prevalence have found no cases of bipolar I disorder before age 13 years (Angold et al in press; Costello et al 1988; Costello et al 1996).

These estimates are uncertain for various reasons. First, few studies possess adequate population samples to estimate prevalence accurately. Second, the definitions of the term *bipolar* have varied, with some authors referring to the spectrum of bipolar disorders (bipolar I, bipolar II, hypomania, and cyclothymia), whereas others have reported just the rates of bipolar I (full blown, acute manic episodes) (Kessler 1994). Third, controversy remains concerning possible differences between clinical presentations of childhood bipolar disorder, which may present typically as a chronic and unremitting condition, versus adult bipolar disorder, which may often be characterized by clear periods of relapse and recovery. Few studies have observed the same individuals over time to resolve this controversy by providing a careful developmentally informed bipolar diagnosis. Hence, the actual population prevalence of prepubertal or adolescent bipolar disorder is unknown.

Bipolar disorder exhibits little gender specificity or gender-by-age variation from adolescence to adulthood. Retrospective studies of adults report an onset beginning in late adolescence (Hammen et al 1990; Kessler et al 1997; Todd et al 1993; Weissman et al 1996). The similarity of 12-month and lifetime rates of bipolar disorder in adults reported in the NCS suggests that, once

established, this disease is chronic. For clinically referred children and adolescents, it also seems that bipolar disorder is a chronic disease (Geller et al 2001a).

The appropriate diagnosis for prepubertal children showing symptoms of mood lability, extreme irritability, or rapid mood cycles remains an unresolved question. Is this an early form of bipolar disorder, or should it be classified differently (Akiskal 1995; Faraone et al 1997; Jan et al 1994; Jones et al 1987; Nottelmann and Jensen 1995)? Fueling this controversy, investigators, clinicians, and advocacy groups have increasingly challenged the view that bipolar disorder in children is extremely rare (Akiskal et al 1985; Carlson 1984; Child and Adolescent Bipolar Foundation <[www.bpkids.org](http://www.bpkids.org). Accessed April 2002.>; Papolos and Papolos 2000; Weller et al 1986). Part of this controversy may hinge on what is considered to be part of the bipolar spectrum.

### **Initial Caveats**

Before reviewing specific findings and recommendations, the Workgroup concluded that four opening caveats were in order. First, the specific causes of mood disorders remain unknown. This observation is true despite substantial advances in our understanding of genetics and the developmental neurosciences, as well as advances in the basic cognitive and behavioral sciences. Second, although many risk factors for mood disorders have been identified, these risk factors are correlates rather than established causes of mood disorders. Third, some of the strongest evidence for experiential influences (e.g., neglect or abuse) on the development of mood disorders derives from nonhuman animal research, and the translation of this research to the human condition is uncertain. Fourth, it is clear that mood disorders are genetically complex and heterogeneous. No single cause or treatment will apply to all affected individuals. With these four caveats in mind, we move to more specific conclusions and recommendations.

### **Unipolar Disorder in Children and Adolescents**

Based on the Workgroup's deliberations, we present several conclusions and three recommendations judged to be of high priority for the field of unipolar depression.

#### *Unipolar Depression is a Recurrent Chronic Disease of Early Onset*

Thirty years ago, there was doubt about whether children could even experience depression. Today, the question is how many adult mood disorders are truly "adult onset,"

and how many are recurrent episodes of a disorder that had its onset in childhood or adolescence?

**RECOMMENDATION 1.** There is a need for a multidisciplinary research initiative on the pathogenesis of unipolar depression that encompasses genetic and environmental risk and protective factors. This research must proceed with a full appreciation that mood disorders are genetically complex and heterogeneous, and that there are multiple pathways to the etiology of unipolar depression.

This recommendation builds on findings from prospective longitudinal studies of depressed youth (Hammen et al 1990; Harrington et al 1990; Kovacs et al 1984; Lewinsohn et al 1999; Weissman et al 1997). Although this recommendation reflects our appreciation of the gains that have been made, we also conclude that there is a need for a more complete understanding of the etiology of depression and for integration across diverse fields that have commonly remained separate. Emerging paradigms supported by basic neuroscience and genetics will most likely provide exciting opportunities for integrative efforts to clarify the origins of depression. Noninvasive brain imaging studies will provide an increasingly sophisticated set of tools to understand the pathobiology of early-onset unipolar disorder. Continued research on the origins and onset of unipolar disorder is important because of the many adverse effects of depression, sometimes predicting a lifetime of disability. Research, treatment, and, above all, prevention urgently need to concentrate on preadult mood disorders.

In the following sections, we identify specific gaps that exist within this broad area of research and propose a series of steps to take full advantage of existing data sets and to develop new programs of research.

*Early Childhood and Unipolar Depression.* There have been no published diagnostic studies of unipolar depression in population samples of children aged less than 8 or 9 years. Indeed, the instrumentation needed to diagnose depression in young children is not yet fully developed. Studies should assess possible early subthreshold manifestations of depression and monitor their persistence over time (Lewinsohn et al 2000b).

*Puberty and Depression.* Recent studies provide clues on the mechanisms behind changes in the risk for depression during puberty, particularly in girls (Cyranowski et al 2000). Several longitudinal studies find an inflection point for rates of depression around age 13 years, suggesting that adrenarche, which occurs earlier, is not the crucial factor. Other hypotheses have emerged concerning the mechanisms behind these time-related changes: 1) changing levels of various hormones, including estrogen and

testosterone, may affect brain function; 2) anatomic changes reflecting sexual maturity may influence social roles; 3) other social changes may influence the number of depressogenic “life events”; and 4) mismatches may occur with the norms of the social group, such as when some girls mature earlier than their peers. Evidence is emerging that exposure to increased levels of testosterone and estrogen at puberty, especially in the context of social stress, independently predicts the risk for depression among vulnerable girls (Angold et al 1999a; Silberg et al 1999). Clearly, high levels of estrogen and testosterone alone cannot explain depression, but understanding the manner in which hormones affect the brain could have great potential for preventing depression in high-risk girls.

*Comorbidity.* Depression during childhood and adolescence is likely to be preceded, accompanied, or followed by other psychiatric disorders (Pine et al 1998, 1999). A meta-analysis (Angold et al 1999b) showed that, controlling for other comorbidities among disorders, anxiety disorders were 8.2 times as common in depressed as in nondepressed children and adolescents, conduct and oppositional disorders were 6.6 times as common, and attention-deficit/hyperactivity disorder (ADHD) was 5.5 times as common. Most studies (Costello et al 1999; Kessler and Walters 1998; Rohde et al 1991) found that the onset of unipolar depression follows the onset of other disorders, with the exception of substance abuse and panic disorder, which usually begin in the middle-to-late teens. The precise mechanisms by which comorbidity patterns change during development remain unclear; however, successful treatment and prevention programs may depend on a better understanding of antecedent disorders and the vicissitudes of comorbidity.

*Maltreatment, Stress, and Depression.* Population-based studies (Brown et al 1999; Johnson et al 2001; Mulder et al 1998) and case-control studies (Famularo et al 1992; Kaufman 1991) document significant associations between major depression and abuse, maltreatment, and related forms of environmental adversity; however, it cannot be assumed that because children are depressed, they were abused. There seem to be multiple pathways to depression in children and adolescents. Further systematic investigation of depressed children with and without histories of maltreatment should help to delineate the unique risk and protective factors associated with the onset of depression in these two groups.

Recent studies document the potential long-lasting effects of stress exposure on human physiology, brain structure, and function (Bremner et al 2000; Rajkowska

2000; Sheline 2000). These findings are consistent with a growing body of animal research on the behavioral and biological effects of potent stressors (e.g., maternal stress late in gestation, prolonged dam-pup separations) occurring at specific points in development (Ladd et al 2000). Adversity during critical periods of prenatal or postnatal brain development seems to induce plastic changes, leading to permanent alterations in perceptions of, and responsiveness to, environmental events (Manji et al 2001). Nevertheless, complications arise in relating animal behavior to human conditions such as depression. Clinical studies do link stress exposure to various developmental psychopathologies, although it remains unclear whether there is a specific tie to unipolar disorder controlling for comorbidity with other disorders.

Problems also arise in attempting to understand how genetic vulnerabilities and stress exposure interact over the course of development. Although stress may differentially affect children at increased genetic risk, one study suggests that family stress may only increase risk in children *without* a family history of depression (Fendrich et al 1990). Other findings suggest that some children may be genetically more liable to stress exposure, as well as to depression (Kendler et al 1995; Reiss et al 1995; Silberg et al 1999, 2001).

*Familial Risk, Parents, and Parenting.* Genetically informed studies of high-risk families have shown that there is a considerable familial component to unipolar depression. This observation has been demonstrated in “top-down” and “bottom-up” studies. In top-down studies, children of depressed parents have been found to be approximately three times more likely to have a lifetime episode of depression than offspring of controls (Weissman et al 1997); in bottom-up studies, the first-degree relatives of depressed children have been found to have significantly elevated rates of major depression (Birmaher et al 1996).

In contrast, the two adoption studies and a growing number of twin studies provide inconsistent support for the role of genetic factors in the etiology of early-onset depressive symptoms (Eley et al 1998; van den Oord et al 1994). For example, in twin studies, the heritability of child and adolescent depression varies by informant. Although heritability estimates of parent-rated depressive symptoms tend to be high ( $>.60$ ), those based on self-reported depressive symptoms are often substantially lower ( $<.50$ ) (Eaves et al 1997; Silberg et al 1999).

It is also unknown whether the presumed inherited effects are for unipolar disorder rather than for various traits or characteristics that confer vulnerability for these diseases, such as neuroticism, negative affectivity, or, indeed, other traits shown to have a heritable component,

such as a tendency to experience stressful life events, social support, and parenting quality, among others (Plomin et al 1994).

Parents may transmit genes that directly predispose toward depression, genes that are functional in some environments but confer vulnerability in others, or genes associated with cognitive styles (e.g., ruminating) that can lead to depression. Some children may carry a genetic liability to other psychiatric disorders that increase the risk of depression (e.g., anxiety disorders). Alternatively, unipolar depression may represent an early manifestation of another disease to which a child has a genetic liability, such as bipolar disorder (Geller et al 2001b). Parental genes may influence not just the risk of disease but the age at which the disease occurs.

Parents also provide the atmosphere in which a child grows up, and aspects of parenting and the home environment that may not be directly associated with a genetic diathesis have been found to influence the risk of psychiatric disorders in general, including unipolar depression, although specificity to depression is unclear. For example, evidence suggests that responsive caretakers may buffer the risk for depression and other forms of psychopathology (Nachmias et al 1996; Werner and Smith 2001). There is also evidence, based in part on preclinical research, that the quality of the caregiver–infant interaction is critical to normal development of affect regulation in the offspring via parental influences on the maturational trajectory of corticolimbic neurocircuits (Kaufman et al 2000).

Despite the mass of research in the past decade on the effects of maternal depression as a risk factor for children’s depression, few studies have used twin and cross-fostering designs that permit us to separate genes and environment and to examine gene–environment interactions or gene–environment correlations. Improved and integrative biological and psychological models of pathogenesis will aid in the prevention and management of depression as a chronic disease. Knowledge of specific genetic vulnerability factors may be useful in guiding the treatment of acute episodes.

*Integrated Models of Pathogenesis.* As a first step toward implementing this recommendation, we urge the NIMH to convene a panel of experts and advocates to review the findings concerning children at high risk for unipolar depression. Joint analyses of existing data sets should examine specific risk factors to refine models of pathogenesis. When ethically appropriate, DNA specimens should be sought from as many of these families as possible to allow these studies to become genetically informative as specific vulnerability genes are identified.

There are also exciting possibilities for integrative programs of research designed to evaluate diathesis–stress models of depression (Reiss and Neiderhiser 2000). Although no specific set of genes, proteins, or environmental factors has been unambiguously linked to the etiology of major mood disorders, several promising hypotheses have emerged, including 1) that the genetic contribution to these diseases is likely to be significant and complex; 2) that perinatal complications or exposure to adverse environmental circumstances serve to sensitize stress-responsive systems during development; 3) that subsequent exposure to trauma may precipitate the expression of these diseases in genetically vulnerable individuals (Reiss and Neiderhiser 2000; Rosen and Schulkin 1998); and 4) that abnormalities in the regulation of postreceptor signaling cascades and neuroplasticity are integral to the pathophysiology of these disorders and will serve as attractive targets of intervention (Duman et al 2000). Unfortunately, far more research examines the latter two ideas in animal models than in developing children. Specifically, there is a clear need to conduct the same structural and functional neuroimaging studies in preadolescents and adolescents that are performed in adults with major depression to determine developmental differences in the neuroanatomic correlates of depression across the life cycle. Indeed, the few neuroimaging studies in depressed children and adolescents offer preliminary evidence that some neuroanatomic correlates of depression may be evident across the life cycle (e.g., frontal lobe and amygdala volume changes), and that others may emerge later in development or secondary to biological alterations (e.g., excess cortisol) associated with persistence and recurrence of disorder (e.g., hippocampal atrophy) (Steinguard et al 1996; Todd and Botteron 2001). The wealth of emerging noninvasive neuroimaging techniques that are suitable for use in children also offer an opportunity to invest in this area of research.

### *Treatment and Prevention of Unipolar Depression Should Pay More Attention to Childhood and Adolescence*

**RECOMMENDATION 2.** A research initiative is needed to achieve a better understanding of the change in treatment effectiveness from childhood to adulthood, and more research is needed on the efficacy of acute treatment with medications and psychotherapy in prepubertal depression.

**RECOMMENDATION 3.** Treatment research is needed to assess the impact of successful treatment of juvenile depression and known precursors of depression, in particular, childhood anxiety disorders. Studies of maintenance treatment with drugs and psychotherapy in adolescent depression are also needed.

*Pharmacologic Treatments.* Although tricyclic antidepressants (TCAs) efficaciously treat unipolar depression in adults, clinical trials with children or adolescents have shown surprisingly little beneficial effect relative to placebo. More than 15 randomized controlled trials support this conclusion. It remains unclear when, and by what mechanisms, this transition to effectiveness occurs.

In contrast, preliminary evidence suggests that selective serotonin reuptake inhibitors (SSRIs) work well in young adolescents and in children as young as 7 years (Emslie et al 1997; Keller et al 2001); however, as is true for psychotherapy, even successful pharmacologic trials reveal a substantial 1-year relapse rate (40% in one of the largest studies) (Emslie et al 1998). Although the acute response to SSRIs is comparable in juveniles and adults, relapse rates may be higher in juveniles. Future clinical trials must evaluate this possibility by focusing on the entire depressive episode rather than just the acute phase (Brent et al 1999). It remains unclear why SSRIs seem effective at earlier ages than TCAs. Understanding why and when changes in pharmacologic effects occur may illuminate neurobiological processes associated with age-by-gender changes in the risk for adolescent depression.

*Psychotherapeutic Treatments.* Several structured psychotherapeutic interventions developed for adults have been found effective in treating older children and adolescents who come to clinical settings. Randomized controlled trials support the use of cognitive and behavioral psychotherapy (CBT) and interpersonal psychotherapy for depressed adolescents (IPT-A) (Asarnow et al 2001; Harrington et al 1998; Mufson et al 1999). On the other hand, systemic family therapy and nonspecific supportive psychotherapy did not prove to be as successful in speedily reducing depression as did CBT (Brent et al 1997), and adding family therapy to CBT did not improve response in one study (Clarke et al 1999). The response rates for acute treatment are comparable in adult psychotherapy and pediatric SSRI trials; likewise, follow-up studies of psychotherapeutic interventions show a high relapse rate (Birmaher et al 2000). As is true for medication, trials of longer-term, more intensive interventions are needed to determine whether it is possible to increase response and decrease relapse rates. In addition, there is an urgent need to develop and test age-appropriate psychotherapeutic interventions for depressed prepubertal children.

*Prevention.* Work on preventing child and adolescent unipolar depression has followed two general pathways: 1) treatment or prevention of postpartum and maternal depression as a potential risk factor for childhood depression; and 2) programs targeted at high-risk groups (e.g., children of depressed parents) or all children through

school-based programs. The first, and larger, group of interventions has successfully reduced maternal depression, but the effects on depression in children and the possible effects on other areas, such as cognitive development or behavioral problems, have yet to be reported (O'Hara et al 2000). In part, this lack of information may result from short follow-up periods that do not extend into periods when childhood depression becomes most prevalent. Several prevention studies are currently under way, and longer-term follow-up data should become available over the next decade.

Programs directly targeting high-risk children and adolescents have had some success (Clarke et al 1995; Clarke et al 2001; Kaslow and Thompson 1998), whereas programs addressed to unselected populations, such as classroom interventions designed to prevent suicidal behaviors, have produced mixed results (Shaffer et al 1990, 1991).

Previous studies have established a temporal relationship between early anxiety and later depression (Pine et al 1998), especially in adolescent girls (Kendler et al 1987, 1992; Silberg et al 2001). Effective cognitive-behavioral (Barrett 1998; Kendall 1994; Kendall et al 1997) and pharmacologic (RUPP Anxiety Study Group 2001) treatments for pediatric anxiety disorders are now available, and preliminary evidence supports prevention-intervention trials in this group (Dadds et al 1997, 1999). In many of these studies, secondary depression outcomes uniformly showed improvement. These data raise questions on the possible role for CBT or IPT in preventing depression either directly or through effects on anxiety (Clarke et al 1995; Mufson et al 1999).

*From Efficacy to Effectiveness.* Formal studies of treatments for child and adolescent depression are still new, and few studies have moved out of academic research settings into the community. Mufson's extension of IPT to inner-city Latino adolescents, using school counselors as therapists, shows considerable promise (HS5-SM52671-03, Laura Mufson, Principal Investigator). At least two other school-based intervention trials are in progress. A 12-site, "real-world," NIMH-funded study is investigating the relative effectiveness of CBT, fluoxetine, both, and placebo for adolescents with DSM-IV major depressive disorder (N01 MH080008-04, John S. March, Principal Investigator). A second six-site study on the treatment of SSRI-resistant depression in adolescents is also under way. Both studies are designed to recruit subjects representative of real-world clinical samples and, as such, include efficacy and effectiveness elements. Industry-funded, multicenter trials are also in progress (mirtazapine, nefazodone, sertraline, and citalopram) or completed (venlafaxine). All of these studies should document the family history of bipolar mood disorders.

## Bipolar Disorder in Children and Adolescents

The Workgroup identified several pressing questions and three high-priority recommendations for better understanding early-onset bipolar disorder. The first of these recommendations, to establish a Collaborative Network of Research Programs on Pediatric-Onset Bipolar Disorder, was judged to be the most important of the seven recommendations made by the Workgroup.

Questions that were identified include the following: How common is bipolar disorder in children? How does it differ from adult-onset bipolar disorder? What are the earlier signs and symptoms of pediatric bipolar disorder? What is the relationship of ADHD and other disruptive disorders to pediatric-onset bipolar disorder?

**RECOMMENDATION 4.** Establish a collaborative multi-site, multidisciplinary Network of Research Programs on Pediatric-Onset Bipolar Disorder to achieve a better understanding its causes and course.

Because so little is known about bipolar disorder in children, longitudinal studies of the young offspring of bipolar parents are needed, especially studies that explore the earliest prodromes or risk markers of bipolar disorder. Studies should include a follow-up of adequate length to identify symptoms and course as well as possible developmental predictors, such as affect regulation, sleep patterns, and social functioning. A strong case can also be made for additional prospective longitudinal studies of children newly diagnosed with pediatric-onset bipolar disorder (Geller et al 2001a, 2001b; Strober et al 1994). Ideally, this program of research should be multidisciplinary and multisite.

In 1997, the National Institute of Child Health and Human Development initiated an international network of 10 Collaborative Programs of Excellence in Autism to unravel the mysteries of autism from its genetic determinants and neurobiological origins to the development of animal models and novel intervention programs. Each of the 10 programs includes investigators from multiple disciplines across multiple sites. A similar effort is needed for bipolar disorder of pediatric onset. Currently, the NIMH has one study in this area, entitled "Children of Bipolar Parents: A High-Risk Follow-Up Study" (R01 MH60952, Boris Birmaher, Principal Investigator, ). More studies using a similar design and employing a range of clinical, neuroimaging, and neurophysiologic measures are needed.

*Identification of Initial Signs.* Strikingly more data are available on precursors and course modifiers in unipolar as opposed to bipolar disorder. In fact, such data have led to a reconceptualization of unipolar depression as predomi-

nantly an early-onset disorder. Emerging data for bipolar disorder raise similar questions.

A consensus has yet to emerge on the most appropriate diagnostic label for the majority of children presenting to clinics with symptoms of extreme mood lability or irritability. Indeed, the most appropriate means for distinguishing bipolar disorder in young children from a range of other possible comorbid conditions, including unipolar depression and a disruptive behavior disorder, represents an area of considerable controversy (Biederman et al 1998).

*Differences from Adult Bipolar Disorder.* Some of the clinical features of pediatric mania may differ from those observed in adults. Most notably, children classified as manic seldom exhibit a euphoric mood (Carlson 1984). In contrast, such cases typically present with a predominantly irritable mood mixed with symptoms of depression (Davis 1979). The type of irritability observed in children classified as manic can be severe, persistent, and often aggressive (Wozniak et al 1995). The outbursts often include threatening or attacking behavior toward family members, other children, adults, and teachers. In between outbursts, these children are described as persistently irritable or angry in mood (Carlson 1984; Geller and Luby 1997). Aggressive symptoms may be the primary reason for the high rate of psychiatric hospitalization noted in these children (Wozniak et al 1995); however, with the exception of euphoria, the frequencies of other symptoms of mania seem to be similar between child and adolescent forms of this disorder (Faraone et al 1997). Another possibly distinctive feature is that the course of pediatric mania tends to be chronic and continuous rather than episodic and acute (Geller and Luby 1997).

*Comorbidity.* Data on the initial presentation of mood problems in children raise questions about precursors or course modifiers. For example, comorbidity, typically with disruptive behavior disorders, usually complicates the presentation in many children when there is a question of a bipolar diagnosis. Its symptomatic overlap with ADHD is a leading source of diagnostic confusion. Systematic studies of children and adolescents show that rates of comorbid ADHD range from 60% to 90% in pediatric patients classified as bipolar (Biederman et al 1996; Borchardt and Bernstein 1995; Geller et al 1995; West et al 1995; Wozniak et al 1995). Conduct disorder (CD) is also strongly associated with pediatric-onset bipolar disorder (Kovacs and Pollack 1995; Kutcher et al 1989; Wozniak et al 1995). Not surprisingly, mania comorbid with CD is associated with poorer functioning and an increased risk for psychiatric hospitalization, which may bias conclusions about comorbidity (Biederman et al 1997a). Although anxiety is frequently overlooked in

studies of pediatric-onset bipolar disorder, studies of youth with panic disorder and youth with mania document an important and bidirectional overlap (Biederman et al 1997b; Wozniak et al 1995).

Careful family-based and longitudinal studies are needed to clarify diagnostic boundaries and the relationships between these disorders. Because the diagnosis of bipolar disorder seems easier to make in adolescents or adults than in children, longitudinal studies should be conducted to examine developmental changes in symptoms among children of classically defined bipolar parents. Similarly, the available data point to the need to examine developmental changes in common symptoms, such as irritability, in large samples of community-identified children as they age into adulthood. Investigators engaged in these studies should be included in the Collaborative Network of Research Programs on Pediatric-Onset Bipolar Disorder proposed by the Workgroup.

*Endophenotypes.* Recent studies of adult bipolar disorder also generate research questions. Bipolar disorder is recognized as among the most strongly genetic of the complex mental syndromes. Such realizations should encourage efforts to identify endophenotypes observable during childhood. Recent studies among adults also have begun to elucidate neural circuits implicated in bipolar versus unipolar disorder (Blumberg et al 1999, 2000). Future longitudinal studies of children at high risk for bipolar disorder should begin as early as possible and should include measures that monitor these potential endophenotypes, as well as cognitive and affective mechanisms involved in the behavioral expression of bipolar disorder. These studies will complement ongoing genetic studies and may elucidate markers of increased biological risk in vulnerable premonitory children. Consequently, efforts to examine endophenotypes and genetic factors should be included in the Collaborative Network of Research Programs on Pediatric-Onset Bipolar Disorder proposed by the Workgroup. Including in this network of studies the offspring of the bipolar probands who have already participated in the NIMH's genetic linkage studies would be sensible and cost-effective.

*Given the Current Diagnostic Controversies and Increasing Use of Psychotropic Medications for Young Children, Does Treatment of Children with SSRIs or Psychostimulants Lead to an Increased Risk of Developing Pediatric Bipolar Disorder?*

**RECOMMENDATION 5.** A research initiative is needed to monitor and assess the potential of antidepressants or psychostimulants to induce the onset of bipolar disorder in vulnerable children.

**RECOMMENDATION 6.** A research initiative is needed to evaluate nonpharmacologic treatments and preventive interventions in children at risk of developing pediatric mania.

*Potential Risks Associated with SSRIs and Psychostimulants.* Given that many psychopharmacologic treatments for behavior disorders can exacerbate mania in adults, research is needed that carefully examines the impact of such treatments on children. The proportion of depressed youth in whom bipolar disorder will eventually develop is unknown.

The relative risk of switching from depression to mania as a function of drug class is unknown, but clinical lore suggests that bupropion and monoamine oxidase inhibitors may present a lower risk than TCAs or SSRIs (Biederman et al 2000; Frances et al 1998; Zarate et al 1995). A randomized clinical trial of a non-SSRI antidepressant against any SSRI in children aged 6 to 12 years with major depressive disorder, stratified on the presence or absence of a first-degree relative with bipolar disorder, might provide evidence concerning the relative effectiveness of these two drug classes and the relative impact of the family history as a risk factor for antidepressant-induced mood switching. The role of specific genetic factors should also be evaluated (Mundo et al 2001); however, it will be a complex task to solve the ethical problems posed by the requirement to balance the urgent need for improved treatment effectiveness against the potential risks to study participants.

Although recent studies examining short-term SSRI effects in children with depression or anxiety disorders document low rates of manic “switching” (Emslie et al 1997; March and Curry 1994; RUPP Anxiety Study Group 2001), longer-term studies in clinically referred patients suggest that the number of depressed children who switch may be high (Geller et al 1994, 2001b). On the other hand, data from population-based samples suggest a much lower risk (Lewinsohn et al 2000a). Moreover, in clinical samples treated acutely with SSRIs, a sizable group of children shows signs of “activation” or irritability. These findings raise questions regarding the predictive relationship between such responses to an SSRI and later risk for bipolar disorder, but the power of these phenomena as risk factors for bipolar depression has not yet been tested in representative population samples.

Factors that predict later bipolar disorder in clinical samples include the presence of unipolar depression, a young age at first depressive episode, psychotic features in the initial depression, a family history of bipolar illness, and hypomania during treatment with antidepressants.

As the nosologic issues become clearer, an intensive effort will be required to understand the type and sequenc-

ing of pharmacologic treatments for ADHD comorbid with signs suggestive of bipolar disorder. The current literature based on open trials is confusing. Some authors suggest that ADHD does not respond to stimulants until mood lability is controlled (Biederman et al 1999, 2000), whereas others note that there is no evidence that methylphenidate precipitates or worsens young adult bipolar disorders in susceptible individuals (Carlson et al 2000).

*Psychotherapeutic Treatments.* Although the efficacy of CBT and IPT in acute unipolar major depression is well documented, no data examine their utility in adolescent bipolar depression. A trial of manualized psychosocial treatment to reduce the risk of, for example, possible drug-induced switching makes clinical sense and provides an ethical context for psychopharmacologic trials in non-responders to psychosocial treatment. At present, efforts are underway to determine whether the family-focused psychoeducational treatment program developed for use with bipolar adults is efficacious for adolescent bipolar patients (Miklowitz et al 2000).

*Prevention.* Current evidence suggests that pediatric health care providers typically do not recognize depressed mothers or children with symptoms of mood disorders (Christiana et al 2000; Heneghan et al 2000). These problems may be compounded by misdiagnosis. Because many pediatricians receive some training on the best way to recognize and treat ADHD but no training on mood disorders, it is not surprising that some children with bipolar disorder might be misdiagnosed and experience severe adverse reactions to stimulants or antidepressants prescribed for ADHD or depression. Consequently, the NIMH should consider funding studies that examine the benefits of educating the public, pediatricians, and other primary health care providers about the risks, symptoms, recognition, and treatment of early-onset mood and anxiety disorders, including bipolar disorder. Recognition of the importance of a family history of mood and anxiety disorders would likely be a key element of such an educational program (Geller et al 1994).

### **Crossing the Boundaries, and the Need for a Capacity-Building Plan**

*Given the Size of the Problem, the Scientific Opportunities, and the Small Number of Well-Trained Clinical Researchers, There is a Clear Need for Innovative Strategies to Increase the Number of Investigators Working in this Area of Research*

**RECOMMENDATION 7.** Develop and fund a capacity-building plan to support the multidisciplinary training of clinical and preclinical investigators interested in pursuing

research careers in the field of childhood-onset mood disorders.

An integrated knowledge base is critical to advancing the etiologic understanding of mood disorders across the life span. As a result, the interdisciplinary training of researchers must become the norm; however, there is an acute shortage of developmentally oriented clinical investigators with sufficient interdisciplinary training to leverage effectively the rapidly advancing fields of epidemiology, genetics, neuroimaging, and the developmental neurosciences. One specific challenge is to reduce the fragmentation of knowledge across the various clinical disciplines and the emerging knowledge base in the developmental neurosciences.

The shortage of well-trained mental health investigators focused on children and adolescents has been recognized repeatedly (Institute of Medicine 1989; Leckman et al 1995; NIMH 2001). A major obstacle to expanding the pool of trainees is the lack of sufficient financial support for research training.

Recently, another NIMH Advisory Council Workgroup has made several innovative proposals, including a loan forgiveness program, funding to support research mentoring, and the development of research supplements (modeled along the lines of supplements for minority researchers) to encourage investigators in other fields to receive training in childhood-onset mental disorders (NIMH 2001). We support the development of these initiatives.

### Conclusions

Before the 1980s and 1990s, when clinical and epidemiologic research on depression was confined almost entirely to adults, it came as a shock when national surveys noted that adults often reported onset of their depressive disorder in the late teens or earlier. Now that studies of children and adolescents are available, it is becoming clear that many, and perhaps most, individuals with a depressive disorder began to experience serious symptoms early in adolescence, and that their vulnerability to develop these conditions may have been established even earlier.

The proportion of federally and industry-funded research on the causes, treatment, and prevention of child and adolescent depression is low when one considers the significance of these findings or the size of the child population. Treatment and prevention research have hardly begun to catch up with the clear evidence that unipolar and bipolar disorders are often diseases of early onset with a potentially lifetime course. If we were considering juvenile-onset diabetes, asthma, or AIDS, other chronic diseases that can begin in childhood, a comparable disparity between the reality and the allocation of research resources would be seen as a major threat to public health.

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All of the authors are members of a Workgroup organized by the NIMH to identify strategically important areas of research concerning the development and natural history of major mood disorders. JFL and CAN were privileged to serve as Chair and Co-chair of the Workgroup. Joan Cole of the NIMH assisted in many aspects of the preparation of this report.

This article summarizes aspects of a longer preliminary report prepared by members of this Workgroup. Six separate topics were addressed in the preliminary report: 1) environmental and biological risk factors in mood disorders (CH, PMP, MMW); 2) age, period, and cohort effects with regard to the development of major depressive illness and bipolar disorder across the life span (EJC, PML); 3) disease onset and progression of major depressive illness and bipolar disorder across the life span (DSP, HHG); 4) neurobiology of early-onset major depressive and bipolar disorder (JK, CAN); 5) opportunities and gaps in the treatment of pediatric mood disorders (JSM); and 6) opportunities and gaps in the prevention and early detection of these disorders (JFL, DSK, MH, KH). Copies of these unpublished documents are available upon request from the chair of each subgroup (the chair is the individual whose initials are listed first). These unpublished documents include the bibliography of the 18 studies tabulated by the age, period, and cohort effects subcommittee in their evaluation of possible cohort effects among youth born in the two decades before or after 1975 (EJC). Some of the views expressed in these unpublished documents are controversial and do not reflect the viewpoint of all members of the Workgroup. These issues were subsequently addressed and resolved so that the final report reflects a consensus of the entire panel.

This manuscript is one of ten prepared by workgroups under the auspices of the National Institute of Mental Health (NIMH) strategic planning initiative for mood disorders research. Each of the workgroups was given the specific charge to 1) review the state of their assigned area; 2) identify gaps and state a vision of where the field should be going and why; and 3) make general recommendations for NIMH to consider regarding research initiatives that would advance and improve the knowledge and treatment of mood disorders. This document reflects the opinions of the authors and not those of NIMH, but was used in an advisory capacity while the actual strategic plan was developed by NIMH staff. Overall guidance was provided by the National Advisory Mental Health Council.

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