The Prevention of Mental Disorders in General Psychiatric Practice:

Implications for Assessment, Intervention and Research

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FOREWORD

The current report provides a systematic review of the scientific literature in five areas that are highly relevant to the practice of general psychiatrists. Because this report is designed for submission to the Council on Research it focuses its review on very specific recommendation to the Council and to the APA. We plan to submit a highly condensed version of this report to the *American Journal of Psychiatry* in order to inform a broad range of practitioners and clinical researches about rapid advances in the science of preventing mental disorders. The current report begins with an Executive Summary and concludes with a detailed set of recommendations to the Council and APA. The meat of the report, however, is in its mid-section: a scientific review of the very promising research in five domains of prevention. Our recommendations are drawn systematically from this scientific review. We encourage readers to review the Executive Summary and our recommendations. However, we feel readers who can examine the scientific review carefully will be richly rewarded. We have provided a detailed Table of Contents to help readers navigate this section. The current report is complete except for cross checking a small number of references. The Task Force, of course, will be responsive to suggestions from the Council

During the last decade, prevention science has come of age. Improved methods of research design and measurement have helped. So has significant funding for large scale and ambitious prevention projects. The essential ingredient, however, has been the extraordinary diligence and patience of prevention scientists. A clinical trial testing the efficacy of a novel pharmacotherapeutic agent can be completed in 6-12 months. Prevention trials often take many years and we have reported on trials for which there follow-ups more than fifteen years after the initial intervention. These trials have been conducted according to very high standard and, for some of them, the results have been breath taking. Our review of the literature illumined for us, as we worked on this report, a field we thought we knew well. It energized us and increased our resolve to engage our colleagues in an extraordinary clinical opportunity: the prevention of major mental illness before it becomes established. We hope this report has a similar impact on its readers.

David Reiss, MD.
May 10, 2005

EXECUTIVE SUMMARY

This report summarizes current scientific knowledge in five domains most relevant to the practicing general psychiatrist. Based on this review of evidence this report makes clear, highly-focused recommendations to the American Psychiatric Association for changes in the DSM system, for its advocacy for preventive screening and intervention, for its support of urgently needed research and for its continuing education of residents and practitioners in the rapidly advancing field of prevention research. The domains of prevention reviewed in this report are: 1) the recognition of prodromes of major psychotic disorders, particularly schizophrenia and bipolar illness; 2) preventive interventions for children of depressed parents; 3) the preventive implications of links between primary and secondary psychiatric disorders; 4) the impact of adverse experiences in early childhood on adolescent and adult psychopathology and the long term effects of early preventive intervention and 5) the prevention of adolescent suicide. Rapid advances in these fields reflect major strides in three scientific areas: epidemiology, controlled clinical trials of preventive intervention and health economics.

The Five Domains Reviewed

Recognizing early signs of psychosis We review evidence for both schizophrenia and bipolar illness. For schizophrenia we review evidence on the importance of early detection and treatment and describe current trials to improve early detection and prompt intervention. We also summarize what is known about the prodromes of schizophrenia and trials underway to reduce the likelihood that patients will convert from prodrome to full-blown illness. There is less research in the area of bipolar illness. We review the controversies surrounding the diagnosis and treatment of early appearing bipolar illness in children and adolescents and recommend, on an urgent basis, a program of research to fill huge gaps in knowledge in this area.

Working with children of depressed parents. We summarize what is known about the links between parental depression and offspring vulnerability to mental disorders as well as the risk and protective factors that might moderate this vulnerability. Intervention strategies, and the results of rigorous controlled trials, are summarized along with a set of specific recommendations for implementing effective prevention programs and expanded research.

Preventing secondary disorders in patients being treated for primary disorders. We summarize the epidemiological evidence of the link between primary disorders and secondary disorders. Most of the literature focuses on links between impulsive disorders and secondary substance abuse disorders. There is also literature linking anxiety disorders and later substance abuse and later depression. Intervention strategies are just making use of these important findings; we summarize the emerging literature and recommend research in two domains: the impact on secondary disorders of successful treatment of primary disorders and the possible risk of secondary disorders that may arise as an unintended side effect of medications used to treat primary disorders.

Preventive interventions in early childhood We summarize current understanding of mechanisms that link early childhood experience with the development of psychopathology years later. We focus on the importance of early secure attachment and review the long-term effects of interventions that enhance parent-child attachment in high-risk settings. Our recommendations focus on the importance of prenatal and postnatal maternal psychopathology; these clinical conditions should be a major target for future prevention trials.

Preventing Adolescent Suicide This section summarizes what is known about the risk and protective factors for adolescent suicide. We then review evidence on the efficacy of prevention programs that treat major risk factors such as adolescent psychopathology as well programs that identify adolescents who are already suicidal. Research is indicating some approaches that do not work and others that do such as programs that enhance adolescent problem solving, coping and social skills. Recommendations focus on

improved screening, enhancing the efficacy of preventive interventions and increasing attention to psychopathology in parents.

Recommendations for the American Psychiatric Association

Patient assessment and DSM V We recommend that DSM V use recent empirical evidence to make it more useful for research, screening and intervention in the field of preventive psychiatry. The DSM revision process should consider four additions to DSM V. First, a new section or axis should permit the clear description of *general risk clusters.* These are risk and protective factors that influence an individual's risk for a range of psychopathology. Second, DSM V should, where scientific data permit, *add information about prodromes and emerging patterns of illness* to its description of specific syndromes. Third, DSM should consider adding to the description of specific syndromes, where scientific evidence is compelling, *the risks of secondary psychiatric disorder*s and the factors that moderate those risks. Finally, where data permit, DSM revisions should consider *the psychiatric vulnerability of children of parents with specific psychiatric disorders* and the risk and protective factors that moderate that vulnerability.

Advocacy for Improved Services We recommend that the new prevention committee *provide scientific input to treatment guidelines* where evidence permits. Moreover, the committee can guide APA's advocacy for adequate screening and prevention services in three areas. First, APA should advocate for *integration of prevention and treatment services into better-articulated clinical plans.* The current report provides several examples. Second, APA should advocate for *improved family-based services* to assure conjoint evaluations of parents and children where such evaluations are critical to prevention efforts. We provide many examples of these opportunities later. Third, as we illustrate later, APA should advocate for treatment *services that are planned around an increasing understanding of child, adolescent and adult development.* Fourth , APA should recognize more clearly the obstacles to screening and prevention in US health care systems, should inform its members as well as legislatures of more successful systems abroad and *take better advantage of US opportunities for improved screening and preventions services such as those in some Medicaid supported medical care settings and employee assistance programs.*

Advocacy for Research We recommend that APA broaden its advocacy of mental health research to include urgent areas in prevention. These include improved approaches for screening, expanded trials for promising preventive interventions, and improved understanding of the interplay between risk factors, including genetic factors, and protective factors.

Continuing Education of Psychiatrists Based on our review of the scientific evidence relevant to prevention, we recommend APA efforts in three areas. First, *residency education in psychopathology should be reoriented to give strong emphasis to the development of psychopathology and to opportunities for prevention*. Second, APA should take a leadership role in *updating its members on advances in prevention research* at annual meetings and in publications. Third, APA *should plan joint continuing activities with professional association that focus on prevention.*

TABLE OF CONTENTS

REVIEW OF PREVENTION SCIENCE

In recent years, the field of prevention science has made dramatic advances as a result of several factors including (1) the refinement of epidemiological research methodologies; (2) the demonstrated efficacy (through randomized, controlled clinical trials) of specific preventive interventions; and (3) a clearer understanding of mental health economics. These advances have powerful implications, not only for psychiatric research and training, but for psychiatric practice as well in that they allow improved assessments (as in schizophrenia, for example), of the likelihood that a mental illness is imminent before criteria for a full-blown disorder are met. Further, controlled clinical trials have suggested new interventions that may prevent the appearance of a clinical syndrome where an individual has been identified as being at risk for developing a mental disorder.

Epidemiological Methods

As a result of advances in epidemiological methodologies, we know much more about *risk and protective factors* that influence the incidence of new disorders, the probability of relapse from existing disorders and the likelihood of secondary clinical problems arising from mental disorders. New epidemiological techniques have moved beyond establishing estimates of disorder incidence and prevalence and can now document the distribution of biological and psychosocial risk and protective factors in well defined populations and even track the course of evolving disorders.

Recent advances in genetic epidemiology are especially noteworthy. Using quantitative and molecular techniques, the distribution of genetic risk in very well specified populations has been established. Recently, promising data have been published on the interplay of these genetic risk factors with well-measured aspects of the social environment enhancing our knowledge of the development of many disorders including schizophrenia, substance abuse disorders, depression and conduct problems (Kendler et al., 1995; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Spotts, Neiderhiser, Towers et al., 2004).

Controlled Trials of Preventive Interventions

Controlled trials have demonstrated increasing evidence of the *efficacy of preventive interventions* in such areas as schizophrenia in adolescents and adults, serious conduct problems in childhood, depression in both children and adults, and substance abuse. Methodological improvements in preventive trials include better sampling of at risk populations, more effective and focused intervention procedures, a better use of data on the importance of the family context of at-risk individuals, and very long term follow-up data, in some studies now extending over 20 years, (D. Olds et al., 1998; Spoth, Redmond, Shin, & Azevedo, 2004). Of particular importance, techniques have been developed for testing the effectiveness of some of these research derived interventions in ordinary clinical practice settings.

Advances in Health Economics

These advances provide an increasingly accurate picture of the loss--from the perspective of productivity, health care costs and human capital--of major metal illness as well the cost effectiveness of preventive treatments. These advances are central not only to the scientific understanding of preventive interventions but for support of funding for screening and preventive treatment procedures (e.g., (Pirraglia, Rosen, Hermann, Olchanski, & Neumann, 2004; Simon et al., 2002; Vinokur, Van Ryn, Gramlich, & Price, 1991). Indeed, government agencies can now rank preventive interventions not only for evidence of efficacy but their cost-benefit ratios. (see report by the State of Washington)

From a broad range of important areas of research we have picked five areas. We used the following criteria to select these five areas. First, the preventable disorders or *clinical outcomes were of serious concern to general psychiatry*. For example, we have included an update on the prevention of schizophrenia, bipolar disorders, psychiatric disorders in children of depressed parents and suicide. Second, in the areas we have selected *research in the area has progressed far enough* to clarify patients at risk for disorders, useful preventive interventions or clear agenda for research. Some domains have progressed far

enough to provide findings relevant to all three of these. Third, we picked topics that cumulatively illustrate the important *relationships between child and adult disorders.* Prevention research summons general and child psychiatrists to combine efforts in both research and practice. The topics we have picked illustrate three facets of these connections. We consider research on the consequences for children of major depressive disorder in one or both parents (section 2 below). We also consider how interventions focused on risk factors in early childhood might prevent adult disorder (section 4 below) and finally we consider how disorders that express themselves first earlier in development may lead to secondary disorders later in development (section 3 below). This report summarizes research data on these five areas. There are many promising areas of prevention we have not reviewed. Some, such as prevention of substance abuse and dependence, have been reviewed extensively (e.g. (Sloboda & Bokoski, 2003). Others such as the prevention of anxiety disorders or posttraumatic stress disorders should be reviewed in subsequent reports.

Recognizing early signs of mental disorder and treating high-risk clinical state

Current diagnostic guidelines and practices for psychotic disorders focus on the manifestations of established illness. However mounting evidence suggests the short and long-term advantages of recognizing *emerging* psychotic illnesses and treating them before they become firmly established.

Research on schizophrenia provides a good example of this strategy. As we will review, there are two foci of research in this field. The first concerns *already established illness where denial and minimization, on the part of the patient or family, inhibits early recognition.* In this domain research centers on how to pierce these barriers in order to bring the patient to early, prompt and effective treatment. The second area of work focuses on *identifying prodromes of illness*. Here the effort focuses on the recent development of attenuated positive symptoms of psychosis and a recent history of diminished social, educational and/or occupational functioning.

More recently, there is a strong interest in applying the same framework to bipolar illness. Motivation for this initiative comes from parents who are bipolar and want to seek the best preventive treatment for their children. However, research that we will review is just beginning in this area and lags behind that in schizophrenia. Nonetheless, there is sufficient data to motivate a broad spectrum of research on early detection of the disorder and identifying prodromes of the disorders, particularly in children.

Working with children of parents who are being treated for a major mental disorder

Research has now provided abundant data on children of parents with a major depressive disorder. As we will document, several studies suggest that at least half the children of depressed parents will develop a major mental disorder in their lifetime. Moreover, in many cases, *parents are concerned about the impact of their illness on their children and usually welcome any help in this domain that clinicians can offer.* Thus, parents' justifiable concern with the mental health of their children is an important focus of work for the general psychiatrists that are treating them. Moreover, results of recent randomized controlled clinical trials suggest specific preventive interventions to prevent these children from becoming depressed.

Preventing secondary disorders in patients with an established primary psychiatric disorder

As detailed in a subsequent section, epidemiological research has clearly demonstrated that some major mental disorders typically appear after an initial or primary disorder. In some cases the primary disorder may be an expression, earlier in development, of an underlying genetic risk factor. The secondary disorder is a later manifestation of the same risk factor. Thus, the appearance of the primary disorder is warning that another disorder, perhaps even more serious, is waiting in the wings. It remains to be documented whether effective treatment of the primary disorder may have help prevent secondary disorders. Additional prevention strategies aimed at the secondary disorder may also be indicated.

Preventing the long-term consequences of adverse experiences in early childhood

As we will review, data is accumulating on the extended effects, often into adulthood, of adverse experiences in childhood. Data support three perspectives on these long term effects: the sustained effects of cumulative risk in childhood, the interplay between adverse experiences and specific, time-delimited periods of sensitivity and the extended impact of fetal exposure to maternal substance use and the

intrauterine consequences of maternal malnutrition and maternal psychopathology. Research attentions has also centered on the protective effects of early, secure attachment. Several intervention programs conducted in early childhood have shown remarkably long-lived effects in preventing serious psychopathology. The effects extend into late adolescence and early adulthood.

Preventing suicide in adolescents Data are accumulating on a broad range of risk factors for adolescent suicide. However, we have only preliminary data suggesting successful approaches to prevention. There is increasing data, for example, on effective prevention of depression in adolescence as well as treatment of depressive disorders once they are manifest. However, we need direct evidence that these effective treatments reduce the incidence of subsequent suicide. School based programs are showing some promise, particularly programs that screen for suicidal adolescents and that focus on teaching social and cognitive skills to high risk teens.

Concepts of Risk

Uniting all approaches to prevention is a concept of *risk for mental disorder*. Concepts and measurements of risk are essential to designing effective preventive interventions and for appraising their efficacy. This report draws on several fundamental concepts of risk.

Most major psychiatric syndromes develop over a long period of time. Although florid clinical symptoms may appear suddenly careful clinical histories and detailed longitudinal studies show that individuals' progression towards illness often reflect heritable risk factors and exposure to environmental risk factors. Thus, in the course of development, risks may accumulate to increase the probability of serious psychopathology a concept called *cumulative risk.* Among those risk factors may be those that are *specific for particular mental disorders*. For example, by age 3, children rated as high in irritability, impulsivity and emotional liability have been found to be 3 times more likely to meet criteria for DSM III R antisocial personality disorders at 18 and 21 years than 3-year-olds with normative scores on these dimensions (A. Caspi, Henry, McGee, Moffitt, & Silva, 1995). Other risk factors are *nonspecific;* they predispose children and adolescents to a range of psychopathology. These include poor nutrition, minority status, severity of parental mental illness and neighborhood violence (A. J. Sameroff, 1998) .

Of particular importance for clinicians, is the concept of *imminent risk.* For some areas of psychopathology a cluster of factors suggest that a full blown and serious psychiatric disorder will soon emerge unless preventive treatment is instituted. We review below, for example, evidence of such risk factors for schizophrenia. Research is also well advanced to identify similar signs of imminent substance abuse disorders in adolescents: temperamental features marked by restless activity, emotionality and aggressiveness coupled with sustained parent-child conflict, alienation from the family, reduced adolescent self control and involvement with deviant peer groups (Wills & Dishion, 2004; Wills, DuHamel, & Vaccaro, 1995; Wills & Yaeger, 2003). This cluster of risk factors can help a clinician determine whether substance use by an adolescent presages serious substance abuse disorders. Indeed the concept of *risk clusters* is becoming increasingly important for clinical and preventive practice and we return to it in our recommendations.

Finally, careful assessment of risk factors alone may be of limited usefulness unless clinicians also assess *protective factors.* Protective factors fall into three broad categories: personal resilience in children and adults, protective features of the family including high quality of parenting for children and satisfying marriages for adults and finally protective factors in the community including physical safety and job opportunities. Evidence for the dramatic role of these protective factors is mounting. For example, adopted children at genetic risk for developing schizophrenia are unlikely to develop this syndrome in well function adoptive families (Tienari et al., 2004). Likewise, children with substantial intrauterine exposure to alcohol show little or none of the cognitive stigmata of this exposure if reared in favorable family environments (Jacobson, Jacobson, Sokol, Chiodo, & Corobana, in press). A satisfying marriage appears to be an important buffer to both adult impulsive disorders and depression (e.g. (Laub, Nagin, & Sampson, 1998) even when the genetic influences on both psychopathology and on the capacity to form intimate relationships are strictly controlled (Spotts, Neiderhiser, Ganiban et al., 2004)

Risk factors are linked to strategies of prevention three ways. Some prevention efforts are both inexpensive and effective and it is feasible to introduce into large populations of individuals. Following Gordon (Gordon, 1987), these are termed *universal* preventive interventions. For example, the good behavior game is a standard classroom procedure for fostering self-control and cooperative behavior in young children. Its effects on developing psychopathology have been rigorously evaluated by Kellam and colleagues (Kellam & Anthony, 1998; Kellam, Rebok, Ialongo, & Mayer, 1994). Some preventive interventions are aimed at children or adults who are at high risk but show no signs of disorder; Gordon has termed these *selected* interventions. Interventions of this kind are described in section 2 and 4 below. Finally, some interventions are targeted at individuals already showing some early signs of disorder. These *indicated* preventions are described in sections 1) and 5) below.

1) Early Identification and Treatment of Schizophrenia and Bipolar disorders

Schizophrenia

Rationale for Early Detection and Intervention

Schizophrenia is a serious mental disorder with a lifetime morbid risk of 1%. Despite being a relatively rare disorder it continues to exert a major economic burden on society. The natural history of schizophrenia is often chronic and debilitating. The rationale for early detection and intervention with schizophrenia has been extensively discussed (T. H. McGlashan & Hoffman, 2000; T. H. McGlashan & Johannessen, 1996; McGorry, 1995). Neurobiological deficit processes associated with the severity and chronicity of schizophrenia are already present at the time of the first episode (T. H. McGlashan & Johannessen, 1996). The interest in this area stems from the belief that early intervention may result in better treatment outcome with better quality of life for the patients and their families (Larsen, Johannessen, & Opjordsmoen, 1998; Loebel, Lieberman, Alvir, Mayerhoff, & et al., 1992; T. H. McGlashan, Miller, & Woods, 2001).

Pathophysiology

Psychosis in all of its schizophrenic spectrum manifestations has an existence long before "official" onset in the form of sub-rosa, neurobiological deterioration that constitutes the core pathophysiology of disorder (T. H. McGlashan & Johannessen, 1996). This process appears to be quite active 2-3 years before onset and sometimes for 1-2 years after onset until a stable plateau is reached in the course of disorder. In fact, the actual disorder with its disabling positive and negative symptoms is not likely to become manifest until late in this process of neurobiological deficit formation (T. H. McGlashan & Hoffman, 2000). We are only beginning to understand the nature of these processes. However, despite our ignorance, there are reasons to hope that antipsychotic and psychosocial treatments in their current forms may be unusually efficacious during this critical period, effective directly with the early phase symptomatic manifestations and effective potentially in preventing progression of the disorder towards deficit and chronicity.

Phases of Schizophrenia

Schizophrenia can be viewed as a disorder that develops in phases: premorbid, prodromal and psychotic; (Beiser, Erickson, Fleming, & Iacono, 1993; Haas & Sweeney, 1992 ; Keshavan & Schooler, 1992 ; Loebel et al., 1992).

The *premorbid phase* contributes to the individual's vulnerability to schizophrenia (Olin & Mednick, 1996). It encompasses the prenatal and perinatal developmental periods and the occurrence of any complications such as obstetrical trauma. It also includes early childhood, when there may be disruption to mother-child bonding or maladaptive learning and abnormal family communication patterns.

The *prodromal phase* involves a change from the premorbid functioning and extends up to the time of the onset of frank psychotic symptoms. (Beiser et al., 1993; Loebel et al., 1992). The average length of the

prodromal phase is between two and five years. (Hafner, Maurer, Loffler, & Riecher-Rossler, 1993) (Beiser et al., 1993; Loebel et al., 1992). During the prodromal phase the subject experiences substantial psychosocial impairment in functioning (Jones, Bebbington, Foerster, Lewis, & et al., 1993). Common early prodromal symptoms are non-specific symptoms such as sleep disturbance, anxiety, irritability, depressed mood, poor concentration and fatigue, and behavioral such as deterioration in role functioning and social withdrawal (Yung & McGorry, 1996). Positive symptoms such as perceptual abnormalities, ideas of reference and suspiciousness develop late and herald the imminent onset of psychosis. (Woods et al., 2001).

An emotionally charged event and/or a stressful environment may precipitate the psychotic episode. The psychotic stage of early schizophrenia (psychosis) can be seen as progressing through an acute phase, an early recovery phase and a late recovery phase. (Beiser et al., 1993). The acute phase refers to the presence of florid psychotic features such as delusions, hallucinations and formal thought disorder. The early recovery phase refers to the first six months following acute treatment and the late recovery phase refers to the following six to eighteen-months period. The period following recovery from a first episode of psychosis and extending for up to five years subsequently has been termed "the critical period." (Birchwood, Todd, & Jackson, 1998). This is because most follow-up studies have shown that up to 80% of patients would have relapsed within this 5 year-period.

Early Treatment Prevention Aims

Reducing duration of untreated psychosis (DUP) in the post-onset phase and introducing antipsychotic treatment in the pre-onset (prodromal) phase aim both to treat and to prevent, i.e., treat active symptoms and prevent course progression. The nature of the prevention aim depends upon the phase of disorder. For example, it is hoped that reducing DUP in the post-onset phase will provide tertiary prevention by reducing the severity and chronicity of established schizophrenia. It is hoped that treating prodromal symptoms in the pre-onset phase will provide secondary prevention by delaying the onset of disorder (reducing prevalence), or primary prevention by averting onset all together (reducing incidence).

Post-Onset Early Identification and Treatment

First-Episode Psychosis and Duration of Untreated Psychosis (DUP)

Internationally, the average DUP has been found to be between 1 and 2 years (T. H. McGlashan, 1999). Longer DUP has been found to be associated with male gender, poor premorbid functioning, an insidious onset of psychosis, and the presence of negative symptoms (Drake, Haley, Akhtar, & Lewis, 2000; Larsen, McGlashan, & Moe, 1996). The reasons for treatment delay accounting for long DUP are multiple and include ignorance, denial, stigma, lack of motivation, absence of information about early psychosis and lack of access to appropriate interventions (Drake et al., 2000; Johannessen et al., 2001).

There is evidence supporting a relationship between DUP and short-term outcome at 1 and possibly 2 years (Norman & Malla, 2001). The relationship is strongest between DUP and outcome at 1 year on measures such as rates and levels of remission and levels of positive symptoms. The outcomes of negative symptoms, disorganization and anxiety are more likely to be influenced by longer-term characteristics such as premorbid adjustment, earlier age of onset, gender and the length of the prodromal period. Lieberman et al. (Lieberman et al., 2001) reported that approximately two-thirds of the studies on DUP showed a significant association between shorter DUP and better outcome on one or more measures and that none showed a significant association between longer DUP and better outcome on any measure.

The relationship between long DUP and poor outcome remains correlational rather than causal. An experimental design that randomizes first episode schizophrenia patients to immediate versus delayed treatment could determine causality but would be unethical. An alternative strategy is to engineer earlier detection of first episode schizophrenia in an entire healthcare sector and compare the clinical presentation, course and outcome of the patients coming to treatment in this sector with first episode patients presenting for treatment in "control" healthcare sectors without early detection (T. H. McGlashan, 1999). A project in Norway and Denmark, begun in 1997, is attempting to do just that, i.e., change DUP experimentally and

measuring the effect of that change on outcome Larsen et al, 1999; (Johannessen, Larsen, & McGlashan, 1999).

The project is known as TIPS, an acronym in Norwegian standing for early detection and intervention in schizophrenia. It is a prospective, longitudinal study of first episode psychosis from four Scandinavian healthcare sectors with equivalent first-episode treatment programs. Two of the sectors designed an early detection program (Early Detection sectors) and the other two relied on usual detection procedures (no Early Detection sectors). This is known as a parallel control design. Within the first two years of the project (1997-1998) it was clear that the early detection program was working in that DUP was significantly shorter in the Early Detection sector than it had been in the same sector in the years 1993-1994, i.e., *before* launching the early detection program (Larsen, Moe, Vibe-Hansen, & Johannessen, 2000). In fact, between 1993-1994 and 1997-1998, the mean DUP was decreased from 2.1 years to 6 months. This is a quasi-experimental study using a historical control design (the same healthcare sector before and after introducing the early detection campaign).

The TIPS parallel control study (i.e., the study with the Early Detection sectors and the no Early Detection sectors) admitted first-episode patients for 4 years, from 1997 to 2001. The Early Detection healthcare sector had 370,000 inhabitants, and the two parallel control sectors in Ulleval, Norway, and Roskilde, Denmark had a combined total of 295,000 inhabitants. For the entire sample, DUP was significantly shorter for patients entering treatment in the Early Detection sectors (median 5 weeks) than in the no-Early Detection sectors (median 16 weeks). At admission, compared to patients from the no-Early Detection sectors, patients from the Early Detection sector were younger, and their clinical status as measured by the Positive and Negative Syndrome Scale and Global Assessment of Functioning was significantly better.(Melle et al., 2004; Yung & McGorry, 1996) Overall, the TIPS findings, to date, strongly suggest that DUP can be reduced and that the reduction results in a healthier first-episode sample at intake. Whether reduced DUP changes the course of disorder awaits planned follow-up investigations.

Pre-Onset Identification and Treatment

Prodromal Phase

The average length of the prodromal phase is between 2 to 5 years; it involves a change from the premorbid functioning and extends up to the time of the onset of frank psychotic symptoms (Beiser et al., 1993; T. H. McGlashan & Hoffman, 2000) Non-specific and negative symptoms develop first. Common symptoms are sleep disturbance, anxiety, irritability, depressed mood, poor concentration and fatigue, and behavioral changes such as deterioration in role functioning and social withdrawal Yung, 1996 #3432]. Positive symptoms such as perceptual abnormalities, ideas of reference and suspiciousness develop late and herald the imminent onset of psychosis (Woods et al., 2001)

Prospective Prodromal Assessment Instruments

Substantial progress has occurred in identifying the prodromal phase prospectively. McGorry and his team developed the 'Personal Assessment and Crisis Evaluation' Clinic (PACE) in Melbourne, Australia to study and treat prodromal patients. They used a 'close-in' strategy to develop a set of criteria for identifying individuals at risk for psychosis There are three separate categories of selection criteria (McGorry, Yung, & Phillips, 2002) Category 1 requires at least one of the following attenuated (subthreshold) positive psychotic symptoms: ideas of reference, odd beliefs or magical thinking; perceptual disturbance; odd thinking and speech; paranoid ideation; and odd behavior or appearance. Category 2 consists of brief limited intermittent psychotic symptoms, which spontaneously resolved within a week. Category 3 combines functional decline in the previous year and genetic risk (a first-degree relative diagnosed with a psychosis or with a schizotypal personality disorder). A structured interview, the "Comprehensive Assessment of At Risk Mental States" (CAARMS) is used to determine whether the criteria are met. The first sample of twenty-one yielded an annual conversion rate to psychosis of 21% (Yung & McGorry, 1996). The second sample of forty-nine reported a 41% annual conversion rate (Yung

et al., 2003). Some highly significant predictors of psychosis were found: long duration of prodromal symptoms, poor functioning at intake, the presence of low-level psychotic-like symptoms, depression and disorganization (Yung et al., 2003).

McGlashan and his team at Yale University formed the 'Prevention through Risk Identification, Management and Education' (PRIME) Clinic and developed an assessment instrument to rate prodromal symptoms, the Scale of Prodromal Symptoms (Scale of Prodromal Symptoms) (T. H. McGlashan, 2001; T. J. Miller et al., 1999). The instrument's scales identify and measure five attenuated positive psychotic symptoms, six negative symptoms, four disorganization symptoms, and four general symptoms. The Scale of Prodromal Symptoms is embedded within a semi-structured interview, the Structured Interview for Prodromal Syndromes (SIPS), designed to diagnose prodromal syndromes and to rate severity of the prodromal symptoms according to the Scale of Prodromal Symptoms. The conversion rate was found to be 46% at 6 months and 54% at 12 months among patients diagnosed as prodromal (Tandy J. Miller et al., 2002).

Both the Comprehensive Assessment of At Risk Mental States and Structured Interview for Prodromal Syndromes have demonstrated good predictive validity (Tandy J. Miller et al., 2002; Yung et al., 2003). Two self-report questionnaires have been developed as initial screening instruments for this group of patients. Loewy, 2002; (Heinimaa et al., 2003; Johannessen et al., 1999)

Despite improved sensitivity and specificity of the present screening instruments, the possibility of unnecessary treatment of the false positive cases remains a major concern. There are presently attempts to enrich the fraction of true positive prodromal patients by using genetic analysis(Gottesman & Erlenmeyer-Kimling, 2001), neuropsychological testing (Hambrecht, Lammertink, Klosterkoetter, Matuscheck, & Pukrop, 2002); Francey et al, 2002; Hawkins et al, 2002], and sMRI (Pantelis et al., 2003).

Clinical Trials of Early Intervention in the Prodrome

Research clinics are being created to study, track, and test treatments for persons meeting criteria for being prodromally symptomatic and at risk for psychosis. For most of the persons who come to these clinics, prodromal symptoms have been distressing to both patients and their families (Woods et al., 2001; Yung & McGorry, 1996). Most of them have previously sought and received psychiatric treatment, including psychotropic medications (Phillips et al., 1999; Preda et al., 2002). Often, they have already accepted the label and role of patient and want to know more about the symptoms they are experiencing. If they meet research criteria for being "prodromal", they are informed of their increased risk and offered a plan of close monitoring and frequent visits to allow for early detection and immediate treatment should they develop psychosis, which could then be treated immediately (with a DUP of zero days). In the event that their "prodromal" symptoms evolve into a diagnosable or treatable psychiatric disorder other than schizophrenia, they will also be rapidly referred for appropriate management.

Some research prodromal clinics have also offered participation in trials of treatment. To date, three randomized clinical trials have been conducted. The first trial conducted from 1996 to 1999 by McGorry and his team was non-blind and patients were randomized to either treatment (risperidone, mean dosage: 1.3 mg/day plus cognitive psychotherapy plus supportive management (n=31)) or management alone without risperidone or cognitive psychotherapy (n=28) (McGorry, Yung, Phillips et al., 2002; T. J. Miller et al., 2003). The rates of conversion to psychosis at 6 months were 9.7% (3 out of 31) for the treatment group and 35.7% (10 out of 28) for the management control group (p=0.03). Minimal side effects were reported. Risperidone was discontinued after 6 months and all patients were offered ongoing management. After a further 6-month follow-up, another 3 patients in the treatment group developed psychosis. The risk of early transition to psychosis appeared to be reduced by the pharmacological and psychotherapy treatment, although one could not determined the relative contribution of either intervention.

McGlashan and his group initiated the second trial in January 1998. It is a four-site North American, double blind randomized study comparing the efficacy and safety of olanzapine (n=31) versus placebo (n=29) in the treatment of prodromal symptoms (T. McGlashan et al., 2003; T. J. Miller et al., 2003). Olanzapine was given in the doses from 5 to 15 mg/day (mean maximum dose: 10.2 mg/day). Both the drug group and

placebo group received the same psychosocial stress management intervention. Patients were enrolled in the trial for two years (one year of drug treatment or placebo and one year of follow up without study medication) before the blind was broken. Patients becoming psychotic at any point in the two years were placed on open-label olanzapine for 6 months.

The short-term (8 week) results revealed significant symptomatic improvement in the olanzapine treatment group (Woods et al., 2003). The one-year double-blind treatment phase results of the 60 patients have recently been reported (T. McGlashan et al., 2003) Sixteen patients developed psychosis, 11 from the placebo and 5 from the olanzapine treatment group (p=.08). Olanzapine was significantly effective in treating prodromal symptoms over the year (p=.04). The main side effect associated with olanzapine treatment was weight gain. The two-year study has just been completed and the results will be available in the near future.

A third trial begun in December 1999 by Morrison and colleagues in the UK focused on psychosocial treatment and randomized non-blindly 58 prodromal subjects to 6 months of cognitive therapy versus treatment as usual (monitoring and crisis intervention). Over 12 months of treatment and observation, cognitive therapy improved positive symptoms and reduced the likelihood of progressing to psychosis (Morrison et al., 2004) .

Early Identification and Treatment: Status Quo of Benefits, Risks, and Treatment Implications

Post-Onset Early Identification and Treatment

The benefits of treating diagnosable first psychosis as soon as possible are clear. The first appearance of psychosis is a major life event, and often a life-threatening event. The irrationality of psychosis is frequently accompanied by panic and lack of insight, states of mind that lead to serious "collateral damage" such as suicide, homicide, bodily harm, prison, coerced hospitalization, stigma from bizarre behavior, and fracture of existing social networks, to name a few of those that are most destructive and irreversible. Rapid treatment provides tertiary prevention by minimizing collateral damage. It also may provide increased treatment benefit insofar as preliminary data suggest that patients who receive treatment earlier in the course of their disorder are less ill to begin with and are more rapidly and completely responsive to treatment than they would be later in the course of their first episode. We do not yet know whether reducing DUP provides secondary prevention in the form of attenuating the development of chronicity in schizophrenia. Studies are underway testing this hypothesis
.
There are essentially no risks associated with post-onset early identification and treatment over and above the usual and established risks of treating first-episode schizophrenia. Given this, it is clear that reducing DUP in schizophrenia should be the focus of major public mental health campaigns designed to increase awareness of psychosis through education of the public, the schools, and healthcare networks.

Pre-Onset Early Identification and Treatment

Pre-onset clinical assessment aims to identify high-risk status, that is, risk for the imminent onset of psychosis. This may lead to a conservative treatment strategy involving close monitoring of the person's clinical state and prescribing active treatment at the time psychosis emerges. A less conservative treatment strategy involves going beyond clinical monitoring and prescribing active antipsychotic treatment for the at-risk state, the aim being to delay or prevent onset.

For the patient who is truly a risk, the benefits of both monitoring and active treatment are clear and are identical to the tertiary preventive benefits of post-onset early treatment. The benefits of treating risk may actually be greater if treatment delays onset to a later age and period of development. The three studies conducted thus far suggest that such benefits are not unreasonable to expect, although more investigation is clearly necessary.

The risks associated with treating versus monitoring the risk state to its denouement, unlike early post-onset treatment, are substantial and reside in the fact that many persons identified as being at risk are false-positives. As such, they are exposed to the stigma of being labeled at risk and to the risks of treatment side effects without receiving any of the benefits associated with treatment. For this reason the less conservative strategy of active treatment in the prodrome requires more research before being implemented clinically. The conservative treatment strategy, however, is endorsed by research, i.e., active monitoring of the patient's clinical state and allowing time to determine whether the patient is truly at risk or not. Such patients may not be exposed to the risk of active antipsychotic treatment, but they are exposed to the risk of being labeled at risk. However, it is our opinion that this risk is justified because the predictive capacity of the new prodromal assessment instruments has been demonstrated repeatedly to be substantial.

Recommendations: **Early Identification and Implications for Research, for Assessment and Nosology (DSM V), and for Mental Health Care Service Systems.**

Research

Progress to date provides a clear mandate for further research in the early identification of schizophrenia in both its pre and post onset phases. The pathophysiology of the disorder wreaks its greatest devastation in the period before and around onset and in order to understand schizophrenia, it must be studied before it becomes a smoking gun. Identifying and studying persons at high risk promises to match investigative technology and hypothesis testing with the phases of greatest disease activity, thus maximizing the yields of translational investigation with genetics, neurobiology, neuroimaging, developmental psychopathology, neurocognition, etc.

Identifying high risk groups, both premorbidly and prodromally, and following and studying them over time clinically and with multiple laboratory measures will generate predictors of conversion to psychosis, thereby allowing refinement of the definition of high risk so that the ratio of true to false positive subjects in any high risk sample will steadily increase (and steadily reduce the likelihood of exposing false positive high risk subjects to the danger of stigma and unnecessary treatment).

Further treatment research is clearly indicated and has been noted above

.

Nosology and DSM V

Our ability to identify high risk syndromes that are valid precursors to identifiable DSM IV diagnostic entities, such as schizophrenia, strongly suggests a new perspective for DSM V. DSM V, for example, should describe active clinical states or syndromes such as the prodrome to schizophrenia. It should also list and describe markers that confer high risk to persons who are clinically premorbid. These individuals might benefit from attention to the predictive markers that can be treated, much as high cholesterol can be treated to prevent heart disease.

Increasing ability to predict schizophrenia prospectively will also require that DSM V define the onset of psychosis in general and schizophrenia in particular. Currently the DSM system specifies the criteria for disorders, but only when they are clearly established as disorders. The system does not delineate the moment of becoming psychotic or schizophrenic. Prospective prediction and prevention require such a definition, not only for research, but also for defining the moment when definitive treatments are appropriate.

Health Care Service Systems

Prevention activities require delivery systems and resources. This holds for early detection, early treatment or both. Therefore, adequate payoff for the time and effort invested in prevention is critical. If prevention is

successful, that payoff is realized as a decrease in the cost of healthcare for the system serving the population. Because of this, prevention programs and initiatives have been of high interest to countries with national health care systems. The TIPS early detection and intervention project, for example, has been funded almost completely by the Norwegian healthcare system, not by the Norwegian Research Council. Parallel incentives toward prevention in the American private system of managed care are few, if any, and any prevention initiatives will most likely be connected with states and public financing.

The ability of different service systems to initiate, administer, and benefit from preventive programs is in itself an important question to be answered by service systems research.

Bipolar Illness

Introduction

There is a vast array of opportunities for earlier intervention in many phases of both childhood onset and adult onset bipolar disorder. Even when the syndrome is clearly diagnosed in adults, treatment from the time of first symptoms that impair function to the time of first pharmacological treatment averages ten years in some clinical series (G. S. Leverich, Perez, Luckenbaugh, & Post, 2002; Suppes et al., 2001). This disparity is consistent with the view that adult-onset bipolar illness is widely under-recognized, under-diagnosed, and under-treated in the community (Hirschfeld et al., 2003; R.C. Kessler et al., 1994) or in primary care (Das et al., 2005). Even when bipolar illness is diagnosed, it is often treated improperly, i.e., with antidepressants without mood stabilizers (Hirschfeld et al., 2003) Concerted new initiatives are indicated to deal with the costly personal and public health missed opportunities for early initiation of long-term prevention strategies once a patient has the full manic syndrome meeting current diagnostic thresholds First, however, we examine current opportunities for selected and indicated preventive intervention in children and adolescents at high and very high risk. This group includes children and adolescents with mild to moderate severity prodromal symptoms that do not yet meet full diagnostic thresholds. If progress is made in this area, it might also have considerable positive extensions and applicability for earlier intervention in childhood and adult onset bipolar illness as well.

Early Detection and Intervention in Bipolar Illness: Defining the Problem

Attempts at prodromal intervention in schizophrenia (see above) are significantly further ahead of those in bipolar illness for a number of reasons.

First, there are complex and often emotionally-charged *controversies about the diagnosis* of bipolar illness in children [McClellan, 1998 #3672];Post, 2004 #3547;Geller, 1997 #3360;Biederman, 1998 #3348;Carlson, 1998 #3337].

Second, and in accord with this perspective, there are highly *varied clinical presentations* of full-blown bipolar illness in children and their associated prodromes. The full-blown form of the illness can present as bipolar I, bipolar II, or bipolar NOS with ultradian cycling (NIMH, 2001). The first manifestations may be depression, cycling, or more classic mania (Robert L. Findling et al., 2001). Since there is not yet complete consensus on the symptomatic presentations and thresholds for the full diagnostic syndromes, considering intervention in the different prodromes would be even more controversial and difficult than in schizophrenia.

Third, as in adults, bipolar illness in children is accompanied by a wide *array of comorbidities*, many of which themselves have controversial diagnostic thresholds. This includes ADHD, ODD, CD, OCD, and anxiety and substance abuse disorders Wozniak, 2001 #3549;Masi, 2004 #3376;Biederman, 2004 #3336].

Fourth, the *psychopharmacological treatment approaches* to fully defined bipolar disorder in children are *not yet well delineated* (Biederman, Mick, Spencer, Wilens, & Faraone, 2000; Faedda et al., 1995; R. L. Findling & Kowatch, 2002; Kowatch et al., 2005; Kowatch et al., 2000). Not only are there sparse numbers

of controlled clinical trials (DelBello, Schwiers, Rosenberg, & Strakowski, 2002; Kowatch et al., 2000), but also insufficient uncontrolled or open clinical trials and case series to guide therapeutics for these highly disturbed children**.** Yet, there are a wide range of options, with multiple classes of medications (lithium, anticonvulsants, mood stabilizers, and atypical antipsychotics), and multiple agents within each class, for treating pediatric bipolar disorder. Thus, in contrast to schizophrenia, where there is general consensus about initiating treatment with atypical antipsychotics during prodroma**l** symptoms or initial full-blown episodes, no such consensus approach yet exists for the parallel phases of bipolar illness in children.

Fifth, corollary problem is that there has been a *cohort effect* over the last 50 years and perhaps a generational or *anticipation effect* as well, accounting for the earlier onset and higher incidence of both unipolar and bipolar affective disorders (Gershon, Hamovit, Guroff, & Nurnberger, 1987; Klerman & Weissman, 1989; Lange & McInnis, 2002; Ryan, Williamson, Iyengar, Orvaschel, & et al., 1992). Whereas prepubertal mania was hardly recognized of several decades ago, childhood onset bipolar illness has now become one of the more major problems in psychiatry for which parents are pressing for information, treatment recommendations, and informed treating physicians (Coyle et al., 2003; Hellander, 2003). However, even several decades ago, there were many children and adolescents with unrecognized bipolar disorder. (Perlis, Des Jarlais, Friedman, Arasteh, & Turner, 2004) indicate that 28% of their adults with well diagnosed bipolar illness had an onset of illness prior to age 13, and 66% had an onset prior to age 19.

Justifications for Early Intervention Studies in Children and Adolescents

First, bipolar illness presents with considerable distress for the children, their parents, and other family members and social acquaintances. Marked *disruption of functioning* in social, family, and educational role (Geller et al., 2002; Geller & Luby, 1997; Geller, Tillman, Craney, & Bolhofner, 2004; NIMH, 2001; Papolos & Papolos, 1999).

Second, early onset bipolar illness in retrospective studies. and (G. S. Leverich et al., 2002; Perlis et al., 2004) of well diagnosed adults is a potent *risk factor* for eventual *poor outcome* (Nolen et al., 2004; Robert M. Post et al., 2003). It is also associated with an increased number of *comorbidities,* including vulnerability to *substance abuse* (T. E. Wilens et al., 2004). In many studies as well, early onset is a correlate of serious *suicide attempts* during adolescence and adulthood (Gabriele S. Leverich et al., 2003).

Third, there is growing evidence that the experience of increasing numbers of affective episodes is, in itself, not only associated with episode-related morbidity, but may also negatively influence the eventual course of illness and treatment responsivity (R. M. Post, 2004; Robert M. Post et al., 2003) Data presented and reviewed by Kessing and colleagues (L. V. Kessing & Andersen, 2004; Lars Vedel Kessing, Andersen, Mortensen, & Bolwig, 1998) in more than 20,000 patients in the Danish Case Registry strongly support the notion that the best *predictor of a depressive recurrence (hospitalization)* is the *number of prior episodes (hospitalizations)* in both unipolar and bipolar illness.

Fourth, it could be argued that those with patients the most severe forms of illness are destined to have the most episodes and treatment refractoriness from the outset, this does not appear to be the case (L. V. Kessing & Andersen, 2004). Moreover, it is important to take the clinically more optimistic perspective that *early intervention and prevention of episodes may interrupt this progressive process* and prevent some of the associated neurobiological alterations (R. M. Post, Speer, Hough, & Xing, 2003). For example, four studies (L. Altshuler, Bartzokis, Grieder, Curran, & Mintz, 1998; L. L. Altshuler et al., 2000; Brambilla et al., 2003; Strakowski et al., 1999) report finding an increased size of the amygdale in adult bipolar illness, including one study linking this enlargement to the number of prior hospitalizations for mania. At the same time the amygdale is small in adolescent onset (DelBello, Zimmerman, Mills, Getz, & Strakowski, 2004) and early in the course of the illness (Blumberg et al., 2003), suggesting that the amygdale may increase in size relative to controls over the course of illness. As another example, whereas a single prior episode of unipolar or bipolar depression does not convey an increased risk factor for the onset of dementia in old age, the occurrence of four prior affective episodes is associated with a significantly increased risk of severe cognitive decline (L. V. Kessing & Andersen, 2004).

Thus, the prevention of cumulative morbidity (Geller, Tillman et al., 2004), comorbidity (T. E. Wilens et al., 2003), and potential disability (MacQueen et al., 2000) and mortality, all indicate the critical importance of early effective intervention, even if processes related to illness progression are not altered.

Fifth, it is possible that early intervention in the bipolar prodrome could prevent the onset of the full-blown syndrome altogether.

Attempts at Intervention in the Bipolar Prodrome in Adolescents

The only study of intervention in the bipolar prodrome in adolescents of which we are aware was conducted by (R. Findling, Calabrese, & Youngstrom, 2003) who attempted to intervene with valproate versus placebo in children and adolescents with: (1) a positive family history of bipolar illness in one parent, and 2) initial symptoms not necessarily meeting full diagnostic criteria. In this study, valproate and placebo did not differentiate from each other and this was likely partially attributable to the very high (around 80%) placebo response rate. This study places a different perspective on the uncontrolled intervention by Chang and colleagues (Chang, Blasey, Ketter, & Steiner, 2003) in children at high risk because of a positive family history of the illness, also with valproate. They found, not surprisingly in light of the data of Findling et al. noted above, that there was a very high apparent response rate to valproate.

High Priority and Practical Studies of Prodromal Intervention and Secondary Prevention in Children and Adolescents

Given the cogent clinical and theoretical rationales noted previously (see "Justifications…" above) for early (prodromal) intervention in children and adolescents at high risk, what might be the most suitable ways of proceeding with pharmacological studies, given the many inherent difficulties discussed (particularly the first, second and third justification, above)? All of the following high priority studies could be conducted in conjunction with, and in addition to, accepted psychosocial interventions.

Interventions in the earliest phases of the full-blown disorder

Perhaps the most conservative approach would be to intervene in the earliest phases of the full-blown bipolar NOS disorder, as described in detail by Geller and colleagues (Geller et al., 1998) and agreed to in a consensus conference (NIMH, 2001). We are not aware of any randomized studies for this highly prevalent diagnostic subgroup.

If one also included the requirement for a positive *family history of bipolar illness* in at least *one* of the *parents* together with the requirement of the presence of a full DSM-IV diagnostic syndrome including bipolar NOS, it would provide a powerful clinical and ethical justification for a series of controlled clinical trials in even the youngest children (ages 3 or 4 in some instances) experiencing these full-blown symptoms (Biederman et al., 2004). It is likely that many of the formal ongoing or planned randomized controlled clinical trials (RCTs) are studying patients in older age ranges, such that any RCT in these very young children would still provide invaluable information about early intervention
.
As issues of *safety* become paramoun*t* when attempting novel early intervention in very young children (in the absence of RCTs showing efficacy in older youngsters, similar to that seen in the treatment of adult bipolar illness), choosing to study agents with a particularly benign side-effects profile would appear to be critically important.

In light of such *tolerability and safety* issues, one might consider choosing to study aripiprazole versus ziprasidone over the more extensively studied atypical antipsychotic olanzapine (with its more problematic incidence of weight gain), or even risperidone and quetiapine (with their lesser risk for weight gain). Even an open randomized acute and continuation study of aripiprazole versus ziprasidone would provide much needed comparative longitudinal data for the field.

Among the acknowledged mood stabilizers in adults (lithium valproate, carbamazepine, and lamotrigine), each has some side effects and safety concerns for of early intervention trials in very young children. Here, too, the less well-studied relative of carbamazepine, *oxcarbazepine*, would appear to have considerable merit from a safety/tolerability/practicality perspective in prepubertal children.

Although the efficacy of *omega-3 fatty acids* in adults with bipolar illness remains controversial, because of the inconsistency of study results to date (R. M. Post, 2004; R. M. Post & Speer, 2002), this novel treatment might also provide another extremely safe avenue for intervention and could even be used *as an active comparator* in a randomized double-blind or open trial against a more traditional agent noted above.

Another type of important early intervention approach might involve study of *somewhat older children* (perhaps ages 8-16) who present with a high risk for developing bipolar disorder by virtue of a parent with the illness, but with bipolar I or II syndromes that do not meet full diagnostic thresholds (i.e., likely prodromes). These older children would be able to provide better informed consent and understanding along with that of their parents, and perhaps have a more precisely defined prodrome to identify and to attempt to intervene in (Chang et al., 2003; R. Findling et al., 2003).

Interventions in children with early onset of dysthymia, depression or psychotic depression

Interventions for the prepubertal child with early onset dysthymia, major depression, or full-blown psychotic depression who is at very substantial risk for switching into mania upon antidepressant treatment (usually estimated to be between 30% and 50%), or eventually showing manic symptoms spontaneously (Geller, Zimerman, Williams, Bolhofner, & Craney, 2001; Kovacs, Akiskal, Gatsonis, & Parrone, 1994). If one added the requirement that these depressed children also have a positive family history of bipolar illness, presumably putting them at even higher risk of becoming bipolar, it would add to the urgency and ethical rationale for comparative studies.

In these instances, a series of randomized trials comparing initial monotherapy strategies as well as augmenting a mood stabilizer with (1) an antidepressant intervention, (2) a second mood stabilizer, or (3) an atypical antipsychotic, would provide profoundly important information to the field and to parents seeking appropriate treatment for these seriously ill youngsters at dual high risk for bipolar illness by virtue of their (1) very early onset depressive symptom presentation, and (2) positive family history for bipolar illness.

Such studies have a particularly high importance and ethical rationale given the current concern about the use of antidepressants in children because of issues of both efficacy and safety, i.e., the potential increased incidence of suicidal ideation (to which one would also add the vulnerability for switching into mania in this particular high risk population). It is interesting that one study of cognitive behavioral psychotherapy found a decreased rate of conversion to bipolarity in depressed adolescents at high risk because of a parental positive history compared with treatment as usual Kochman, 2003 #3565].

Interventions in the earliest phase of a prodrome

If one were to attempt to intervene in the earliest phases of a prodrome (i.e., indicated prevention), one would need to have a population of *extremely high-risk individuals* in order to provide cogent scientific and ethical rationale for drug studies.

One way of achieving this goal would be to consider studies in the highly selective group of children whom we label at *very high risk* for an affective disorder by virtue of having a *bi-lineal (both parents) family history* of affective disorders with at least one parent being bipolar. Such children are known to have an approximately 70% lifetime risk of experiencing an affective disorder, as revealed in the studies of Gershon and colleagues (Gershon et al., 1982) and in the meta-analysis of Lapalme et al. (Lapalme, Hodgins, & LaRoche, 1997).

This strategy could be sharpened by recent genetic research. For example, many studies now support val66val BDNF as a single nucleotide polymorphism (SNP) associated with vulnerability to onset of

bipolar disorder (Geller, Badner et al., 2004; Lohoff, Sander, Gallinat, & Berrettini, 2004; Neves-Pereira et al., 2002; Sklar et al., 2002). Several of these studies have indicated that the val66val SNP is a marker for early onset illness as well (Geller, Badner et al., 2004; Skibinska et al., 2004). Use of such a marker or preferably a group of putative markers to improve identification of high-risk patients would provide an additional rationale for early intervention.

Using a combination of positive family history and positive SNP markers would provide even stronger evidence of high risk for bipolar illness, further enhancing the justification for study and intervention.

Use of these clinical and SNP markers would also be invaluable in ultimately identifying individual predictors of clinical response to a given individual drug. These studies will be of great importance even in the very near future (2-5 years) given the wide range of pharmacological options available for potential treatment (based on adult forms of the illness) and the associated significant need to better match patients to the most appropriate drug or drugs from the outset.

Given this population at such high risk for affective disorder, one would have a strong rationale for attempting to intervene at a defined set of first symptoms (that under ordinary circumstances of no genetic vulnerability may or may not be a precursor to more serious problems). Such studies, targeting the earliest prodromal symptoms, if successful, could later lead to similar attempts of presymptomatic or primary prevention in this very select population of children at extremely high risk for developing major psychiatric problems in the affective and bipolar disorder spectrum.

Other Factors Related to the Feasibility of Studies of Early Intervention

In a survey of adults knowledgeable about bipolar illness, we found convincing evidence that the respondents, particularly when they were personally diagnosed with bipolar illness, were highly supportive of such clinical trials and early interventions in children (Robert M. Post, Leverich, Fergus, Miller, & Luckenbaugh, 2002). There was a *high willingness to enter their children into such controlled clinical trials*, depending on (a) the safety of the drug being studied, (b) the methodological approach (comparative trials being more supported than placebo-controlled trials), (c) the severity of prodromal symptoms, and (d) the age of the child in question. Perhaps not surprisingly, such informed parents were much more willing to consider these types of clinical trials justified than were mental health professionals or other physicians in the community in many instances. The high motivation of parents who have themselves suffered from major depressive disorders (see Section 3 below).

Clinicians, families, and the child-patients themselves are *desperate for a consistent body of empirical data* from which they can make rational decisions about early intervention. More phone calls to the National Alliance for the Mentally Ill (NAMI) and the Depression and Bipolar Support Alliance (DBSA) are centered on this issue than any other problem in psychiatry (personal communications from the executive directors of both of these advocacy groups).

Thus, the time is appropriate and the rationales urgent for acquiring such data on early intervention in children and adults. The hurdles noted earlier can be readily surmounted by: (1) using *individuals at high and very high risk* by virtue of a respective uni-lineal or bi-lineal parental history of bipolar illness and combining this clinical information with the growing evidence that the val66val BDNF allele is an SNP vulnerability marker for bipolar disorder; (2) *precisely specifying symptom severity thresholds for both the prodrome and full syndrome (*thus obviating some of the diagnostic dilemmas inherent in bipolar diagnoses in children; and (3) choosing from the currently available range of *safe and tolerable candidate drugs* to be studied first.

Given a combination of these strong clinical and theoretical rationales, ethical justifications, and critical clinical need for such important public health information, it would appear most timely to support a series of initiatives on early intervention in bipolar disorder and its prodromes in children and adolescents.

Increased education and awareness would appear to be at the crux of the problem, as well as the solution, to the long duration of untreated bipolar disorder in adults. Such educational efforts could be targeted most productively at (a) those patients at high risk themselves as well as family members, (b) those treating clinicians using psychotherapy, and (c) physicians, both in psychiatry and those in primary care and medical specialties, (Das et al., 2005). Moreover, in prison populations, a substantial percentage of will receive a bipolar diagnosis with appropriate diagnosis interviews, but the average duration of untreated bipolar disorder in one such incarcerated population (Elhaj & R, 2004) was 18 years!

All of these family and medical community members should recognize that characteristics of depression itself in adults (such as lack of motivation and feelings of hopelessness and helplessness) might inhibit treatment seeking. Similarly, attitudes associated with hypomania and mania may lead to a lower incidence of treatment seeking and diagnosis as well. In mania, these might include the sometimes very positive attributes of this phase of the illness, including increased energy, sociability, and decreased need for sleep. However, there may also be an accompanying lack of insight and denial of illness that fails to elicit appropriate questioning or precludes accurate responses to diagnostic questions if they are, in fact, asked.

Given these illness characteristics that inherently inhibit treatment-seeking in adolescents and adults, it would appear that suggestions and urging by family members, friends, and associates that symptomatic patients obtain appropriate evaluation and treatment could help lower these barriers. This is often not done because of a lack of information as well as very powerful and continuing issues of stigma. A lack of health care access, especially that associated with lack of health insurance, may also interact with such lack of information.

Clinicians and physicians need to be further educated about critical screening questions, particularly in those patients presenting with an apparent episode of unipolar or recurrent unipolar depression. Since multiple studies document that some 25-40% of these individuals are actually bipolar (Angst et al., 2003; Benazzi, 1997), one needs to include questions that may be answered positively and non-pejoratively that could lead to further consideration of such a diagnosis. Asking about prior or current periods of increased energy and decreased need for sleep as part of any diagnostic and treatment evaluation would be particularly helpful. A positive family history for bipolar illness only occurs in about 50% of individuals with clear bipolar disorder. However, asking about this and obtaining a positive answer should also increase one's alertness to the possibility of a bipolar diagnosis. The mood disorder screening questionnaire (MDQ) developed by (Hirschfeld et al., 2003; Hirschfeld et al., 2000) , is also a convenient way of screening for bipolar symptoms in depressed patients in office-based clinical and medical treatment as well as in many other venues.

Many of these approaches require more global public health and educational initiatives, and in some ways are more difficult to conceptualize in a focused research agenda than the previously discussed possibilities for studies on interventions in children with the full bipolar syndrome or its prodrome. As such, the more focused childhood research agenda perhaps should receive priority consideration. Then one can hope that many of the initiatives in the area of childhood- and adolescent-onset bipolar illness would directly and indirectly assist in the long-term goal of reducing the unconscionably long delay between first illness symptoms and first treatment, in some studies averaging 16 years, in those with onsets prior to age 13, and 12.5 years in those with onsets prior to age 19.

In parallel, one would hope that such work would also propel initiatives in the more traditional areas of tertiary prevention, i.e., prevention of episode recurrence and illness progression after a single full-blown episode. This most important second goal of treatment of bipolar disorder (after the first goal of acute mood stabilization) receives relatively little formal study, despite its clinical importance and inherent difficulty and complexity.

***Recommendations*: Early Intervention and Prevention of Bipolar Disorders**

Assessment and DSM-V

The field desperately needs to resolve some of the current controversies about the diagnostic thresholds for childhood onset bipolar disorder. One way to accomplish this in an expeditious fashion would be to have a consensus conference in order to agree on a temporary set of guidelines and cut-offs for both a (possible or probable) prodrome and a (likely or definite) full syndrome for each of the forms of bipolar disorder, i.e., I, II, and NOS. This could readily be accomplished by the same group who agreed on preliminary treatment guidelines for approaching bipolar illness in children and adolescents.(Kowatch et al., 2005)

Once there was temporary agreement about some of the most controversial aspects of the nosology, one could more readily collect prospective data in a systematic fashion about the longitudinal course and ultimate outcome for these children with either the arbitrarily defined prodromes or the full syndromes. Similarly, treatment interventions could be placed in this context as well.

After the much needed longitudinal prospective data become available, then one could go back and revise and reset the appropriate diagnostic thresholds based on the emerging clinical data. Waiting only for the usual time frame of resolution of these controversies based on definitive prospective data would incur both extraordinary delays and continue to limit clinical care and research in this most pressing area.

In a related fashion, it would be important for DSM-V to consider a child's age of onset, current age, and duration of illness in conceptualizing important qualitative and quantitative differences in the presentation of bipolar disorder over the life span and over the course of illness evolution. In any case, longitudinal assessment and consideration of the stages and course of the illness should do much to lessen the areas of controversy. Because the illness is so pleomorphic and can fluctuate so rapidly, traditional cross-section evaluations are often inadequate.

We also recommend the inclusion in DSM-V of the assessment of both well-known and putative risk factors associated with the onset and progression of childhood and adolescent onset bipolar illness. We term an evidence based set a *risk cluster*. In this case the bipolar risk cluster contains both general risk factors and those specific to bipolar illness. The bipolar risk cluster could include: a positive family history in first degree relatives (in one or both parental lineages) of bipolar (specific) and unipolar, alcohol, and substance abuse disorders; in utero exposures to drugs or viruses; and early extreme environmental stressors such as parental loss, physical or sexual abuse and a prodrome involving bipolar-like symptoms and dysfunction (specific). If these types of data are collected in a systematic fashion in advance of knowledge about ultimate outcome for the prodrome or full syndrome, they will facilitate the subsequent validation of the potential risk factors that prove to be important for bipolar disorder onset, progression, and treatment response.

Services

This is a critical problem area for children and adolescents in which the lag from first symptoms with dysfunction to first treatment averaged more than a decade in adults who reported childhood and adolescent-onset bipolar illness. Not only is there a deficient knowledge database from which to make important clinical, diagnostic, and treatment decisions about childhood-onset bipolar disorder, but across the U.S. there is also a deficit of well-trained psychiatrists in the area of pediatric psychopharmacology. Thus, critical treatment information needs to be more readily available to the general medical community and services accordingly be developed to deal with large numbers of highly disturbed children with a treatable disorder.

Tragically, the Department of Social Services from the state of Virginia reported (Washington Post, 11/29/04, pg. B-1) that 2,000 or more than one in five children currently in foster care were placed in custody in order to obtain otherwise unavailable or unaffordable mental health care. Given that this situation is likely replicated in many communities throughout the U.S., systematic approaches to this national health care crisis are indicated.

Research

As outlined above, the research needs in this area are extraordinary, both for early intervention in the bipolar prodrome as well as for the full syndrome. Given the critical need to accelerate systematic treatment data in both of these arenas in young children with bipolar-like presentations, we suggest several areas of differential emphasis from the traditional measures that might be most highly recommended in academic settings.

This is such a dire mental health need that an immediate infusion of new monies and commitment would be indicated. One way of accomplishing this within the current budgetary restraints would be to have systematic clinical trials in well-characterized children with bipolar and bipolar-like presentations that are funded by a broader range of funding sources including those that now specialize in services research. Their studies of care and outcome are not typically geared to individuals with a single diagnosis. However, in this instance of a major health care crisis, we believe specific attention to clinical evaluation and treatment outcome studies in childhood bipolar disorder per se is warranted. Such services research sponsored studies could use open active treatment arms, particularly if two potentially good options are randomized, and in this fashion tolerability and a preliminary view of efficacy over time could be ascertained. This would provide preliminary information that could be used to inform further, more controlled studies.

We also urge that APA advocate strongly for support of proposals in the area of comparative longitudinal clinical trials for childhood and adolescent onset bipolar illness treatment research. The adult area has been recognized as under funded for more than three decades, and without systematic new initiatives (such as the STEP-BD Sachs et al.), this is not likely to change. Specific support for proposals would facilitate the conduct of easier to complete, less elegant studies that would rapidly provide a modicum of preliminary information about a wide range of treatment options in order to better inform the field. If one relies on just obtaining high priority scores in the traditional funding mechanisms, it is highly likely that the area of early onset and early treatment of bipolar illness (given its many empirical and conceptual controversies) will continue to be relatively neglected.

Even for traditional sponsored research, funding less controlled designs such as randomized open comparisons of two presumptively active treatment options would begin to provide the most readily and rapidly attainable type of data based on ease of cost, ethical dimensions, and parental endorsement. We would also recommend that these trials include a spectrum of children with bipolar illness ranging from bipolar I through bipolar II and NOS to be included in such randomized treatment trials, because a very considerable percentage of prodromes and early onsets appear to be accounted for by the bipolar II and NOS syndromes. Once a modicum of treatment-related data begin to be acquired for the different bipolar subtypes, one could then more readily prioritize treatments requiring definitive efficacy assessment using more formal RCT methods.

Lastly, since there is a complete absence of systematic data about the best treatment for prepubertal onset of dysthymia and major depression (both of which are associated with a high risk of a manic switch upon treatment with antidepressants), a series of randomized (even open) comparisons between one mood stabilizer versus another, a mood stabilizer versus an antidepressant, or an atypical antipsychotic versus a mood stabilizer or an antidepressant would begin to provide critically needed data and have an enormous immediate impact in beginning to inform clinical practice.

Overview of Recommendations

Given this concatenation of major deficiencies in the portfolio of research on childhood onset bipolar illness and the corresponding great pressing need for treatment effectiveness data, it would appear highly useful to consider the formation of a series of clinical trial networks geared to function at different levels of scientific rigor in order to begin to provide the necessary information in an expeditious fashion. Networks could be organized both in formal academic centers that could conduct more systematic and intensive assessments, and in clinical practice settings wherein less formal trials and more limited outcome measures could be utilized. The current paradigm of tens of thousands of youngsters with presumptive bipolar disorder being treated with a large variety of psychopharmacological agents, in many instances in

combination or complex combination therapy, without any way of acquiring data from this experience, would appear to be a great waste of a powerful opportunity.

It should be noted that many of the recommendations for study prioritization for prevention research in bipolar disorder are not at all in parallel with those for early intervention in schizophrenia and its prodromes, as indicated in the previous section. In those instances in schizophrenia research where the diagnostic and therapeutic issues are much better delineated, conducting formal RCTs with a placebo parallel group design is perhaps the most effective approach to acquiring high quality data that could potentially change the field of pharmacotherapeutics. In contrast, given the dramatically increased number of largely untested therapeutic options for the treatment of bipolar-like presentations in children and adolescents and given the heterogeneity of the symptom presentations, their frequency, severity, and valance (manic or depressed), a much wider range of research methodologies would appear indicated. The urgency and magnitude of the problem seems to warrant the label of "a national health care crisis". Such a label may help foster new research and treatment initiatives in this critical arena.

2) Working with Children of Parents who are being treated for a Major Mental Disorder

There has been a rapid expansion in knowledge both about risk and protective factors in children whose parents have major mental illness. One of the areas in which psychiatrists and other mental health practitioners can have a large impact is in helping mentally ill parents with their concerns about their children. A series of expert panels have strongly recommended developing programs for the children of parents with mental illness, in particular, for depression (Mrazek & Haggerty, 1994) (Clark et al., 1997; Coyle et al., 2003) (Hollon et al., 2002). There are several efficacy trials for the prevention of depression in children and adolescents, some of which involve family perspectives with manualized prevention programs that offer models that can readily be adapted to clinical practice (Beardslee, Versage, & Gladstone, 1998; Clarke et al., 2001). Moreover, advances in the neurosciences and in the understanding of the interplay between genetic and environmental influences will define many more opportunities for prevention.

From a clinical point of view, risks to children and the resources that parents need vary considerably depending on how impaired the parent is and on the age of the child. Across many approaches to prevention are four common themes. First, *mental illness is profoundly misunderstood* by parents who suffer from it and by their families. In fact, mental illness is a family calamity. Thus, helping families make sense of the illness is essential. Second, the starting place for helping the family and the individual is to *make sure that good treatment for the parent* is received and stays in place. Third, *parents need psychoeducational approaches* not only about the illness but also about risks and, perhaps more importantly, about how to build resilience in their children. Finally, a growing body of empirical literature on preventing a wide variety of psychiatric disorders supports *strategies that strengthen the family.* Successful interventions focus on helping families to take the first positive steps. (Maton, et al., 2002)

The development of effective preventive interventions rests on an understanding of risk and protective factors, areas of research that have seen rapid growth over the past two decades with the promise of more to come. Perhaps the most important scientific construct to emerge from this large body of work is that of developmental plasticity (Eisenberg, 1995). Whether at the level of the genes, the child, the family, or the society, more and more evidence accumulates that genetic influences are not fixed but can be modified by *the social environment. Indeed, the influence of a specific polymorphism of the serotonin transporter gene on depression may be moderated both by the level of parental abuse in early childhood and by a broad range of severe stressors in late adolescence and early adulthood. (Avshalom Caspi et al., 2003). These genetic data suggest, that in * the case of the child, perhaps the most important interactions early in life are with the parents or other primary caregivers. However, at the present time, we already know enough both about risk and resilience to offer substantial help to families.

Epidemiology.

There is consensus across studies of children of parents with mental illness that they are at increased risk for the illness of their parents. In illnesses that are relatively common (i.e., substance abuse, anxiety disorders, depression), there are relatively high rates of the disorder in the children. For rare disorders (i.e., schizophrenia), while there is an increased risk, the percentages of those who actually develop the disorder are much lower.

Conceptualization of Risk: The Adversity Index

In looking across the risks to children of parents with mental disorders, epidemiological studies have repeatedly emphasized that it is rarely any one factor that leads to the occurrence of illness in the child of a mentally ill parent but rather the assembly of adversities. In a classic epidemiologic study, Michael Rutter (Rutter, Cox, Tupling, Berger, & Yule, 1975) identified six risk factors, one of which was maternal psychiatric disorder. However, if one risk factor was present, including maternal psychiatric disorder, the rates of disorder in children did not increase over those with no risk factors. As soon as two risk factors or more were present, the rates increased significantly and were even higher with three. Focusing on women with mental illness enrolled during their pregnancies, Arnold Sameroff and colleagues [Sameroff, 1987 #3673] found similar effects on the cumulative impact of risk factors on a child's outcome. In examining four types of psychiatric disorders and following the cohort from shortly after birth into adolescence, they found a range of factors (e.g., severity of the illness, minority status, the presence of adverse life events, large family size, and lack of social support) together explained poor outcomes while no single factor did. Moreover, it was clear that it was not the presence of any particular diagnosis but the level of impairment of the mother that predicted outcome. Moreover, Sameroff has extended this analysis to an inner-city sample in Philadelphia and looked at the same variables and, in addition, school, community and neighborhood variables. The analysis showed again that it was the assembly of either risk or protective factors, not any one factor, that determined outcome [Sameroff, 1998 #3613]

Thus, parental mental disorder should be seen as one risk factor for the development of disorder in children. Quite often, it also serves as the identifier of a constellation of risk factors (i.e., downward social mobility, social isolation, or poverty) that taken together lead to the increased risk to children. Studies that have examined cohorts enrolled because of a single diagnosis in parents have consistently demonstrated much higher rates of disorder in the children of parents with the identified disorder than comparison groups with parents with no diagnosis. Often, however, in examining these results, it has become clear that the parents have not only parental mental illness but also many other factors. In short, the Adversity Index principle operates in these situations as well.

The concept of the Adversity Index is applicable to many other prevention efforts, in particular, the discussion of suicide prevention (page 45) and of early childhood adversity (page 34).

Mechanism of Transmission

While the exact mechanism of transmission and the rates of disorder in children and parents with a single diagnosis vary considerably by the diagnosis and the chronicity and severity of the illness, there is a considerable body of understanding about the interplay between genes and environment. For adolescents, data from Reiss and colleagues (Reiss, Neiderhiser, Hetherington, & Plomin, 2000) suggest that specific parenting practices may mediate the effect of genetic influences on the evolution of depressive symptoms. In adults, Kendler and his colleagues have shown that stressful life events may augment the effects of genetic factors on the development of a depressive disorder. (Kendler et al., 1995) All the models involve the intersection between stress and nonspecific risk factors such as loss or exposure to violence and a specific vulnerability/proclivity towards the illness. In Kendler's work, about half of the variance in the onsets of depression in young women can be explained by the factors that are known. The two largest contributors are current life stress and family history.

In Table 1, we present the risk factors for depression identified in the Institutes of Medicine's report on the prevention of mental disorders. This table emphasizes that there are many risk factors. Some are highly specific, for example, having a close relative with mood disorders while others are powerful yet nonspecific in the sense that they lead to a variety of poor outcomes. True prevention involves addressing both sets of risk factors and the detailed study of the prevention of any one disorder inevitably leads to a balance between highly specific risk factors and general public health risk factors.

As our understanding of the genome progresses, we are likely to have a much better sense of who is at risk and, therefore, able to time preventive interventions more appropriately and also to estimate what intensity of intervention is needed. None of the models have been applied to childhood depression as yet, but they offer considerable promise.

Resilience and Protective Factors

The study of protective factors against mental illness and of resilience in the children of mentally ill parents has rapidly expanded. Though some difficulties about measurement remain (Luthar, Cicchetti, & Becker, 2000), it is clear that many children grow up with parents with mental illness and lead normal lives. [Garmezy, 1991 #3674]has argued that resilience can best be understood in three domains: the child, the family, and the community. Longitudinal studies such as that of (Werner & Smith, 1982, 1992) on the Island of Hawaii documented that different protective factors exist at different points across the lifespan and that as the child grows, the range of protective factors moves from the family to the larger community and eventually, as youngsters emerge into adulthood, into such things as job opportunities.

Within the domain of the family, three areas have received particular importance: (1) the capacity of the child to accomplish appropriate developmental tasks; (2) the child's involvement in relationships; and (3) the quality of parenting despite the illness. In addition, the child's understanding of the parent's mental illness has been shown to be an important determinant of how children fare in the face of serious mental illness (Beardslee and Podorefsky).

Approaches to Preventive Intervention

Preventive intervention approaches are typically built on an understanding of how to enhance resources and strengths. In terms of preventive intervention studies, there is consensus about the need for psychoeducational programs for families facing mental illness. In some areas such as Carol Anderson's work on families with a schizophrenic measure, multifamily groups proved to be quite useful (Hogarty, Anderson, Reiss, Kornblith, & et al., 1991)while in others, interventions targeted directly to families have shown merit [Gillham, 2000 #3675]. The multiple family group has also been used for families facing chronic medical disorders in parents. (Gonzalez, Steinglass, & Reiss, 1989)

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For children of depressed parents, Beardslee and colleagues (Beardslee, Wright, Rothberg, Salt, & et al., 1996) (Beardslee, Gladstone, Wright, & Cooper, 2003) developed public health based interventions to be used with families where parental depression was identified to be available to all children in the family. The approach combined education about depression and the need for treatment, education about how to recognize depression in youngsters and obtain treatment with an emphasis on building resilience in the child through encouraging activities, involvement in relationships, and building self-understanding. Beardslee's work centered on family meetings in which parents were able to discuss with children both what their illness was and what was being done about it and emphasize the positive and resilient qualities that would be supportive. In a randomized trial comparing the transmission of these constructs versus through a manual-based clinician centered intervention which actually led to the conduct of a family meeting, Beardslee showed sustained effects for both interventions in a positive direction with increases in family understanding and communication two and one-half years after the preventive intervention. Moreover, as the intervention was centered on increasing positive family interactions, it was noteworthy that families that changed the most in response to intervention had youngsters who also increased the most in their understanding.

Clarke and his colleagues using a cognitive behavioral group intervention pursued a different approach. Clarke and Associates applied the coping with stress course, a manual-based treatment for depression for youngsters at risk (Clarke, 1995) In later studies, Clarke and Associates recruited adolescents with depressed parents from an HMO. They enrolled children who had subsyndromal levels of depressive symptomatology and showed that a 15 session one-hour cognitive behavioral group led to significant reductions in rates of major depression. In the experimental condition, rates were less than 10% over a subsequent 15-month period while under controlled conditions; they were nearly 30% (Clarke et al., 2001) Clarke's approach is built on an understanding of normal cognitive development and intent to increase the child's cognitive flexibility, a form of cognitive restructuring. Section 5) describes a related strategy for preventing depression adolescents: using individual risk factors in the adolescent such as depressed cognitive style.

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Of particular concern are the alarmingly high rates of depression in low-income women raising children. For example, for mothers enrolled in early Head Start, almost half meet the criteria. Almost half are depressed. There is considerable interest in developing programs for these mothers and a number of approaches look promising.

The examples of depression simply illustrate the kinds of approaches that have been used with some other mental illnesses, as well. More generally, a comprehensive approach to the prevention of depression would involve a focus on programs for those specifically at risk for depression (i.e., children of parents with mood disorders or in adulthood, for example, those undergoing bereavement) and also address the large nonspecific risk factors that intersect with a specific vulnerability (i.e., poverty, exposure to violence, diminished economic resources, and social isolation). These factors run throughout other sections of the report, as well.

Summary

Every major report over the last two decades about prevention has targeted children of mentally ill parents. There needs to be much greater awareness of and attention to families in which parents are mentally ill. There are important opportunities for prevention and for increased family understanding.

Recommendations: **Improving care for children of depressed parents.**

Assessment

We need to include assessments of other family members, particularly children, when a parent presents with mental illness. Such assessments should involve the identifications of strengths as well as difficulties and be done in the context of supporting parents.

Intervention

The core principle is *consideration of the family as a whole* is crucial in many aspects of preventive intervention, but particularly so for parents who struggle with mental illness. Often the most effective way to reach them is enabling them to be better parents. Far too few of our training and clinical resources are directed to family-centered as opposed to individual centered care. In addition, approaches that have a strong cognitive orientation and build strengths and resources are likely to be most effective. In either clinical terms or preventive intervention terms, treatment and prevention are inseparable. In a given family, there may be individuals who need treatment and others who are candidates for prevention. In all families, an understanding of the mental illness in a non-stigmatizing way based on a medical model is likely to be most helpful.

Research

This section has outlined some of the most promising strategies to date but far more research is needed. This should include both further studies of the current strategies in contrasting samples and for the

development of new strategies. As our understanding of the various causes for mental illness and of the various mechanisms in the intergenerational transmission of mental illness evolves, many more opportunities will present themselves for effective preventive intervention. *Consideration of preventive intervention opportunities should be part of the basic science of research on child development.* Incorporating concerns about preventive intervention from the beginning of these studies on child development greatly heightens the likelihood of eventual success of programs. There is great promise in the study of the unfolding dynamic interactive balance between risks and protective factors. The science of understanding the unfolding of development and its vicissitudes will progress dramatically over the next ten years because of the sequencing of the human genome, the development of non invasive imaging techniques, and detailed epidemiologic studies. These will offer many opportunities for preventive intervention in the future.

Perhaps most interesting for the future will be developments in understanding the complex *dynamic unfolding of risk and resilience, of protective factors, and vulnerabilities across time.* As we come to understand more about how systems interact with individual lives and how systems reform at the local, city, state, and national levels can affect individual lives, we will have multiple opportunities to design more effective and comprehensive prevention programs. Similarly, as basic advances in neuroscience, developmental epidemiology, and genetics evolve, these will offer many opportunities for the development of preventive intervention programs. We believe that consideration of these such preventive interventions should be built in from the beginning.

While some treatments and prevention programs have been tested in different countries and different cultural settings, *very little work has been done on understanding either resilience differently in different cultures or the delicate unfolding interplay of risk and protective factors and how this evolves in different cultures and different countries.* Understanding the vicissitudes in risk and resilience in different cultural and national contexts is an important goal in and of itself and will also substantially advance the development and evaluation of preventive interventions. Similarly, understanding the impacts of different kinds of health care systems, those that incorporate prevention and those that do not, for example, would aid a great deal in understanding how to be most effective in mounting preventive interventions. As a complement to this, of course, is the need for much further work on understanding cultural competence and developing prevention programs that reflect such competence.

Much research is needed on *programs that utlize multiple preventive interventions simultaneously* that address a single condition but using multiple strategies working in concert. These approaches have been used successfully in combating smoking and risks for cardiovascular disease and a number of community-wide and school-based intervnetions have shown promising long-term effects in randomized controlled clinical trials (Catalano, Berglund, Ryan, Lonczak, & Hawkins, 2002). However, more comprehensive efforts to coordinate and integrate approaches, particuarly the combination of health promotion and disease prevention strategies in mental health, is needed.

3) Preventing secondary disorders

Epidemiological research has clearly demonstrated that some major mental disorders typically appear after an initial or primary disorder. The degree to which these links represent an etiologically meaningful association remains a major research topic; however, it remains clear that where there are causal pathways from earlier to later onset disorders, effective treatment of the primary disorder may help to prevent the secondary disorder. In addition, recent findings in genetic epidemiology indicate that common factors underlie conditions that appear at different developmental stages. Thus, strategies to prevent or ameliorate certain childhood conditions will be useful as well for the later onset conditions.

Concepts and strategies to distinguish primary and secondary disorders

In considering prevention of secondary disorders, first we must define what is meant by "primary" and "secondary" disorders. Because the causal links among disorders remains murky--especially where details on the progression from one illness to another are concerned, temporal sequence can be used to rule in/out plausible pathways. Regarding the relationship of substance disorders and other mental conditions, for example, (Lehman, Myers, & Corty, 1989), proposed several theoretical constructs: mental illness causes substance dependence; substance dependence causes mental illness; both diagnoses occur independently; and both could be caused by some common factor. These constructs are related to temporal association. For example, if mental illness results in substance dependence, then mental illness must, by definition, start first. If substance dependence results in mental illness, substance dependence would have to start first. If the two disorders occur independently or are caused by some common factor, temporal relationships will primarily depend on developmental factors and other forces explaining age specific onset. Robins and colleagues (Robins, Munoz, Martin, & Gentry, 1972) used the terms "primary" and "secondary" to identify a temporal sequence of syndromes, not necessarily implying a causal relationship. This approach has been taken by a number of researchers (e.g. (W. M. Compton, Cottler, Phelps, Abdallah, & Spitznagel, 2000).

The next question is how to distinguish secondary conditions from other outcomes of psychiatric disorders. We provide a distinction in this report between psychiatric syndromes occurring after the onset of a disorder ("secondary disorders") and other outcomes. These other outcomes (e.g. other health outcomes, social outcomes, suicidal behavior, etc.) are described under tertiary prevention.

From epidemiology research, it is clear that certain psychiatric conditions are much more likely to appear after the onset of other disorders. The prevalence of the second disorder is elevated above the rate in the unaffected population. Evidence for this relationship comes from retrospective dating of onset of disorders in cross-sectional studies (e.g. [Kessler, 1997 #3250], and from longitudinal study (e.g.(Brook, Brook, Zhang, Cohen, & Whiteman, 2002). Further, effective treatment of the primary disorder may prevent or delay onset of the secondary disorder. Such longitudinal intervention studies provide evidence for useful prevention interventions and provide compelling evidence concerning causal pathways from one condition to another.

Recent findings on primary and secondary disorders

Given this framework, what types of psychiatric disorders are related to one another in a primary/secondary framework? The most prominent and well described are the substance and non-substance disorders. In general, psychiatric disorders are much more common than expected among patients with substance use disorders and substance use disorders are more common among psychiatric patients [Regier, 1990 #3731], (Costello et al., 2002; Grant et al., 2004). Further, this overlap appears to be etiologically meaningful in that early use of substances predicts later onset of mental illness (e.g. (Arseneault, Cannon, Witton, & Murray, 2004; Brook et al., 2002). These findings may be interesting in and of themselves but they also have important treatment and prognostic implications. For example, psychiatric symptoms among patients with substance use disorders have been shown to be associated with higher rates of drug relapse following

treatment. In addition, comorbidity has been shown to complicate treatment of both the drug and non-drug problems.

Which conditions begin first? How are the different categories of illness related to one another? One major line of research has demonstrated the increase in substance use disorders among those with pre-existing childhood externalizing disorders. In fact, when specifically examining conduct disorder and adult antisocial personality disorders, secondary antisocial syndromes are rare (W. M. Compton et al., 2000; Dinwiddie & Reich, 1993). The converse is not true: secondary substance use disorders among those with externalizing disorders, especially conduct and antisocial syndromes, is nearly ubiquitous. Do the earlier childhood externalizing disorders represent the earliest manifestation of a common vulnerability? Recent work in genetic epidemiology provides evidence of such a relationship by demonstrating that common genetic factors links adult antisocial behavior, childhood conduct disorder, drug dependence and alcohol dependence (e.g.(Hicks, Krueger, lacono, McGue, & Patrick, 2004). Furthermore, early childhood interventions impact a broad range of adolescent externalizing outcomes emphasizing the inter-related nature of these conditions (e.g. (Hawkins, Catalano, Kosterman, Abbott, & Hill, 1999; Kellam & Anthony, 1998; D. Olds et al., 1998).

A key question is whether interventions to treat childhood disorders impact later onset adolescent conditions [Glantz, 2002 #3730] A recent review of the evidence for the effects on substance use outcomes of treatment of pre-existing childhood disorders demonstrates positive associations for treatment of disruptive behavior disorders and ADHD with decreased rates of subsequent substance use disorders (Farmer, Compton, Burns, & Robertson, 2002)) but no specific data regarding the relationship of treatment of internalizing disorders with subsequent substance use disorders (S. N. Compton, Burns, Egger, & Robertson, 2002).

Researchers have noted the relationship of one non-substance psychiatric disorder to another. For, example data suggest the relationship of early childhood anxiety disorder to later depression (e.g. (Roza, Hofstra, van der Ende, & Verhulst, 2003). It is not clear whether the early anxiety disorder represents an early expression of a disorder which later assumes the form of a depression or whether the pre-existing anxiety disorder predisposes children to later depression in a causal pathway. In either case, a comprehensive approach to identifying children at risk for later depression (see Sections 1) and 2) above) must now include identifying children with anxiety problems.

The other main issue to be considered is whether early prevention or treatment of the substance use disorders has an impact on later, secondary, psychiatric conditions. To the extent that causes are common across these multiple conditions, intervening on the common risk factors may have an impact on both "primary" and "secondary" illnesses. In vulnerable youth will delay or reduction in drug use onset reduce the onset of psychosis? These questions remain to be addressed because the public health and clinical implications are critical.

Recommendations

The implications for assessment are related to the clinical management of patients being treated for one disorder. In this case, a high index of suspicion should be contemplated regarding typical co-occurring and *the risk for subsequent* conditions. Further, in managing patients with childhood onset disorders, there is an increased likelihood of later onset of other psychiatric disorders such as substance use disorders following either internalizing and externalizing disorders. Thus, careful attention to the early signs of these secondary conditions should be considered.

For intervention and research, a key question to be addressed is whether an early intervention will reduce the onset of a secondary condition. For example, does early treatment of childhood depression or anxiety reduce the onset of later substance use disorders? Little evidence yet sheds light on this important clinical issue (S. N. Compton et al., 2002). On the other hand, as mentioned above, interventions targeting early problem behaviors have shown promise in attenuating later substance use. For example, Kellam and Anthony (Kellam & Anthony, 1998) showed that boys assigned to a 2-year behavior-improving classroom program, compared to boys assigned to usual classroom environments, were less likely to begin smoking

cigarettes in early adolescence. Similarly, Hawkins and colleagues (Hawkins et al., 1999) showed that an intervention focusing on school and family bonding in early childhood reduced onset of substance use. A key remaining question is whether these delays and reductions in onset of substance use will translate into meaningful reductions in substance use disorders (Ellickson, Martino, & Collins, 2004). In the meantime, these studies simultaneously provide potentially useful prevention interventions and provide rigorous tests of etiologic hypotheses about substance use risk factors.

A related and compelling clinical and research topic is whether stimulant treatment of attention deficit disorder in children reduces or increases subsequent onset of substance use disorders. Wilens and colleagues (T. Wilens, Faraone, Biederman, & Gunawardene, 2003) conclude in their meta-analysis of 7 longitudinal studies that treatment with stimulants is likely protective regarding future development of substance use disorders. But the studies used in this meta-analysis were not clinical trials and the comparability of the intervention and control groups is not well established. Thus, much work remains to determine whether early treatment of attention-deficit disorder has an impact on later substance use disorders.

A clear implication of the work on secondary disorders is that additional research is needed, both observational and intervention. Observational studies are needed to elucidate the pathways and periods of risk for transition from one condition to another. Perhaps most importantly, intervention studies are needed to determine the long-term impact of intervention with one condition to reduce the onset of subsequent disorders (Ronald C. Kessler & Price, 1993).

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4) Preventive interventions in early childhood: models of risk and strategies for prevention

The central importance of the caregiving context in mediating the impact of developmental risk in early childhood has been reinforced by research over the last 3 decades (Zeanah, Boris, & Larrieu, 1997). But it has not been until the last decade that new models have informed research on the complex processes by which developmental risk, and its impact on caregiving, leads to maladaptive trajectories of child and adolescent development and eventual psychopathology. This section will begin with a review of three leading models that have influenced research design on early development, the caregiving context and risk. Following the review of theoretical models, research on attachment in early childhood, informed by these models, will be reviewed. The implications of attachment-based research for preventive intervention will then be highlighted and selected evidence-based prevention programs reviewed. It is clear that both developmental and intervention research findings can inform psychiatric practice, particularly because parental psychopathology is one major factor which impacts the caregiving context and the child's development. This section concludes with recommendations for how the practicing psychiatrist can mitigate the impact of parental psychopathology on the care of young children.

Early Experience and Developmental Outcomes—Theoretical Models

As already noted in this document (see section 2) on children of depressed parents) one important model for understanding how early risk leads to psychopathology has been the *cumulative risk model* (e.g., adversity index). Put simply, the cumulative risk model suggests that a collection of different risks may lead to the same outcome and that the same risk can, when combined with others, lead to widely divergent outcomes [Cicchetti, 1995 #3677] While the cumulative risk model has the strongest empirical evidence to

support it)(A. J. Sameroff, 1998), the idea that risks typically act in a non-specific fashion or, put another way, that specific risk factors do not in some cases lead to specific outcomes, has been challenged. (O'Connor, 2003)has recently reviewed two other models of how early experiences may influence later pathology and argued that each is supported by emerging evidence. These models, in turn, are informing our understanding of developmental psychopathology and prevention approaches.

The second model for further understanding how early experiences shape later pathology focuses on *sensitive periods*. As O'Connor (O'Connor, 2003)notes, this term is not always consistently defined in the literature. The concept, however, is that children may be particularly sensitive to a specific risk condition during a specific developmental period [Bornstein, 1989 #3685]. Many lines of research have converged to support the contention that there may be more specificity in how *certain* risks shape *certain* biological and psychological functions than accounted for by the cumulative risk model[Greenough, 1987 #3687]. The leading edge of research on sensitive periods is animal research, mostly because study of how specific risk conditions impact the developing organism can more easily be controlled than in human cohorts. Nevertheless, even research in humans has, for instance, documented the specific effect of lack of visual input early in infancy on the development of stereoscopic vision [Maurer, 1999 #3688]. Until recently, links between specific risk exposure at developmentally sensitive periods and later psychopathology have been limited. Intriguing longitudinal data on prenatal famine and later psychopathology (schizophrenia and affective disorders) have, however, reinforced the sensitive period model (Brown, Butow, Culjak, Coates, & Dunn, 2000). *In utero* exposure to famine is associated with later psychopathology, though exposure in the first trimester increases the likelihood of hospitalization after age 18 for schizophrenia while exposure in the second and third trimesters are associated with hospitalization for affective disorders. Data such as these suggest that early risk exposure during a sensitive period increases the likelihood of psychopathology years later, through mechanisms which are plausible but not yet adequately studied (Brown et al., 1996) (MacCallum, Browne, & Sugawara, 1996).

In fact, study of how environmental perturbations early in development influence later pathology has led to a third model referred to as the *fetal or developmental programming* model (O'Connor, 2003; van den Bergh and Marcoen, 2004). In some ways, the developmental programming model is an extension of the sensitive period model. However, rather than stipulating that early risk exposure during a sensitive period necessarily leads to later pathology, the developmental programming model suggests that early risk exposure leads to adaptation by the organism *and the change in the organism through adaptation* makes it more susceptible to the impact of later risk conditions. The best evidence for developmental programming comes from longitudinal epidemiological research on nutritional deprivation in the prenatal period and catch-up growth in the early postnatal period as they relate to glucose tolerance and coronary artery disease in adulthood[Barker, 1998 #3708] Erikkson et al., 1999; Khan et al., 2004). The concept behind developmental programming is one already introduced in this manuscript: developmental plasticity. In the developmental programming model early risk exposure leads to shifts in the organism's physiological response system and these shifts then make the individual more (or, perhaps, less) responsive to later risk events and disease outcomes. In terms of psychopathology, there is recent prospective evidence that maternal anxiety in pregnancy may lead to behavioral disorders in offspring evident many months or years later, and these data best fit the fetal developmental programming model [Huizink, 2002 #3690][Huizink, 2003 #3694]2004; O'Connor et al., 2002, 2003; Van den Bergh and Marcoen, 2004)(O'Connor, Pickering, Dunn, & Golding, 1999). Animal models for how set points in systems like the fetus' hypothalamic-pituitary axis are shifted by exposure to the kinds of maternal physiologic dysregulation associated with anxiety are the subject of much research and support the prospective findings while providing a window into possible mechanisms of change [Kofman, 2002 #3696].

On the other hand, it is important to remember that none of the three developmental models presented regarding risk and outcome (cumulative risk, sensitive period, or developmental programming), or the data supporting them, are consistent with determinism (Rutter, O'Connor et al., 2004). In other words, the relationship between early risk exposure and later outcome is probabilistic; intervening developmental events may further shape how risk and outcome relate. Children exposed to key risk conditions at key points or many risk conditions across years will not necessarily develop psychopathology. What these models and data do point out, however, is that early intervention may be particularly indicated

to counterbalance early risk exposure and, potentially, leverage early sensitive periods in which interventions might have greater effect. The prenatal, infant and early childhood periods of development appear to be ones in which the developing brain is most plastic [Greenough, 1987 #3687]. The importance of secure attachment between parents and young children is the best investigated of these areas. Research has documented the important protective effects of these bonds, even in the face of adverse circumstances.

Attachment, Risk and Resilience

John Bowlby conceived of attachment as a cross-species, homeostatic, bio-behavioral system that was selected for as the species evolved Bowlby, 1988 #1469]. Attachment may be defined as the organization of behaviors in the young child that are designed to achieve physical proximity to a preferred attachment figure at times when the child seeks comfort, support, nurturance or protection. Under usual conditions, preferred attachment unfolds gradually over the first year of life and infants become attached to caregivers with whom they have had significant amounts of interaction (Boris, 1999). In our culture, this is usually one to four adults whom the infant learns through experience that he/she can count on to provide comfort, support, nurturance and protection, especially in times of stress. These "attachment figures" appear to be arranged hierarchically in terms of strength of preference, so that the infant has a most preferred caregiver, a next most preferred caregiver, etc.

By 12 months of age, it becomes possible to reliably assess the quality of an infant's attachment to a discriminated attachment figure. A laboratory paradigm known as the Strange Situation Procedure (Ainsworth, Blehar, Waters, & Wall, 1978), involves a series of interactions between a young child, an attachment figure and an unfamiliar adult, including separations and reunions. Four patterns of attachment, secure, avoidant, resistant, and disorganized, have described individual differences in the organization of an infant's attachment behaviors with respect to an attachment figure in this procedure. The Strange Situation Procedure has been conducted in many cultures throughout the world. Although there is variability in distributions within and across different cultures, the same four patterns are evident(van Ijzendoorn & Sagi, 1999). These patterns of attachment are relationship specific rather than within-the-child traits in that the same child's pattern of attachment may be different with different caregiving adults (Steele, Steele, & Fonagy, 1996). These patterns have been associated with different types of caregiving in the first year of life (Sroufe, 1988) and with differing adaptation in the preschool years and beyond (Weinfield, Sroufe, Egeland, & Carlson, 1999) (Sroufe, 1988). In fact, type of attachment to the primary caregiver is one of the strongest predictors from infancy to subsequent social and emotional outcomes in children (Weinfield et al., 1999) (E. A. Carlson, 1998). The attachment system evolves from infancy to the preschool period and specific coding procedures for preschoolers are necessary. However, even children with significant disabilities show attachment behavior, confirming the universality of this bio-behavioral system.

Strange Situation classifications of attachment are neither clinical diagnoses nor indicators of psychopathology. Rather, insecure attachment (avoidant or resistant attachment) is a risk factor and secure attachment is a protective factor associated with increased or decreased probability of maladaptation or developing psychopathology. Disorganized attachment is the pattern most strongly associated with subsequent serious problems (G. A. Carlson, 1998), including aggression and disruptive behavior disorders (K. Lyons-Ruth, Alpern, & Repacholi, 1993) and dissocializes symptomatology (Ogawa et al., 1999). Nevertheless, even disorganized attachment is generally considered a risk factor for later psychopathology rather than a diagnosis (van Ijzendoorn, Schuengel, & Bakermans-Kranenburg, 1999).

Longitudinal data from the study of children raised in institutions tells a particularly interesting story about the relationship between early attachment and later development (O'Connor, Rutter & The English and Romanian Adoptees Study Team 2000; O'Connor, 2003; [Zeanah, 2002 #3692]). While only a minority of children adopted from institutions has disturbed attachment patterns over time, those who are affected show considerable stability in deficits, even over several years following placement in stable adoptive families. These children are generally described as superficially sociable and often seek physical contact with strangers. They may, for instance, climb uninvited into a strange adult's lap and caress his or her hair. At the same time, caregivers often perceive affected children's social connections to be shallow. Some exhibit hyperactivity and attention problems as well as difficulties in peer relationships(O'Connor et al., 1999). Analysis of outcomes from one particular sample of these children (O'Connor, 2003) suggests

that individual differences in outcomes were not predicted by contemporaneous measures of family functioning in the adoptive home. Instead, there was a dose-response relationship between length of institutionalization and later attachment behavior. Models based on neuroscience research are beginning to fill in how early deprivation might lead to later psychopathology in much the same way that models link prenatal maternal anxiety impacts the fetus' developing brain (Mirescu, Peters, and Gould, 2004).

Evidence that early attachment security or insecurity are predictive of later functioning, including certain types of psychopathology and that gross disturbances in early care (e.g., institutionalization) are associated with long term developmental consequences in a subgroup of children beg the question of just what types of early experiences might be promoted to prevent attachment disturbances. The pioneering work of Ainsworth suggested that high levels of observed caregiver sensitivity correlated highly with secure attachment (Ainsworth et al., 1978). Just how attuned even very young infants are to their caregiver's interactions has only more recently been appreciated, however. In fact it has been argued that even in the first months of life, dyadic mutuality (e.g., reciprocal verbal and non-verbal exchanges) can be captured using microanalytical review of videotaped interactions (Peck, 2003). The dance of mutual dyadic response is complex: the infant may evoke responses from the caregiver and vice versa. Emerging evidence suggests that both genetic and sibling-specific environmental factors are at work in shaping dyadic mutuality, though good long-term data is lacking (Deater-Deckard & Petrill, 2004) Nevertheless, the literature is consistent in linking early dyadic mutuality with emotion regulation in the developing child(Schore, 1994). Furthermore, even parents of infants who are irritable or reactive, with intervention, can be coached to improve their reciprocal responsivity leading to more secure attachment (van den Boom, 1994). However, one well-documented barrier to dyadic mutuality is maternal depression.

Postnatal maternal depression has been shown to impair dyadic mutuality and disrupt early attachment (Karlen Lyons-Ruth, Connell, Grunebaum, & Botein, 1990; Zeanah et al., 1997). However, as with prenatal exposure to anxiety, the infants' responsivity may be impacted by depressive symptoms even before birth; mothers' depressive symptoms during pregnancy are associated with infant behavioral and physiologic dysregulation in the first days of life(Field et al., 2000). Furthermore, there is limited evidence that fetal responsiveness, tested *in utero*, is affected by maternal depression, or a co-factor (Allister, Lester, Carr, & Liu, 2001). When a depressed mother and a dysregulated infant interact after birth, both conditions may worsen. The continuation of depressive symptoms across the postpartum period, even in low risk families, negatively impact maternal-infant interactions and a broad range of developmental consequences ensue (Le, Munoz, Ghosh Ippen, & Stoddard, 2003); see also [Murray, 1999 #3697] for a review). Recent research has moved from documenting interactive and developmental consequences of maternal depression to considering the neurobehavioral pathways involved in affected infants. Evidence that 15-17 month old infants of depressed mothers show differential patterns of EEG activity (compared with infants of non-depressed mothers) when interacting both with familiar and unfamiliar adults suggests that the interactive deficits associated with maternal depression generalize across relationships (Dawson et al., 1999). Longitudinal data showing that exposure to maternal depression in the first two years of life is predictive of cortisol dysregulation in middle childhood is also compelling, though available studies do not adequately account for the influence of genes shared between the depressed mothers and their offspring (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002)

Intervention Models: Using Research on Early Attachment to Prevent Subsequent Disorders

Research on attachment would suggest that family-based interventions, targeting parents of young children might shift child attachment toward security by influencing dyadic mutuality. What is needed then, are longitudinal studies of family-based interventions tested using rigorous experimental designs that have been shown to impact the developmental course of offspring and reduce psychopathology. Such model interventions exist. The best studied of these is the Nurse-Family Partnership (NFP) developed by David Olds and colleagues (D. Olds, 1997). The data from the NFP are compelling enough to have been labeled one of the programs after which the "next generation" of preventive interventions in mental health should be modeled (Rotherum-Boris and Duan, 2003). On the other hand, though one of the theoretical frameworks behind the intervention was attachment theory (D. Olds, 1997) the NFP was not created as a mental health preventive intervention per se.

The Nurse-Family Partnership was first tested in upstate New York in the 1980's. Three things separated this trial from previous evaluations of home-visiting programs. First, the intervention was based on three basic theories selected for their relevance to family reorganization at the time of a woman's first pregnancy: attachment, self-efficacy and human ecology. Nurses carrying out the intervention were comprehensively trained in how to apply these theories in interaction with their clients(D. Olds, Kitzman, Cole, & Robinson, 1997) Second, the research design of the trial used randomization and followed the original sample, which totaled 400 intervention and control mothers, longitudinally. Finally, the intervention was intensive, beginning during each subject's pregnancy and following the index mother through the second year of her infant's life with biweekly and then monthly visits.

The goals of the research trial were to diminish poor pregnancy outcomes, improve parental caregiving and impact maternal life course (D. L. Olds et al., 1997). The results of this trial were remarkable. Mothers receiving the intervention showed significantly *better health-related behaviors in pregnancy* (David L. Olds, Henderson, Chamberlin, & Tatelbaum, 1986). Furthermore, *there were significantly fewer state-verified child abuse cases* in intervention families and reductions in health care visits for accidental injury or ingestion in the target infants and toddlers (David L. Olds et al., 1986). Finally, *reduced rates of unintended pregnancies were documented in the intervention group*, while the *duration of maternal employment in the intervention group* was higher than controls in the four years after delivery of the first child (David L. Olds, Henderson, Tatelbaum, & Chamberlin, 1988). Follow-up cost analysis showed that program costs were recouped in the form of diminished government spending by the time the index children reached age 4 (D.L. Olds & Kitzman, 1993). An independent follow-up study by the RAND Corporation calculated that cost savings from the intervention by the time the children reached age 15 would amount to 4 times the original investment (Karoly et al., 1998).

These data have inspired a series of associated research efforts to further test the model. The original sample was in Elmira, New York, a semi-rural community where the vast majority of families are Caucasian. A large-scale trial (N=1125 families) began in Memphis, TN in 1987, this time funded by a consortium of federal agencies and private foundations and focused on an urban, minority population. An almost identical intervention model was used in this trial and corresponding effects have been documented [Olds, 2004 #3611].

At the same time, the National Institute of Mental Health funded a 15-year follow-up of the original New York sample. Two findings from this analysis stand out. First, the *reductions in child maltreatment, latency to subsequent pregnancy, and overall welfare dependence have endured across the 15 years* (D. L. Olds et al., 1997). Second, *rates of conduct problems in the intervention offspring have been found to be significantly lower than non-intervention offspring, while academic and social functioning were correspondingly better* (D. Olds et al., 1998). One of the major strengths of these studies is that the researchers did not rely solely upon self-report to document group differences. Instead, reports from the state Departments of Corrections and Child Protective Services were used to provide objective data on group differences. This is a critically important part of this research initiative and this intervention project stands alone in offering this level of data on effectiveness.

While the Nurse-Family Partnership is clearly one way forward for preventive intervention, other early intervention efforts are equally promising and may impact a child's developmental capacities across several domains. For instance, longitudinal data on publicly funded large-scale early learning programs for urban high-risk children have been shown to lead to both more positive educational outcomes as well as fewer conduct problems fifteen years later (Reynolds, Temple, Robertson, & Mann, 2001) Of course, program quality, intensity and duration as well as family involvement are likely key factors in positive outcomes Frede, 1995 #3605]. Not surprisingly, ideal program design is rare and corresponding long-term effects are relatively uncommon (Schweinhart, 1999). Early Head Start programs offer great promise, though the fact that almost 50% of mothers of participant children are above the screening cutoff for maternal depression highlight the challenges of serving those at high social risk (Administration for Children and Families, 2002). Here, as in our review in section 2, the very high impact of the *combination of maternal depression and poverty stands out as a major public health problem.*

Recommendations: **Research and Intervention**

The emerging findings regarding sensitive periods and developmental programming have obvious implications for preventive intervention.

Screening for and treating prenatal anxiety

The intervention of a practicing psychiatrist *treating an expecting mother with an anxiety disorder may prevent psychopathology in her offspring*. Studies of pharmacotherapy during pregnancy are lacking; however, evidence that psychotherapy for both anxiety and mood disorders is effective suggests that treatment or referral is indicated (Watkins & Williams, 1998). We need studies to clarify how treating maternal anxiety during pregnancy will impact the post-partum development of her child.

Prenatal care visits offer the opportunity for screening for anxiety symptoms and training of obstetrical/gynecological and family practice residents as well as continuing education targeting primary care practitioners who treat pregnant women should include discussion of the links between maternal anxiety and child outcome. Screening and referral algorithms should be reviewed. Psychiatrists should be involved in both training initiatives and the study of the application of screening and intervention protocols. Longitudinal studies of interventions for maternal anxiety on both maternal care and children's development are indicated.

Assessment: Recognizing and treating post-natal depression

Similarly *psychiatrists should recognize the developmental implications of post-natal depression on parent-child interactions*. (Though the impact of depression on fathers is less well-studied, recent and very high quality epidemiological data suggest the impact of paternal depression on offspring psychopathology is as great as that of maternal depression (Lieb, Isensee, Hoefler, Pfister, & Wittchen, 2002). Referral to a child psychiatrist familiar with the assessment of the developing attachment relationship (cf., (Boris, Fueyo, & Zeanah, 1997) is indicated, particularly for severe or prolonged postnatal parental depression. Because of both the scale of treating depressed high-risk women and limited access to mental health care in many parts of the country, proven interventions that link patients, psychiatrists and primary care physicians to improve care of depression in community settings should be broadly expanded Oxman, 2002 #3591].

Screening for parental depression during postnatal visits with either obstetricians or pediatricians should be routine and educational initiatives for trainees and practitioners are indicated (Currie & Rademacher, 2004). Screening and referral algorithms should be developed and incorporated into trainings. Psychiatrists should be involved in both training initiatives and the study of the application of screening and intervention protocols.

There is already evidence that intervention for post-partum depression is effective. The next level of intervention studies should focus on the relative cost-benefit of pharmacologic interventions versus psychotherapy with particular attention to the impact of pharmacotherapy on breastfed infants.

Services: Linking large-scale, successful early interventions to specific, parental psychopathology.

Model early preventive interventions such as the Nurse-Family Partnership have, until recently, not targeted mental health problems in mothers (Boris, 2002). Given the widespread adoption of the Nurse-Family Partnership in many communities (Olds, 2003) and its use with families who have first-time, low-income mothers (a group likely at high-risk for both antenatal anxiety and/or post-partum depression), adoption of family-based interventions targeting these conditions is indicated. Psychiatrists should play a key role in both advocating for the development of these interventions and assisting with their design.

Similarly, large-scale early childhood interventions, such as Early Head Start, need to develop and study sustainable mental health interventions linked with program sites

Interventions based in attachment theory that measurably shift dyadic mutuality and increase attachment security need to be refined. One promising group approach, tested with Head Start populations (Marvin et al., 2002), is already being used in other high-risk populations. Studies of these types of interventions are particularly important given evidence that secure attachment is a protective factor associated with better developmental outcomes and less psychopathology.

5) **Prevention of suicide in adolescence**

Epidemiology of youth suicide

Magnitude of problem

In most industrialized societies, adolescent suicide is one of the leading causes of death in this otherwise generally healthy age group. Although completed and attempted adolescent suicide share many risk factors with suicide in other age groups, the sharp rise in suicide rates with the onset of puberty, the marked relative prevalence peak in male adolescent/young adult suicides, and secular changes in the adolescent suicide rate suggest that distinctive developmental and social factors contribute to suicide risk in this developmental epoch.

Although completed suicide is a leading cause of death in this age group, *completed* suicide is relatively rare (1.5 per 100,000 in 10-14 year-olds; 8.2 per 100,000 in 15-19 year olds), while suicidal *ideation and attempts* are common. To appreciate the magnitudes involved, one can estimate from CDC data that while 1,611 youngsters, age 15-19 committed suicide in the US in 2001, 3.4 million youngsters in this age group seriously considered suicide; 1.7 million made a suicide attempt; and 590,000 made a suicide attempt sufficiently serious to require medical attention (Grunbaum et al., 2004).

Attempted suicide

As with many uncommon conditions, the relative rarity of completed suicide poses formidable statistical challenges for screening, prediction, and prevention because, although the known risk factors for adolescent are sensitive (i.e. are found in most cases of suicide), they are very non-specific and are found in a very large number of adolescents who do not commit suicide (Shaffer, Garland, & Bacon, 1989).

An alternative preventive approach to targeting completed suicide is to target attempted suicide and its concomitants. This approach has considerable merits, given the fact that attempted suicide has significant physical and psychosocial morbidity and economic costs in its own right. Adolescent suicide attempters have high rates of subsequent repeat attempts and are at elevated risk for motor vehicle and other accidental injuries and homicidal death Boergers, 2003 #3513;Brent, 1997 #3517]. Furthermore, compared to youngsters without a history of attempted suicide, youngsters with a history of attempted suicide have a markedly increased risk of subsequently completing suicide (a three-fold increase in girls and a thirty-fold increase in boys).

The Youth Risk Behavior Survey (YRBS) of 50,000 high school students, conducted biennially by the Centers for Disease Control since 1991 provides detailed epidemiological data on the prevalence and correlates of suicidal ideation and suicide attempts in successive national samples of adolescents. Although the sample does not include adolescents who have dropped out of school, this community sample avoids the biases inherent in clinical samples of suicide attempters.

The 2003 YRBS (Grunbaum et al., 2004) found that 16.9% of high school students reported that they had seriously considered suicidal ideation within the last 12 months, 16.5% reported having made a suicide

plan, 8.5% reported having attempted suicide one or more times, and 2.9% reported having made a suicide attempt that required medical attention.

Risk and protective factors for adolescent suicide

Completed suicide

Increasingly sophisticated psychological autopsy and case control methods have elucidated the diagnostic and other psychosocial risk factors for adolescent suicide (Madelyn S. Gould, Shaffer, Fisher, & Garfinkel, 1998) (Madelyn S. Gould, Shaffer, & Greenberg, 2003) (Madelyn S. Gould, Fisher, Parides, Flory, & Shaffer, 1996). About 90% of adolescent suicides in the US have at least one diagnosable major psychiatric disorder, especially depressive disorder, substance abuse, and conduct disorder. The small minority of adolescent suicides without a major psychiatric diagnosis still show elevated rates, compared to community controls, of family psychiatric disorders, past suicidal ideation or behavior, legal or disciplinary problems in the prior year, and firearms in the home (Brent et al., 1993). Other important risk factors include a prior history of suicide attempt (in one-quarter to one-third of young suicides) and family history of suicide (Shaffer, Garland, Gould, Fisher, & et al., 1988). Additional psychosocial risk factors for completed suicide include: isolative or impulsive character traits; hopelessness; recent life stressors, such as interpersonal loss or legal or disciplinary problems (especially in youngsters with substance abuse or disruptive disorders); and family history of suicide, depression, or substance abuse (Brent, Johnson, Perper, Connolly, & et al., 1994; Madelyn S. Gould, Greenberg, Velting, & Shaffer, 2003; Madelyn S. Gould, Shaffer et al., 2003). Although there is marked variation between ethnic groups, socioeconomic status (SES) does not appear to influence completed suicide rates. Problematic parent-child relationships and non-intact family of origin also appear associated with youth suicide, although the magnitude of this factor is unclear, especially once parental or youth psychopathology is controlled for.(Madelyn S. Gould, Greenberg et al., 2003; Madelyn S. Gould, Shaffer et al., 2003) "Contagion" or clusters of completed suicide are estimated to involve from 1-13% of youth suicides (M. S. Gould, Wallenstein, & Kleinman, 1990), and may be facilitated by sensationalized media coverage of suicide(Madelyn S. Gould, 2001).

Suicidal ideation and attempts

Epidemiological data suggest adolescent suicidal ideation and attempts are associated with the presence of a psychiatric diagnosis such as substance abuse, mood, anxiety, and disruptive disorders (Madelyn S. Gould, Greenberg et al., 2003; Madelyn S. Gould, King et al., 1998; Madelyn S. Gould, Shaffer et al., 2003). In addition, it is apparent from the YRBS and other data that there is a high degree of overlap between adolescent suicidal ideation and attempts and other impulsive, sensation-seeking, or high-risk "problem behaviors", such as substance use, fighting, and anti-social behaviors (even at levels below threshold for the diagnosis of a of substance abuse or disruptive disorder); onset of sexual intercourse; weapon-carrying; etc. (King, Ruchkin, & Schwab-Stone, 2003; King et al., 2001).

Gender

In addition to being much more common than completed suicide, attempted suicide is far more common in girls age 15-19 years old than in same-aged boys. Girls in this age group attempt suicide about twice as often as boys, while boys complete suicide about five times more often than girls. Thus, the ratio of completed to attempted suicides for girls is about 1:3,7000, but the ratio for boys is about 1:470

The impact of risk factors varies by gender, as illustrated by the (Shaffer et al., 1988) case control study of adolescent suicides in the greater New York area. For boys, the risk of completed suicide was increased most by a history of a prior attempt (approximate odds ratio 22.5 compared to the general adolescent male population), followed by major depression (OR 8.6), substance abuse (OR 7.1) antisocial behavior (OR

4.4), and family history of suicide (OR 3.0). In contrast, for girls, major depression was the predominant risk factor (OR 49), followed by history of a prior attempt (OR 8.6), antisocial behavior (OR 3.2), and family history of suicide (OR 2.7), while substance abuse did not contribute to suicidal risk in girls (OR 0.8). In 49% of the suicides, one or more psychiatric disorder had been present for at least three years and 46% of these young suicides had had a prior mental health contact (Shaffer et al., 1996)These findings suggest that screening for major depression and history of prior attempts is likely to identify the largest population of adolescents at risk for completed suicide.

Cognitive and personality factors

In addition to diagnostic risk factors, a variety of cognitive and personality traits, including impulsivity, aggression, hopelessness, and impaired social and problem-solving skills appear to be important risk factors for adolescent suicidal ideation/behavior and may provide targets for therapeutic or preventive interventions (Madelyn S. Gould, Greenberg et al., 2003; Madelyn S. Gould, Shaffer et al., 2003); (Alan Apter, Gothelf, Orbach, Weizman, & et al., 1995; A. Apter, Plutchik, & Van Praag, 1993; Alan Apter & Wasserman, 2003; Horesh, Gothelf, Ofek, Weizman, & Apter, 1999; King et al., 2003).

Biological risk factors

Biological factors appear to play an important role in the vulnerability to depression and suicide in adults, but are less well studied in adolescents; genetic factors may account for some of these vulnerabilities in children and adolescents, over and above the deleterious environmental impact of parental psychopathology; (Alan Apter & Wasserman, 2003; Brent & Mann, 2003; Brent et al., 2004; Brent, Perper, Moritz, Baugher, & et al., 1993)

Demographic factors

Demographic factors also influence vulnerability to suicide. Youth suicide is especially common among Native Americans, among whom high rates of social anomie, ready access to firearms, and high rates of substance abuse are presumed to play a role(Middlebrook, LeMaster, Beals, Novins, & Manson, 2001). The suicide rate for young white males exceeds that of non-white males, although in recent years the discrepancy between white and African-American youth has narrowed, for reasons that remain unclear (Shaffer, Gould, & Hicks, 1994; Willis, Coombs, Drentea, & Cockerham, 2003)

Methods of suicide and their relevance as potential foci for prevention

Firearms are the commonest means of youth suicide, used in 49% of suicides, age 5-19, followed by hanging/suffocation and ingestion, which account, respectively, for 38 and 5% of suicides in that age group (CDC 2004). Males in this age group use firearms more frequently than females (52 % of young male suicides vs. 35% of young female suicides), while the opposite is true of ingestions (17% of young female suicides vs. 3% of young male suicides). Given the larger number of male suicides and the greater lethality of most gunshot attempts compared to ingestions, efforts to reduce the ready availability of firearms to suicidal youth is likely to have a greater impact on completed suicide rates than efforts to restrict the availability of ingested agents.

Developmental factors

Until recently, most studies of adolescent suicide were correlative and cross- sectional in design. Prospective longitudinal studies are now beginning to shed light on developmental risk and protective factors for suicidality over the course of childhood(Fergusson, Woodward, & Horwood, 2000; Johnson et al., 2002).

Developmental risk factors A variety of family factors are associated with adolescent suicide attempts, including residential instability, change in caretaking parent, foster care, running away from home, family conflict, perceived low parental care and social support, and physical and sexual abuse(Beautrais, 1998; Beautrais, Joyce, & Mulder, 1996; Fergusson et al., 2000; Johnson et al., 2002). Childhood physical abuse

is associated with adolescent suicide attempts and completed suicide, especially in youngsters with poor social skills in middle adolescence (Johnson et al., 2002;Johnson, 2002 #3540]. Although suicidality in adolescents may be due in part to the environmental stressors of poor parental care and family adversity and violence, it is difficult to exclude a possible role for genetic transmission of impulsive/aggressive personality traits and mood, substance use, and disruptive disorders which might underlie both parental psychopathology and the suicidal vulnerability in adolescent offspring.

As Brent and Mann (Brent & Mann, 2003) point out, these associations have important clinical implications. In assessing an adolescent suicide attempter, it is essential to inquire about parental psychopathology and suicidal risk, since the presence of these parental factors may exacerbate the adolescent's suicidal vulnerability. Conversely, these authors note, in assessing suicidal or depressed adults, it is important to assess the extent to which adolescent offspring may also be at risk for these difficulties.

Youngsters who are having school difficulties or who have dropped out of school are at increased risk for completed suicide and serious suicide attempts,(Beautrais, 1998; Beautrais et al., 1996; Madelyn S. Gould et al., 1996), most likely reflecting both underlying vulnerabilities and the anomic effects of being isolated or alienated from their peers' milieu.

Developmental protective factors Family cohesion, with high levels of perceived mutual involvement, communication, and emotional support appears to be associated with lower levels of suicidal ideation or attempts (Rubenstein et al., 1998, (Kandel & Davies, 1991; King et al., 2001). Jessor's work on adolescent problem behavior suggests that a family factor of "conventionality" (value on academic achievement, involvement with church/community organizations, intolerance of deviance, compatibility of parent and peer values) serves as a protective factor against delinquency, substance use, risky driving, and precocious sexual activity, all activities associated with increased levels of suicidal behavior.

The multidimensional process leading to adolescent suicidal behavior

As is apparent from the above discussion, there appear to be multiple pathways leading to adolescent suicidal behavior; these usually involve an interaction over time between acute events and circumstances and more persistent vulnerabilities (Brent, 1997; Shaffer & Craft, 1999). Persistent psychopathological traits (such as depression or hopelessness, impulsivity, impaired regulation of affect or aggression, and/or poor social problem solving abilities) are frequently non-specific background risk factors. In most cases, an acute stressful event (which may often be the result of these vulnerabilities), such as a disciplinary crisis (e.g. school suspension, legal difficulty, fight with parent), interpersonal loss (e.g. breakup with romantic partner), or humiliation (e.g. teasing, bullying), induces an acute, intense state of emotional distress (e.g. panicky dread, despair, rage) that the adolescent experiences as unbearable. At this point, the balance of inhibitory (or protective) factors vs. facilitating (or enabling) factors may determine whether a suicide attempt results and whether it is lethal (Shaffer & Craft, 1999). Inhibiting factors include the presence of others and the perceived availability of social supports and lack of access to lethal means. Facilitating factors include isolation, disinhibition due to alcohol or drugs, ready access to lethal means, and familiarity with recent examples of suicidal behavior by peers or in the media. Family and cultural values may serve to provide either a strong taboo against suicide or an implicitly permissive attitude towards such behavior.

This multidimensional pathway leading to adolescent suicidal behavior also suggests multiple points for possible intervention (Madelyn S. Gould, Shaffer et al., 2003).

Approaches to prevention of adolescent suicide

As (Shaffer et al., 1989) note, the features of a risk factor that are most relevant from a prevention perspective are 1) that it account for a large proportion of the cases of the disorder and 2) that it be modifiable at a reasonable cost.

In the case of adolescent completed and attempted suicide, the most important risk factors appear to be depression, substance abuse, conduct disorder, and family history of suicide, with background factors, such as family adversity, and traits, such as anxiety proneness, impulsivity, aggression, and poor social and problem solving skills, playing an important, but less well quantified role (Madelyn S. Gould, Greenberg et al., 2003; Madelyn S. Gould, Shaffer et al., 2003; Shaffer et al., 1988).

School provides the setting for many, if not most, studies of preventive interventions for adolescent psychopathology, such as depression and suicidality. It is estimated that 70-80% of children who receive *any* mental health services do so in the school setting (Burns et al., 1995; Ringeisen, Henderson, & Hoagwood, 2003). Logistically, the school setting offers ready access to large numbers of youngsters, who may be difficult to reach by other means. Furthermore, children with mental health needs identified in the school setting are more likely to receive treatment when it is offered in the school setting than through other channels (Catron & Weiss, 1994). Hence, schools are a critical context for the identification and modification of risk factors for suicide. Despite this importance, relatively little research has addressed which organizational and ecological aspects of the school context are likely to facilitate preventive interventions and how these might be optimized(Ringeisen et al., 2003)

Prevention addressed to antecedent risk factors

Family adversity as a risk factor

Various forms of family adversity serve as risk factors for adolescent suicidality. The *cumulative risk model* and its implications for early preventive intervention are discussed throughout this report (see introduction and sections 2) and 4), in particular). More specifically, parental psychopathology, especially a history of suicide or suicide attempts, is a well documented risk factor for adolescent suicide and may operate through a variety of interacting mechanisms including genetically transmitted vulnerability, increased family conflict and adversity, stress-inducing perturbed parent-child interactions, and social modeling. As discussed in section 2), clinical identification of depression, substance abuse, or other serious psychopathology in an adult parent should trigger inquiry about the mental health and development of any children in the family; signs of vulnerability in the children should lead to not only individual clinical interventions directed at affected offspring, but also family-based interventions to help strengthen family coping skills.

Preventing and treating psychopathological risk factors for adolescent suicide: depression, substance abuse, conduct disorder and anxiety

Prevention: Studies of targeted preventive interventions for adolescent depression have been done primarily in the context of youngsters at high-risk by virtue of parental depression or identified as at-risk because of self-reported depressive symptoms, parental conflict, or negative attributional style (Costello et al., 2002; J Garber & McCauley, 2002). As noted in Section 2), Clarke et al.'s Cognitive-Behavioral Group Preventive interventions (e.g. [Clarke, 1995 #2336] and the University of Pennsylvania group's School-based Cognitive Behavioral Preventive (POP) (summarized in (J Garber & McCauley, 2002)interventions proved effective in reducing major depression, depressive symptoms, and/or negative attributional style (a risk factor for depression) in the school setting with at-risk children.

The impact of these targeted school-based interventions is complex. Gender-related differences may further complicate the task of evaluating interventions. For example Petersen, 1997 #3706] examined an intervention for preventing depression in seventh graders selected for depressive symptoms, stressors, and poor coping skills. The school-based intervention included cognitive restructuring, problem-solving techniques, and teaching social skills. Post-intervention, better coping and fewer internalizing and externalizing symptoms were found in the intervention group compared to control subjects. However, although the prevention group girls showed fewer depressive symptoms than control girls, boys in the intervention group reported *more* depressive symptoms than did boys in the control group. Furthermore, no differences were found in the rates of clinically diagnosable depression between the treatment and control groups. The durability of seemingly effective interventions also requires further study. For example, the

initially beneficial effects of the POP program on depressive symptoms however did not persist beyond two (Gillham & Reivich, 1999).

Universal preventive interventions for adolescent depression focused on unselected populations (e.g., classroom based interventions) have produced mixed results (J Garber & McCauley, 2002; Shaffer, Garland, Vieland, Underwood, & et al., 1991; Shaffer et al., 1990; Shochet et al., 2001) and appear generally less effective than targeted programs. For example, early studies of school-based primary prevention programs for adolescent depression with unselected high school students, using either educational (knowledge-only) or a behavioral intervention to increase pleasant activities failed to produce any persistent decrease in depressive symptoms (J Garber & McCauley, 2002)

Directly targeting depressive symptoms may not be the only preventive approach for depression or suicidality. Adolescents with anxiety, substance abuse, and/or conduct disorder are also at increased risk for subsequent depression and/or suicidality through a variety of mechanisms(A. Apter et al., 1993; Eaves, Silberg, & Erkanli, 2003; Renaud, Brent, Birmaher, Chiappetta, & Bridge, 1999), and targeting these areas of psychopathology may be helpful in preventing depression or suicidality. Although there is some preliminary evidence for the effectiveness of preventive interventions with anxious children (Dadds et al., 1999), the impact of such interventions on outcomes such as subsequent depression or suicidality has not been well studied.

Co-morbid conditions such as substance abuse or conduct disorder are important not only as potential precursors of depression or suicidality; when present, these conditions may complicate the treatment or prevention of depression. For example, (Rohde, Clarke, Mace, Jorgensen, & Seeley, 2004)studied the effectiveness of their Adolescent Coping With Depression (CWD-A) course, a cognitive-behavioral group intervention, in non-incarcerated depressed adolescents with comorbid conduct disorder, identified through the juvenile justice system. Despite some post-treatment improvement in depression scores of youngsters in the treatment group (compared to a life skills/tutoring comparison group), at 6- and 12 months there were no significant differences between the groups on either depression recovery rates or persistence of conduct disorder.

Identifying which symptom or functional areas should be the target of preventive interventions also requires further study, since interventions to improve general school or social functioning may have untargeted secondary beneficial effects on the vulnerability to depression. For example, (Kellam, Rebok, Mayer, Ialongo, & Kalodner, 1994) found that among the effects of a yearlong universal reading enrichment program for first grade children was an improvement in depressive symptoms in boys who showed a gain in reading achievement.

Selective prevention: Treatment of depressed adolescents. Effective methods for treating adolescent depression are now available(Hollon et al., 2002). Although there has been much debate regarding the risk-benefits of antidepressant treatment of adolescent depression, the recent randomized placebo-controlled TADS trial found the combination of fluoxetine and cognitive behavioral therapy (CBT) superior to placebo or either active treatment alone in reducing depression scores (Treatment for Adolescents with Depression Study (TADS) Antonuccio, 2004 #3529]; the combination of medication and CBT was the most effective in reducing suicidal ideation. CBT alone had an effect size of 0.33 in reducing suicidal ideation.

Randomized controlled trials of CBT and interpersonal psychotherapy (ITP-A) have also found them effective for depressed adolescents [Asarnow, 2001 #3699]; [Harrington, 2003 #3573]; Mufson et al., 1999;Compton, 2004 #3524].

The need for long-term clinical follow-up of depressed adolescents, however, is apparent in that even successful pharmacological trials have a substantial one-year relapse rate (up to 40%) (Emslie et al., 1998); psychotherapeutic interventions for depressed adolescents also show a high relapse rate (Birmaher et al., 2000). Indeed, long-term studies suggest that childhood depression may have high rates of recurrence in

adolescence and adulthood, on the order of 40-75% over two to five years (summarized in (Costello et al., 2002; J Garber & McCauley, 2002).

Potential impact of treating depression on adolescent suicide rates –Reasons for hope? Recent secular trends in the adolescent suicide rate provide some hope that more effective treatment of adolescent depression may be effective in preventing suicide. After tripling from the early 1960's to the mid-1990s, the adolescent suicide rate has fallen steadily from 1995 to the present. For white males, age 15-19 years old, the rate fell from approximately 20 per 100,000 in 1988 to 13 per 100,000 in 2001. (Both the rise and fall in completed suicide rates occurred somewhat later for African-American adolescent males.) Based on a variety of epidemiological considerations, Shaffer and colleagues
[Gould, 2003 #3394;Gould, 2003 #3393]; (Olfson, Shaffer, Marcus, & Greenberg, 2003) have argued that this decline reflects better detection and more aggressive psychopharmacological treatment of adolescent depression, rather than changes in economic factors, substance use, or methods of suicide

Prevention efforts addressed to identifying and referring suicidal adolescents

A series of recent national and federal initiatives have been aimed at encouraging prevention programs for youth suicide (Children's Mental Health Screening and Prevention Act, 2003; Garrett Lee Smith Memorial Act, 2004; [Goldsmith, 2002 #3446] U.S. Public Health Service, 1999).As part of these efforts, the collaborative federal National Strategy for Suicide Prevention http://www.mentalhealth.org/suicideprevention/default.asp, accessed April 15, 2005) and the Suicide Prevention Resource Center (http://www.sprc.org/, accessed April 15, 2005) provide public information, training, technical assistance and resources (including an Online Registry of Evidence-Based Practices in Suicide Prevention) to help states and communities develop, implement, and evaluate suicide prevention programs.

Attempts to identify and treat suicidal adolescents face many challenges in defining who should be screened, in what settings, for what conditions. As noted earlier, school is the institutional setting in which the largest numbers of adolescence spend many hours a week in interaction with adults; hence, school-based programs have an obvious appeal as a means of reaching large numbers of teens, although there is evidence that youngsters who drop out of school may be at higher risk for suicide than those who are school attendees. Other potential venues for screening adolescents include the primary care setting and, for more selected populations, colleges (Silverman, M, F, M, & M, 1997) [Barrios, 2000 #3700], juvenile detention centers, and the military (A. Apter et al., 1993; Knox, Litts, Talcott, Feig, & Caine, 2003).

School-based programs

In response to federal and state mandates for youth suicide prevention, school systems have implemented a variety of suicide prevention programs, often lacking in demonstrated efficacy Gould et al., 2003b](Kalafat & Elias, 1995).

Curriculum-based approaches. The curriculum-based approach is intended to teach students about the warning signs of depression and suicidality and to destigmatize help seeking either for oneself or potentially suicidal peers. The initial generation of school-based didactic programs focused on increasing awareness of teen suicide. These programs alerted students and staff to recognize potential signs of depression or suicide risk and encouraged them to seek appropriate help. Evaluating these programs, Shaffer and colleagues (Shaffer et al., 1991; Shaffer et al., 1990)and Garland)(A. Garland, Shaffer, & Whittle, 1989; A. F. Garland & Zigler, 1993) criticized this approach on the basis of studies finding them to be ineffective in increasing self-identification or help-seeking behavior (Vieland, Whittle, Garland, Hicks, & et al., 1991). Furthermore, a follow-up study suggested that, compared to students not exposed to such a prevention program, exposed students were significantly *less* likely to encourage a depressed friend to seek clinical help or to seek help for themselves; indeed, Shaffer et al. argued that the "destigmatization" of suicide produced by such programs was likely to be counterproductive to the extent it encouraged students to "consider suicide (as) an understandable, possibly reasonable response to stress," (p. 72) rather than as a symptom warranting intervention.

A newer generation of universal curriculum-based programs attempted to correct the defects of earlier programs through more comprehensive and sustained interventions, promoting alternative responses to emotional distress, and more robust multi-method post-test assessment of intervention effects (e.g. (Klingman & Hochdorf, 1993). Culturally specific models were also developed, such as a suicide prevention program focusing on life and social skills training for Zuni high school students (LaFromboise & Howard-Pitney, 1995). These newer programs have been more promising than earlier ones in improving coping and problem-solving skills and increasing information concerning suicide and helping resources. Whether such programs actually produce beneficial changes in suicide related behaviors, as opposed to attitudes, remains in need of empirical evaluation(J Garber & McCauley, 2002; Mazza, 1997).

Case finding or "gate-keeper" based approaches A second school-based approach is that of educating "gate keepers," such as school personnel and primary care physicians to identify youngsters at risk for depression or suicide (Madelyn S. Gould, Greenberg et al., 2003). Such programs appear to be well received by school personnel with accompanying improvement in their knowledge, intervention skills, and perceived preparedness for coping with suicidal crises (e.g., King & Smith, 2000 (Project SOAR)); the effectiveness of such programs in actually decreasing student suicidal behavior has not been demonstrated. A comparable approach has been employed in training primary care physicians to improve their routine screening of patients for suicidal ideation (Madelyn S. Gould, Greenberg et al., 2003). A training workshop for primary care physicians in Australia, markedly improved inquiry rates about suicidal ideation and identification of suicidal patients, but did not result in significant changes in patient management [Pfaff, 2001 #3702]. An intensive program aimed at improving Dutch general practitioners' diagnosis and treatment of depression resulted in a transient decrease in the adult suicide rate, but with subsequent return to near previous levels after three years, underlining the need for measures to maintain clinicians' vigilance Rihmer, 1995 #3658]. Similar studies targeting adolescent patients and their health care providers are needed.

Active screening or case-finding approaches School-wide direct screening of adolescents, using self-reports and structured interviews, to identify suicidal adolescents and those at risk for suicide have also been studied as a step towards clinical referral and intervention [Gould, 2005 #3703] (Madelyn S. Gould, Greenberg et al., 2003). These multistage assessments have sought to identify students with current or recent depression, substance abuse, recurrent suicidal ideation, or past suicide attempts. Because sensitivity (minimizing false-negatives) is more important in suicide screening than specificity (minimizing false-positives), more detailed and systematic second stage clinical assessments are necessary to exclude youngsters *not* at risk for suicide and to clarify the service and referral needs of those youngsters who truly are.

[Gould, 2005 #3703] summarize the evidence for the clinical validity and reliability of various school-based screening procedures, such as the Suicidal Ideation Questionnaire Reynolds, 2001 #3610], the Suicide Risk Screen (E A Thompson & Eggert, 1999) and the Columbia Teen-screen(Shaffer & Craft, 1999) as validated against suicidal status on a more detailed second-stage assessment using the Suicidal Behavior Interview or Diagnostic Schedule for Children. As an example of one such screening program, Shaffer and colleagues (Shaffer et al., 2004) have developed the Columbia TeenScreen a brief, self-administered questionnaire intended to identify high school students at risk of suicide; the instrument exhibits a sensitivity of 75-88%, and a specificity of 76-83% (Shaffer & Craft, 1999; Shaffer et al., 2004) In a field trial, almost two/thirds of the suicidal teens identified by the instrument were not previously known by school personnel as having significant problems (Scott et al, 2004). Only one-third of students identified by the screen as having major depression and half of those found to have made a past suicide attempt were known by school personnel to have significant problems and were receiving help (Columbia TeenScreen website, accessed 3/13/05).

Beyond the psychometric issues of what screening procedures are most effective in identifying suicidal students, institutional and systems issues often pose the greatest barrier to such active screening approaches, which school staff may regard as intrusive or raising liability issues. Despite lack of experience with such screening programs, school principals rate such school-wide student screening programs as significantly less acceptable than curriculum-based and staff in-service approaches (D. N. Miller, Eckert, DuPaul, & White, 1999). (Indeed, some school systems take a "don't ask/don't tell"

attitude that excludes suicide items from surveys of students' health and risk-behavior, out of fear of liability issues).

One common objection raised by educators or other non-clinicians is the fear that asking about suicidal thoughts or acts will somehow increase adolescents' risk of suicide or "put ideas in their heads." Using a careful experimental design, Gould and colleagues (2005) were able to show that such inquiry about suicidal ideation or behavior did *not* increase distress or suicidal ideation in the experimental group of adolescents queried about these items as part of a screening program (compared to a control group which was surveyed with a screening survey that did not include items about suicidal ideation or behavior). Indeed, adolescents who were distressed and/or previous suicide attempters in the group so queried reported feeling significantly less distressed and suicidal following the survey than the control group that was not initially queried about suicidal ideation or behavior.

Finally, the effectiveness of such screening programs in reducing teen suicidal behavior is ultimately determined by the effectiveness of the clinical referral and treatment program put into place for students identified by screening as being at-risk. Treatment adherence and follow-up is a serious problem even for adolescents seen in hospital emergency rooms for suicide attempts or ideation (Boergers & Spirito, 2003). Development of systematic, effective triage, referral, and treatment procedures for students identified by school-based screenings as at-risk for suicide is a largely unstudied challenge

Skills-based programs. Another promising approach is that of programs that aim to enhance problem-solving, coping, and other social and cognitive skill, in the hopes of enhancing protective factors and reducing risk factors. Compared to programs that lack this focus, such skills training programs are more likely to produce significant reductions in suicide risk behaviors and increases in protective factors (E. A. Thompson, Eggert, Randell, & Pike, 2001). Targeting high school students at high risk of drop out, Randell et al. (Randell, Eggert, & Pike, 2001) compared the impact of 1) a brief assessment and intervention protocol; 2) a 12-session peer-group, life-skills training program added to this assessment and crisis intervention; and 3) "usual care". All three interventions decreased suicidal risk; both active treatments were associated with a decrease in depressive symptoms, and the combined treatment was associated with increased personal control, problem-solving coping, and perceived family support. A replication study (E. A. Thompson et al., 2001) found significant declines in suicidal ideation associated with the experimental interventions, which were also more effective than usual care in reducing depression and hopelessness. The experimental treatments also produced greater reductions in anxiety and anger in girls, while the combined treatment was most effective in enhancing and sustaining personal control and problem-solving coping for both males and females. A different multi-site replication (Eggert, Thompson, Randell, & Pike, 2002) found decreases across all three treatments in suicide-risk behaviors, depression, and drug involvement, with intervention-specific effects in decreasing depression. These studies emphasize the need for rigorous assessment methodologies that include comparison and "usual care groups," as well as the importance of trying to tease out mediating variables and gender-specific effects.

Assessing the effectiveness and durability of interventions entails assessing their impact on multiple domains, both attitudinal and behavioral, over time. For example, as summarized by Gould et al., although the Signs of Suicide program (Screening for Mental Health Inc, 2005) (which includes both an educational and screening component) was well accepted by school personnel and produced a short tem decrease in suicide attempts, help-seeking behavior and suicidal ideation were not affected (Aseltine, 2003; Aseltine & DeMartino, 2004).

Other community-based approaches

Beyond school-based approaches, a variety of community based interventions or approaches to preventing have been tried, but generally have not been well-assessed with respect to adolescents. These include hotlines/crisis centers; means restriction (access to firearms, lethal quantities of medication, etc); and media education to reduce contagion effects.

Hot lines/crisis centers. As reviewed by Gould et al., 2003b, 14-18% of suicidal youth report having used hotlines, but there are few data regarding the efficacy of the services received; the impact of hotlines on adult suicide is equivocal (Lester, 1997).

Restricting access to firearms. Brent (2001) reviewed the existing relevant epidemiological, case-control, quasi-experimental, and prospective studies and concluded that gun availability in the home is a significant risk factor for adolescent suicide. There is some evidence that greater restrictiveness of gun control legislation is associated with declines in firearm suicides, often without substitution of other methods (which in any case are usually less lethal). On the individual case level, the apparent facilitation of impulsive adolescent suicide by ready gun availability has lead to the recommendation of counseling parents of youth at risk for suicide about restricting gun access. Such recommendations however have only limited effectiveness. (Kruesi et al., 1999) found that when parents of adolescent suicide attempters were counseled about the dangers of firearms in the house, only 5/8ths of the parents removed the guns or stored them more securely. Similarly, (Brent, Baugher, Birmaher, Kolko, & Bridge, 2000) found that following recommendations to remove firearms from the home, only about a quarter of parents of depressed children entering a clinical treatment trial had complied with this recommendation at follow-up.

Suicide and contagion: the role of the media. Clusters of attempted and completed suicides, including adolescent ones, have been observed both locally and nationally, often related to sensational news coverage of suicides or programs featuring fictional suicides (Madelyn S. Gould, 2001; M. S. Gould et al., 1990) (Madelyn S. Gould, Greenberg et al., 2003; Madelyn S. Gould, Shaffer et al., 2003). Various studies have tried to delineate the subject, content, and media characteristics that influence the risk of imitative suicide (see(Madelyn S. Gould, 2001). A variety of media guidelines have been promulgated by the Centers for Disease Control (CDC, 1994, 2004), American Foundation for Suicide Prevention (2001), and other organizations around the world to try to limit contagion effects. These include trying to limit sensational or prominent coverage; avoiding romanticizing or glorifying the suicide or presenting it as a reasonable form of problem solving.

Although the media have been successfully engaged in this effort in some countries, systematic studies of the impact of such guidelines on actual media coverage or, more important, suicide rates, are for the most part lacking.

Recommendations.

Given the complexity of factors underlying youth suicide, effective intervention strategies will need to be broad-based and address not only suicidal thoughts and behaviors themselves, but also the broader nexus of individual, family, and social risk factors. In addition to addressing these risk factors, interventions that enhance children's and adolescents' social and emotional coping skills will be important to bolster protective factors than may help to mitigate the deleterious impact of both expectable and extraordinary stressors.

Assessment

Four recommendations are paramount

First, *reliable and valid means of screening adolescents for depression and suicidal ideation/behavior* are increasingly available and can be beneficially employed in school and other settings to identify adolescents at risk for suicide.

Second, *early identification and intervention with young children exposed to abuse, neglect*, or other forms of social adversity are important in reducing subsequent vulnerability to suicide.

Third, *screening for and identification of adolescents involved with substance abuse and other high-risk behavior* is likely to reveal a large number of teens who are also at high risk for having or developing suicidal ideation/behavior.

Fourth, in the clinical setting, it is important to *screen the off-spring of suicidal, depressed, substance-abusing, or conduct disordered adults for potential depression and/or suicidal behavior/ideation*; conversely, in clinically evaluating adolescents, it is important to inquire about family history of substance abuse, conduct disorder, depression and/or completed or attempted suicide.

Interventions

Current research suggests five initiatives here.

First, *primary prevention efforts aimed at mitigating early childhood adversity* (such as abuse or neglect) and fostering optimal child and family development are likely to also reduce the development of adolescent suicidal ideation/behavior.

Second, *training teachers, primary care physicians, and other "gate-keepers" in contact with adolescents to identify adolescents at risk for suici*de is an important goal. However, such training is likely to be durable and effective only if ongoing and linked to implementation of specific screening procedures.

Third, identification of at-risk adolescents can be facilitated by *interventions that help to remove the stigma of seeking help* for metal health or psychosocial problems.

Fourth, *effective procedures for triaging, referring, and treating adolescents identified in such settings as suicidal* need to be developed, as well as systematic efforts at fostering treatment adherence and follow-up.

Fifth, given the frequent co-occurrence of parental psychopathology and adolescent depression/suicidality, *therapeutic interventions should target not only the adolescent, but also disturbed parental and family functioning*.

Research

Research is needed in the following areas related to assessment:

First, *what screening procedures are most acceptable and efficient* in terms of specificity and sensitivity for detecting suicidal ideation/behavior in various groups of adolescents?

Second, *how can screening of adolescents most effectively be implemented* in the various settings in which teens are found (school, juvenile detention, primary care, military)?
How often need screening be repeated in a given population to identify youngsters who may have become at increased risk of suicide since earlier screening?

Third, *what biological/genetic markers show promise* in identifying youngsters at high risk for suicidal behavior?

Research is need in the following areas related to intervention:

First, research must ask is *the optimal prevention approaches for adolescent suicide should be universal vs. targeted?*

Second, *do preventive interventions for early childhood adversity influence adolescent vulnerability to depression/suicidality?* Depression and suicidality in adolescents should be an explicit outcome measure in assessing the long-term effectiveness of such early intervention programs. As clearly documented in the preceding section research now strongly supports the long-term impact of interventions aimed at improving maternal care and reducing violence towards children.

Third, *what interventions are indicated for adolescents who have been identified as at-risk for depression/suicide?* Further research is needed on the optimal psychotherapeutic and pharmacological approaches to adolescent depression/suicidality (Hollon et al., 2002). In light of recent controversies regarding the relationship of the SSRIs to adolescent suicidality, treatment trials should explicitly assess at baseline and subsequently the presence, de novo appearance, exacerbation, or mitigation of suicidal ideation/behavior or other deliberate self-harm behaviors. What family interventions are optimal to reduce adolescent suicidality/depression? What are the mutative mechanisms of effective preventive or therapeutic interventions for adolescent depression/suicidality?
Are there significant gender differences in the effects of interventions? How durable are the benefits of preventive interventions and how can the durability of effective interventions be maximized? As noted in section 2) are different approaches indicated for youngsters from different ethnic or socioeconomic backgrounds?

Fourth, *multiple assessment measures are needed to evaluate the impact of interventions* on risk and protective factors, as well as actual suicidal ideation and behavior. Given the non-specific effects of many interventions, rigorous methodological designs are needed with appropriate comparison and/or control groups to demonstrate efficacy and to identify the effective components of proposed interventions.

OVERALL RECOMMENDATIONS OF THIS REPORT

Each of the five sections in this report has carefully delineated important recommendations in the areas of more comprehensive assessment, improved services and the most urgent research needed. Here we briefly outline recommendations drawn from all five sections of this report that require immediate and urgent attention by the American Psychiatric Association. We recommend the establishment of a standing Committee on Prevention to review and summarize advances in research in the area of prevention in the service of improving clinical assessment and services as well as sharpening and focusing research advocacy.

Assessment

DSM IV provides no guidelines for preventive psychiatry. Further, its format does not lend itself easily to inclusion of empirically based assessments critical for prevention. Thus, it contributes nothing to the standardization of measures of risk or resilience or of identifying treatable prodromes for major mental illnesses. As we have illustrated there is now a strong empirical base for reorienting the DSM process to make it useful for epidemiological, longitudinal and preventive intervention research and to provide clearer guides for clinical care and public policy. Our review of current evidence suggests these additions be considered for DSM V:

1) The addition of a new section or axis for careful assessment of *general risk clusters.* These would include the most important general risk factors that sharply increase the risk for several psychopathological syndromes as well as the best-documented individual, family and community protective factors. Such a section or axis would both guide and, interactively benefit from, research on screening vulnerable populations such as adolescents at risk for suicide. It would also energize APA's advocacy for adequate preventive screening and, where indicated, preventive intervention. These services are unlikely to be provided in the offices of general psychiatrists in private practice and are not likely to be a focus of work for child psychiatrists. However, there are service settings that could be strongly influenced by a standardization of risk assessment. These include Medicaid-supported clinical services which, technically, are required to screen and provide preventive services. Also large employee assistance programs and some mental health carve out insurers have recently expressed an interest in providing proven mental health screening and services (Yuh, Maloy, Kenney, & Reiss, in press).

2) As research permits the description of psychiatric syndromes should include descriptions of well identified *imminent risk factors or prodrome.* Such syndromes are likely to present to child and general psychiatric practitioners in emergency services and in office practices. It is likely that by the time that DSM V is being prepared evidence will justify their inclusion in the clinical description of adolescent substance abuse disorders, anxiety disorders, depression and schizophrenia. If the vigorous research program we have advocated for juvenile bipolar disorder is carried out, data may also be available to characterize imminent or emerging forms of this disorder as well. Also emerging are clusters of specific risk factors—including temperament, parent-child relationships and behavior patterns—that anticipated serious conduct disorders and antisocial personality disorders. These improvements will inevitably lead to better characterizations of *emerging* disorders as called for in our previous discussion of schizophrenia and bipolar disorders. Here, sensitivity to development phases in childhood and how they are linked manifestation of illness is essential.

3) DSM V should consider adding to its description of illness, where data permit, *the risk to offspring of parents with psychiatric disorders.* Throughout this report, particularly in sections 1, 2 and 5 we have illustrated the opportunities for prevention of psychiatric disorders in children of parents with well-documented disorders. Adding information about theses risks to DSM V will encourage clinicians to make sure these children are properly evaluated and treated.

4) Epidemiology is also yielding a clearer picture of the relationship between particular *primary and secondary* disorders. DSM V description of primary disorders, where research evidence permits, should

more clearly delineate possible secondary disorders and the circumstances that make their emergence more likely

.

5) The *proposed Committee on Prevention should have an active role in providing clinical research data to the current DSM V process* sponsored by APA, NIMH, NIDA and NIAAA..

Services

Our report has already articulated several important changes that are required to improve screening and prevention services. They are worth repeating and summarizing here.

1) In many instances both *treatment and prevention services can be integrated into a well articulated clinical plan*. This is dramatically illustrated in the care of mentally ill parents. The parents must be treated but they are highly motivated, in most cases, for screening and, if necessary, for treatment of their offspring.

2) It follows that *many approaches to prevention must be family-based.* Clinicians need better training in understanding family relationships in order to provide the needed combination of prevention and intervention services. Moreover, as our report has amply demonstrated, clinicians working with psychiatric ill parents must attend to the risk for psychiatric disorder (see section 2) and suicide (see section 5) in their children. Also, child and adult practitioners must have a keener awareness of the intersection of pre- and post-partum psychiatric disorders on mother-infant attachment. Likewise, the proper care of children with ambiguous disorders requires a detailed understanding of the psychopathology of their parents; we have amply illustrated this in our discussion of juvenile bipolar disorders and on the recognition of suicide risk in children adolescents. Child and general practitioners must not only maintain skills for diagnosis mental disorders across the full range of development but must understand and implement the role of positive family relationships in moderating these disorders. As we have indicated at several points in this report, positive and supportive family relationships are important protective factors that can reduce the risk for major mental disorder. These start with protective behaviors of mothers and fathers during pregnancy, continue to factors that promote positive parent-child attachments and continue to the development and maintenance of satisfying marriages.

3) Prevention services must also be *organized around an improved understanding of child, adolescent and adult development.* Thus, prevention focused on very early risk factors such as intrauterine exposure to drugs, toxins and malnutrition or early childhood exposure to maltreatment and insecure attachment may reduce the risk for a broad range of psychiatric disorders. (Sections 4 and 5, for example, provided extensive data on the developmental pathways to psychiatric disorder and suicide). These efforts should link psychiatrists with other medical specialties such as obstetrics and pediatrics. Later in development when early indications of impending disorders emerge, screening and prevention may be targeted to the reduction of risk for specific syndromes as they are manifest at particular stages of development

4) There are substantial opportunities for improved screening and prevention services in this country. As we have noted Medicaid supported health services, employee assistance programs and some mental health carve out plans are reasonable targets for screening and prevention. Section 5, on suicide prevention, clarified an emerging data base on school systems as important settings. As Section 5 illustrates clearly, even when school systems are engaged in effective screening is accomplished, vulnerable children must be engaged in sustained treatment and follow-up. The APA should actively promote such screening and prevention in these health service systems. Despite this important range of opportunities we must acknowledge that the US health care system lags far behind health care systems in other countries. We have already indicated the strong support of the Norwegian health care system in identifying the earliest appearance of schizophrenia. Other European countries also organize health services to respond to research on screening and prevention. American psychiatrists need to have a *more complete understanding of the advantages of more advanced health care systems* and wherever possible they should serve as bench marks for APA's advocacy of improved mental health care in the United States.

In some areas of prevention there is enough research to *inform APA treatment guidelines*. Indeed, a regular responsibility of the proposed Committee on Prevention should be the review of all treatment guideline in order to recommend where screening and prevention should become part of standard practice. By way of illustration, Table 2 provides a summary of randomized clinical trials for prevention of depression in children and adolescents (this research has been summarized both in sections 2 and 5).

Research

Our review makes clear that voluminous research supports two major points. First, prevention of the evolution of major psychiatric disorders is possible through both the reduction of risk factors as well as the direct treatment of well-defined prodromes and early appearing forms of illness. Second, prevention and early treatment can forestall a great deal of unnecessary human misery as well as the sustained deficits in function that are now well understood consequences of delays in imitating treatment. Third, there is reason to hope that we will soon have effective and practical programs to help prevent adolescent suicide. However, there are wide gaps in our understanding of etiology and prevention. Thus, cumulating across the five sections of our report, these recommendations stand out.

1) Intensive research must be directed at *improved sensitivity, specificity and predictive validity of screening and assessment procedures*. We need better methods for detecting suicidal adolescents, better evidence-based criteria for early appearing forms of bipolar disorder and efficient screening procedures for determining which children of depressed parents are at imminent risk for developing depression, conduct disorders or substance abuse. Moreover, continuing research is needed to more clearly specify prodromes of major disorders.

2) *Preventive intervention research is urgent*. As we have noted there is a desperate need for information on the treatment of early appearing forms of bipolar disorder. Indeed, APA in its research advocacy, should give this highest priority. Moreover, there is much to be learned in open trials of novel medications or combination of medications. In other domains large scale RCTs of well-developed intervention are required as well as research on how screening and preventive intervention can be effectively integrated into various systems of mental health services. Cutting across all sections of report these are highest priority areas for research. First, we need a better understanding of the *durability* of preventive interventions. Some programs, such as the Nurse-Family Partnership described in section 4), have remarkably durable results, the effects lasting up to 15 years without any booster interventions. Others, like some depression prevention programs (as noted in Section 5 and in Table 2) have much less durability. Second, we need a much clearer understanding of the interplay between *culture* and preventive intervention. For example, cultures vary in their relationships of risk factors to suicide. As noted in section 5, mental disorders are the primary risk factors for suicide in the US but are less important in China. In India, shame, humiliation, a husband's death, examination failure and family conflict loom very large. Also, culture vary in their stigmatization of mental disorders (Goldsmith, Pellmar, Kleinman, & Bunney, 2002). Third, research is needed on *large-scale implementation of successful intervention programs.*

3) We need an improved understanding of the interplay of risk and protective factors in child and adult development. The evidence we have presented in the report suggest the importance of integrating neurobiological and psychosocial research in these efforts. The discovery of specific alleles linked with psychiatric disorders or with endophenotypes that are critical components of those disorders will play an increasing important part in this work. But these polymorphisms do not operate, as our review has indicated, independently of the social environment of the developing child. There is now ample evidence that genetic risk for major mental illness can be moderated, often in dramatic fashion, by favorable or unfavorable social environments. Moreover, some of the mechanisms by which genetic influences are expressed require the mediation of the child and adult's social environment. For example, heritable characteristics of children or adults may expose them to hazardous environments that are high in stress or low in social support (Kendler & Eaves, 1986; Kendler et al., 1995; Ronald C. Kessler, Kendler, Heath, Neale, & Eaves, 1992). In addition, heritable characteristics of children evoke negative reactions form the

social environment that, in turn, increase the risk of mental disorders (Deater-Deckard et al., ; Ge et al., 1996; Neiderhiser, 1995; Reiss et al., 2000).

Continuing Education of Psychiatrists

Prevention and early detection of major psychiatric disorders is not part of the core curriculum in the training of either general or child psychiatrists and is a negligible part of the continuing education efforts of the American Psychiatric Association. This is domain that can be directly influenced by the APA and its members and, when the urgency is recognized, in a relatively brief period of time. We have three recommendations.

1) *General and child psychiatric residency programs should include careful study of preventive interventions as part of teaching about psychopathological syndromes*. This basic strategy should not lead to yet another skirmish about adding requirements to an overburdened residency curriculum. Rather, it is a recommendation on *how* to teach about psychopathology. Members of the task force have explored several formats for introducing prevention into residency teaching. First, required research courses and journal clubs should include some of the remarkable RCTs on preventive intervention that demonstrate clearly the reduction of risk for major psychiatric disorders. Second, seminars on psychopathology should include readings on risk and protective factors as well as on efforts at prevention. Third, clinical case presentations, particularly where a detailed case history is available, should focus more discussion not just on the best course of treatment of the current disorder but on what techniques or strategies might have been used to prevent the disorder. Fourth, clinical supervision of residents treating parents with psychiatric disorders should, as a matter of course, focus attention on the patient's concerns about their children, on evidence-based methods for assessing the risk for each child in the family and proper referral of children—where indicated—for treatment or available prevention services.

2) In order to improve psychiatrists understanding of prevention, *APA must take a vigorous lead in providing continuing education to general and child psychiatrists on preventive intervention.* The merging evidence base in prevention should be featured in several scientific symposia at each annual meeting under the active encouragement of the Program Committee. An honorary annual lectureship on prevention should be established. Prevention should be a major a topic heading in all program announcements and listings. The program committee, the Council on Research and the proposed Committee on Prevention should encourage clinical courses at APA meeting son screening, early detection of illness and on specific, evidence-based preventive interventions.

3) *APA should develop a strong collaborative relationship with professional organizations that focus on preventive interventions and early detection of psychiatric disorders.* Every annual meeting should have at least one activity jointly sponsored by APA and one of these organizations. Organization to be considered are the the Prevention Committee of the American Academy of Child and Adolescent Psychiatry, The Society for Research in Child Development (SRCD), Society for Prevention Research (SPR), and the International Early Psychosis Association (IEPA)

TABLES

Table 1. Longitudinal Studies on Risk and Protective Factors for Children of Depressed Parents

Study	Initial Sample			Analysis		
	Number	Diagnosis	Child's Age	Number	Reference	Variables Associated with Outcomes
(D. N. Miller et al., 1999).	153 [a] vs. 67 [b]	SADS-L	6-23	158 offspring	10 years	Daughter's MDD at T10 with: Low self-esteem at T1 (odds ratio=11.9. CI=1.3-107.2), controlling for MDD at T1 Daughter low self-esteem at T1 with: Perceived maternal attectionless-control at T1 (odds ratio=8.4, CI=1.1-75.4)
(Weissman, Fendrich, Warner, & Wickramaratne, 1992)	153 [a] vs. 67 [b]	SADS-L	6-23	174 offspring	2 years	Incidence rates of substance abuse with: Affectionless control (11.1% versus 2.1%), parental divorce (10.4% versus 1.9%) Incidence of conduct disorder with: Affectionless control (28.1% versus 5.7%), low family cohesion (19.6% versus 4.3%)
(Hammen, Burge, Burney, & Adrian, 1990)	96 from MDD, bipolar, illness, and	SADS-L	8-16	90	3 years	Children's MDD at 6-month follow-up with: Stressful life events ($\triangle R^2$ =.03), maternal disorder stress ($\triangle R^2$ =.10), interaction between events and maternal stress ($\triangle R^2$=.04),

	control groups					initial MDD($\triangle R^2$=.21)
(Judy Garber & Little, 1999)	185 [a]	SCID, BDI, MMPI	6th grader	18 decreased vs. 33 high competence	2 years	Competence with: Commitment to achievement, better family functioning alone or interaction with school hassles, greater social support, positive coping
(Beardslee, 2002)	120	SADS		15	2 ½ years	The capacity for and deep involvement in intimate human relationships; The ability to get tasks done outside the home; The capacity for reflection and self-understanding

Note: [a] represents adolescents of depressed parent(s). [b] represents adolescents of parents without disorders.

SCID= The Structured Clinical Interview; BDI= The Beck Depression Inventory; MMPI=The Minnesota Multiphasic Personality Inventory; SADS-L: The Schedule for Affective Disorders and Schizophrenia Lifetime

Table 2. Examples of Depression Prevention Programs with Children and Adolescent

Study	Participants	At-risk Status	Program Format	Results
1. Reducing psychosocial risks				
(Beardslee, Salt, Versage, Gladstone, & et al., 1997) (Beardslee, Versage, Wright, & Salt, 1997) (Beardslee, Salt, Porterfield, Rothberg, & et al., 1993) (Beardslee et al., 1996) (Beardslee, Wright, Salt, & Drezner, 1997)	Study 1: N_{cli}=12 families, N_{lec}=8 families Study 2: N_{cli}=19 families, N_{lec}=18 families Families who had a child aged 8-15 years	A history of serious parental affective disorder during preceding year	Clinician-based intervention (CBI): 6-10 sessions; Lecture intervention: Two 1-hour lectures and discussion	Study 1: Decrease in the amount of upset in both. More satisfaction and changes in CBI; Study 2: Satisfaction with the intervention in both. More changes, improved communications, children's greater understanding in CBI; 3 yrs follow-up (51): More benefit in CBI.
2. Reducing the incidence of post-intervention depression				
1) For children of depressed parents who are elevated symptoms levels				
(Clarke et al., 2001)	Offspring of adults treated for depression who aged 13-18 years: N_{exp}=45, N_{con}=49	Subsyndromal youth and/or CES-D>24	Fifteen 1-hour group cognitive therapy prevention	Effects for the CES-D and GAF; at 15 months follow-up, 9% of incident MDE in Exp. Vs. 29% of incident MDE in Con.
2) For children in general or children who have elevated symptoms				

(Seligman, Schulman, DeRubeis, & Hollon, 1999)	231 college students	Being in the most pessimistic quarter	Eight 2-hour cognitive-behavioral group workshop	Fewer MDE/GAD, fewer depressive/anxiety symptoms, improvement in explanatory style, hopelessness, and dysfunctional attitudes
(Jaycox, Reivich, Gillham, & Seligman, 1994) (Gillham, Reivich, Jaycox, & Seligman, 1995)	5^{th} - 6^{th}graders: N_{exp}=69, N_{con}=73 2-year follow-up: N_{exp}=69, N_{con}=49	Z-scores of CDI + CPQ>.50	Twelve 90 min group sessions on explanatory style training	Fewer depressive symptoms, improved classroom behavior, and externalizing problems; follow-up: Fewer depressive symptoms and improvements in explanatory style
(Cardemil, Reivich, & Seligman, 2002)	5^{th} - 6^{th} graders. Latino: N_{exp}=23, N_{con}=26; African N_{exp}=47, N_{con}=56		Twelve weekly 90 minute group intervention	Reduced depressive symptoms, fewer negative automatic thoughts, long-term effect on self-esteem , only for Latino sample
(Yu & Seligman, 2002)	220 Chinese children from 8 to 15 yrs.old	Top 25% in Z scores of CDI+Subscales of FES	Ten weekly 2-hour Chinese Optimism Penn Program	Fewer depressive symptoms, A more optimistic explanatory style as mediation in the prevention of depressive symptoms

(Clarke et al., 1995)	9^{th}- 10^{th} graders: N_{exp}=76, N_{con}=74	Depressive symptoms: CES-D=>24	Fifteen one-hour group cognitive therapy prevention	Effects for the CES-D and GAF, at 12 months follow-up, 14.5% (8/55) in Exp. Vs. 25.7% (18/70) in Con. for affective disorder incidence rates
(Clarke, Hawkins, Murphy, & Sheeber, 1993)	Study1: 9^{th}- 10^{th} graders, N_{exp}=36 N_{con}=261 Study2: 9^{th}- 10^{th} graders, N_{exp}=190 N_{con}=190	None	Study1: Three 50 min. classes Study2: Five-session training	Study1: Short-term reduction in symptoms among boys that did not last beyond 12 weeks; Study2: No differences

See notes (next page)

Note: N_{cli}=Number of participants in clinician-based intervention; N_{lec}=Number of participants in lecture intervention; N_{exp}=Number of experimental group; N_{con}=Number of control group; CDI=Children's Depression Inventory; CES-D: Center for Epidemiological Studies – Depression scale; CPQ=Child's Perception Questionnaire; FES=Family Environment Scale; GAD=Generalized Anxiety Disorder; GAF=Global Assessment of Functioning; MDE=Major Depressive Episode

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