Psychosocial Intervention Development for the Prevention and Treatment of Depression: Promoting Innovation and Increasing Access

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Great strides have been made in developing psychosocial interventions for the treatment of depression and bipolar disorder over the last three decades, but more remains to be done. The National Institute of Mental Health Psychosocial Intervention Development Workgroup recommends three priorities for future innovation: 1) development of new and more effective interventions that address both symptom change and functional capacity, 2) development of interventions that prevent onset and recurrence of clinical episodes in at-risk populations, and 3) development of user-friendly interventions and nontraditional delivery methods to increase access to evidence-based interventions. In each of these areas, the Workgroup recommends systematic study of the mediating mechanisms that drive the process of change and the moderators that influence their effects. This information will highlight the elements of psychosocial interventions that most contribute to the prevention and treatment of mood disorders across diagnostic groups, populations served, and community settings. The process of developing innovative interventions should have as its goal a mental health service delivery system that prevents the onset and recurrence of the mood disorders, furnishes increasingly effective treatment for those who seek it, and provides access to evidence-based psychosocial interventions via all feasible means. Biol Psychiatry 2002;52:610–630 © 2002 Society of Biological Psychiatry

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Introduction

This workgroup was charged with considering how the National Institute of Mental Health (NIMH) can advance the development of psychosocial interventions for the mood disorders, including unipolar and bipolar disorders, as well as suicide. This goal can be advanced either by developing wholly new psychosocial interventions or by enhancing the efficacy of extant interventions and developing novel applications for their use, including the prevention of onset in people at risk. In a chronic recurrent disorder, prevention may be as important as treatment. One potential advantage of the psychosocial interventions is that many of them involve learning emotion regulation or interpersonal skills that may reduce the risk of onset and minimize the need for ongoing treatment (Hollon et al 1992).

Many psychosocial interventions can be delivered via nontraditional means such as television, telephone, printed materials, and the Internet (Christensen et al 1978). Such nontraditional methods can deliver programmed interventions with fidelity and greatly extend the numbers and types of people who can be reached with services. They can also be used to study the change process because of their suitability for providing selected components of interventions in a highly replicable, controlled fashion. With rapid advances in technology now the norm, such nontraditional methods should be developed and tested; if effective, they can provide opportunities for large numbers of flexible and individually adapted interactions that allow rapid investigation of specific interventions.
The process of innovation is best pursued within a theoretical framework that seeks to determine not just whether an intervention is efficacious, but why, that is, one that determines the mechanisms that mediate and the predictive factors that moderate its effects (Kazdin 2000). A focus on theory facilitates framing questions in terms of mechanisms and provides a basis for moving from basic research to clinical innovation. In so doing, the efficacy of promising interventions may be refined through identifying their active ingredients. Moreover, such a focus provides a framework for identifying moderating factors that influence treatment effects, including patient characteristics (such as ethnicity, comorbidity, or suicide risk) or therapist and setting factors that undermine the effectiveness of interventions when transported into applied clinical settings. Attention to the mechanisms behind these moderating factors can be used to make interventions more effective for a full range of people in real-world settings and may inform about the nature of the underlying disorder.

State of the Field

Nature of Mood Disorders

Depression is a usually recurrent and potentially chronic disorder that ranks fourth among all medical and psychiatric disorders in disease burden and is the number one cause of disability (Murray and Lopez 1997). Unipolar disorder involves depression only, whereas bipolar disorder also involves mania or hypomania. Unipolar disorder is more common, occurring in about 20% of all women and about 10% of all men, whereas bipolar disorder occurs in only 1% to 2% of the population and affects the genders equally (Kessler et al 1994). Both recur at high rates; most patients experience multiple episodes. Many patients show a chronic course, and even minimal symptoms are associated with greater risk for subsequent episodes and considerable functional impairment (Judd et al 1998). Suicide is a major concern in both disorders (especially bipolar disorder), and other comorbid psychiatric or medical conditions often complicate the picture (Kessler et al 1994).

Figure 1 (adapted from Kupfer 1991) depicts the course of a prototypic episode (with a range of potential outcomes) and highlights several possible points of intervention. Time is arrayed along the horizontal axis and severity along the vertical axis, with euthymia at the top and deviations toward lower mood levels going down until the threshold (dotted line) for a clinical depressive episode is crossed. Hypomania and mania can be envisioned as deflections upward. Prevention is designed to avert onset before crossing the threshold into a clinical episode and ideally would prevent initial onset before the first episode. The acute phase of treatment usually begins when people are acutely symptomatic (at or near the trough in the figure) and typically continues until some resolution is obtained. By convention, response refers to a relative improvement in symptom status, whereas remission refers to a full normalization of mood and associated symptoms. Remission can occur in the absence of treatment, but many people have a chronic course with only minimal or partial improvement.

A return of symptoms during the first 6 to 9 months following remission is termed a relapse and is presumed to represent the reemergence of the treated episode (Frank et al 1991). Patients are thought to be at elevated risk during this remitted interval (until the underlying episode has run its course), and continuation treatment is often provided for the purpose of preventing relapse, particularly among medicated patients (Prien and Kupfer 1986). Patients who survive this period without relapsing are considered recovered (out of episode) and the subsequent recurrence of symptoms is presumed to reflect the onset of a wholly new episode. Treatment provided following recovery to prevent recurrence is called maintenance treatment. Antidepressant medications have been shown to reduce relapse when continued after response or remission and to prevent recurrence when maintained following recovery among patients with unipolar depression (American Psychiatric Association [APA] 2000). Lithium and the mood stabilizing anticonvulsants are the prophylactic agents of choice for bipolar disorder (APA 2002).

Treatments with enduring effects can prevent subsequent relapse or recurrence even after they are discontinued. Psychosocial interventions that result in learning emotion regulation or interpersonal skills or in changes in social relationships are thought to have particular potential for producing enduring effects.
Treatment of Unipolar Disorder

Unipolar disorder responds both to medications and to several different psychotherapies. Interpersonal psychotherapy (IPT) and cognitive–behavioral therapy (CBT) have the strongest empirical support (APA 2000). Both have demonstrated efficacy in the acute treatment of depressed outpatients, although questions remain about the efficacy of CBT among the more severely depressed (Elkin et al 1995; but see also DeRubeis et al 1999). Traditional psychodynamic and experiential interventions (including eclectic approaches to therapy) have not been particularly effective in most of the relatively few studies in which they have been tested (APA 2000).

Both IPT and CBT appear to reduce risk for relapse or recurrence so long as they are continued or maintained (Frank et al 1990; Jarrett et al 2001). Moreover, CBT appears to have an enduring effect that extends beyond the end of treatment (Hollon and Shelton 2001). Acute treatment with CBT has been shown to reduce risk for subsequent relapse (Blackburn et al 1986; Evans et al 1992; Simons et al 1986) and adding CBT to medications during continuation treatment reduced risk for both relapse and recurrence (Fava et al 1998; Paykel et al 1999). There are even indications that CBT can prevent the initial onset of the disorder in persons at risk (Gillham et al 2000). These indications deserve to be pursued; it would be important to determine if CBT has a preventive effect.

Interpersonal psychotherapy may have a specific (if somewhat delayed) effect on interpersonal functioning and the quality of relationships (Weissman et al 1974, Weissman et al 1981). Given that interpersonal relationships are themselves important and that problems in this domain may contribute to onset and prolongation of mood disorders, we strongly recommend support for research to determine whether IPT improves the quality of interpersonal life.

Combined treatment involving medication and evidence-based psychotherapy typically provides a modest increment over either single modality alone with respect to the reduction of acute distress (and more in selected populations) and appears to retain the specific additional advantages produced by each with respect to other indices (Hollon and Shelton 2001). For example, medications typically produce more rapid symptom relief than IPT (DiMascio et al 1979; Watkins et al 1993), whereas IPT has the broader effect on the quality of interpersonal life already described. Similarly, combining CBT with medication appears to compensate for any relative limitations CBT may have in the treatment of more severely depressed patients while retaining its enduring effects (Hollon and Shelton 2001).

Less is known about the treatment of depression in children, although work in that regard has been promising, with most involving the application of structured cognitive and especially behavioral interventions in school-based settings (Curry 2001). Work with adolescents has been more impressive still. Compared with clinical monitoring, IPT has been found to be more effective in reducing depressive symptoms and enhancing social functioning among depressed adolescents (Mufson et al 1999). Similarly, CBT has been found to be more effective than either systematic behavior family therapy or individual nondirective supportive treatment (Brent et al 1997) and more effective than wait-list controls in two separate studies (Clarke et al 1999; Lewinsohn et al 1990). Both IPT and CBT were found superior to a wait-list control in a Latino population, with IPT having a specific effect on social adaptation (Rossello and Bernal 1999). These studies suggest that the same interventions that are effective with adults may be efficacious in the treatment of depressed adolescents. Research should determine whether these effects extend to children in clinical settings and whether adapting treatment to involve the family can enhance response.

Despite these advances, the current state of affairs is not wholly satisfying. As with antidepressant medications, not all patients respond to treatment and only a minority achieve full remission (APA 2000). Incomplete response increases the risk of relapse (Prien and Kupfer 1986), and many patients will have chronic or recurring problems if they do not stay in ongoing treatment (Hollon and Shelton 2001). Even with such treatment, some patients will suffer relapse or recurrences. Patients with a history of chronic depression or long-standing personality disorders appear to be particularly unlikely to respond to brief interventions (Shea et al 1990). Moreover, little is known about the effects of existing treatments on work disabilities and other dysfunctions that often constitute the primary concerns of depressed patients. Clearly, new treatments must be developed and existing interventions strengthened to deal with these limitations.

Work is underway adapting existing evidence-based interventions for use with chronic or treatment-resistant populations. There is a growing recognition that the duration of the disorder may be as important as its severity; even milder forms of chronic mood disorder like dysthymia have a worse course and may produce more functional impairment over time than purely episodic major depression (Wells et al 1992). Interpersonal therapy recently has been modified to encourage dysthymic patients to reconceptualize their self-perceived lifelong character flaws as chronic mood-dependent symptoms, a chronic but treatable “state” rather than immutable “trait” (Markowitz 1998). This approach is currently being tested in an NIMH-supported, randomized trial. In a related
study, IPT was found to enhance interpersonal and social functioning when added to medications (Hellerstein et al 2001). Similarly, CBT has been modified in recent years to make it more effective for patients with long-standing personality disorders and dysthymia (Beck et al 1990). This modified approach (called schema-focused therapy) is presumed to take longer to implement than conventional CBT and is only recommended for patients who are likely to be treatment refractory. Exploratory research that seeks to adapt existing interventions for new indications should be encouraged.

The newly developed Cognitive Behavioral Analysis System for Psychotherapy (CBASP) represents an innovative blend of cognitive, behavioral, interpersonal, and psychodynamic treatment components particularly tailored for use with patients prone to chronic depression (McCullough 2000). The combination of CBASP and medication was found to be considerably more effective than either modality alone in the treatment of chronic depression (Keller et al 2000). It remains to be seen whether this enhanced effect is specific to CBASP or a general consequence of working with chronic patients, but the study has stimulated renewed interest in the potential beneficial effects of combined treatments for depression. Given the blend of treatment components involved, further research will be required to determine whether CBASP shares IPT’s breadth of effect on interpersonal functioning or CBT’s enduring effects on the prevention of relapse and recurrence.

Other recent innovations are also promising. Mindfulness-based cognitive therapy (MBCT) uses principles and strategies drawn from dialectical behavioral therapy for borderline personality disorder (acceptance and meditation) to help patients reduce their depressive ruminations (Teasdale et al 1995). It focuses more on the process of thinking than its content (unlike conventional CBT) and draws heavily on basic cognitive theory. In the only trial conducted to date, MBCT was shown to have an enduring effect that reduced risk for relapse among patients with major depressive disorder who were first treated to remission with medication (Teasdale et al 2000). Given that MBCT can be provided in an economic group format, it is likely to have considerable appeal. It will be important to determine whether its enduring effect extends to the prevention of recurrence and whether MBCT can be used to enhance acute response.

Behavioral activation (BA) is a newly developed intervention that uses a contextual approach to help patients eliminate avoidance behaviors and act more effectively on their environments (Jacobson et al 2001). Behavioral interventions fared well in early comparisons to cognitive interventions (Rehm et al 1987; Zeiss et al 1979); however, interest in more purely behavioral approaches had diminished in recent years until a component analysis suggested that behavioral elements alone may account for the bulk of CBT’s efficacy (Jacobson et al 1996). Although BA has yet to be extensively tested, a randomized placebo-controlled trial currently underway suggests that it may work at least as well as medication or CBT in reducing acute distress and preventing subsequent relapse (Hollon 2000). Given that behavioral activation is probably easier to implement than cognitive restructuring (and a single component is easier to implement than a full treatment package), it may be that BA will prove easier to disseminate than CBT. Work should be done to determine whether these effects can be replicated and the ease with which BA can be disseminated.

The Coping with Depression (CWD) Course (Lewinsohn et al 1989) is a psychoeducational group intervention that teaches participants how to modify thoughts, activity levels, and interpersonal contacts to achieve healthier mood states. A meta-analysis of its many applications indicates great promise, particularly among less severely depressed patients (Cuijpers 1998).

Mindfulness-based cognitive therapy, behavioral activation, and Coping with Depression were designed with an eye to dissemination. Access to treatment is often severely limited, in part because evidence-based treatments are not widely used. We need to better understand why this is the case and to change the process of treatment development and adaptation to make more user-friendly interventions that are easier to disseminate.

Many other forms of psychotherapy have been described but not yet adequately tested. Some are widely used despite a relative absence of empirical support. It is important to learn whether such treatments are effective. A few investigators have taken preliminary steps to study outcomes. For example, supportive/expressive psychodynamic psychotherapy (Luborsky 1984), one variant in a widespread field, has been tested in several time-limited randomized controlled trials with other patient populations and with some success in an open trial for depression (Diguer et al 1993; Luborsky et al 1996). Barber and colleagues are currently conducting an NIMH-funded study comparing supportive/expressive psychotherapy to medication and placebo in the first randomized controlled trial of this treatment (J. Barber, personal communication, October 2001). Conversely, experiential psychotherapy has many adherents and has been proposed as a treatment for depression but has yet to generate much in the way of empirical support (for a recent effort in this regard, see Greenberg and Watson 1998). Clearly, any approach that is widely used in clinical practice should be tested in a methodologically adequate fashion.
Treatment of Bipolar Disorder

The treatment of bipolar disorder remains problematic. The pharmacologic guidelines for treating bipolar patients during acute, continuation, and maintenance phases are well established (APA 2002). Nonetheless, most patients have breakthrough episodes or significant residual symptoms even while on medications (Gitlin et al 1995; Kalbag et al 1999). Problems with adherence further undermine the stability of response (Colom et al 2000). Episodes of the illness are associated with significant social and occupational problems, and functional deficits often remain even when patients are not in an episode (Harlow et al 1990).

There is little evidence that traditional unstructured forms of psychotherapy enhance the efficacy of medication treatment. Studies of these approaches are few and the outcomes relatively unimpressive (APA 2002). Until recent years, more structured interventions went largely untested, with the exception of an early randomized trial that showed that CBT could be used to enhance medication adherence (Cochran 1984). On the whole, the field has acted as if bipolar disorder could be treated only with medications.

That now appears to be changing (Craighead and Miklowitz 2000). Family focused therapy (FFT) is aimed at reducing expressed emotion (especially criticism) and enhancing the frequency of positive family or marital interactions. It has been shown to reduce risk for subsequent relapse and rehospitalization in medicated bipolar patients in two separate trials (Miklowitz et al 2000; Rea et al 2002; Simoneau et al 1999). Similarly, IPT modified to incorporate attention to stabilizing patients’ social rhythms (also known as IPSRT) has shown considerable promise (Frank et al 1999). There is also renewed interest in applying CBT to the treatment of medicated patients (Basco and Rush 1996); CBT has been found to reduce the frequency of depressive relapse in medicated patients (Lam et al 2000) and, when aimed at early recognition and treatment of prodromal symptoms in medicated patients, to be more effective than medications alone in delaying manic relapses (Perry et al 1999). Psychoeducation has also been done within a group format using the Life Goals program, which has been found to increase patients’ knowledge and understanding about bipolar disorder (Bauer et al 1998).

More must be done to refine existing treatments and develop novel interventions for bipolar disorder. The fact that many patients do poorly even while on medications (despite their evident benefits) speaks to the importance of developing or extending adjunctive psychosocial treatments. Manual-based psychosocial interventions are likely to be most effective when they include a component of education about the disorder, notably, teaching patients, caretakers, or both to identify early warning signs of relapse and obtain preventive interventions. Educational interventions that include early detection strategies may be especially relevant to young people who are at risk for bipolar disorder by virtue of subsyndromal mood fluctuations or a family history of affective disorder.

To be of maximum benefit as an adjunctive treatment, psychosocial interventions need to address the tendency for patients to be inconsistent with their mood stabilizing medication regimens. Developing adherence interventions can be facilitated by identifying risk factors for nonadherence among individual patients (for example, simple forgetting, problems in communicating with physicians, lack of education about or denial of the disorder). Interventions can then be designed that target these factors for change (for example, teaching patients to recognize drug side effects and how to communicate with their physicians about them; addressing dysfunctional cognitions about the meaning of taking medications and its implications for their life goals).

Sequential models need to be developed that parallel the changing course of the illness. Research is needed to determine the optimal composition and sequencing of an overall empirically based treatment approach. Preliminary clinical observations are that behavioral activation, family support, and cognitive restructuring may be useful during the depressed phase, whereas emphasizing medication regularity and social rhythm stabilization may be especially important when patients are beginning to escalate into mania. Family or marital issues that typically arise during a postepisodic period, such as escalating verbal conflicts about managing the disorder, problems with intimacy, or disagreements about raising children, often may be best addressed once patients are at least partially stable on medications. Finally, it would appear that during the postepisodic period, social skills training or vocational rehabilitation can be added to medication to enhance the patient’s likelihood of succeeding in the occupational milieu.

Prevention of Suicidal Behavior

Little is known empirically about the prevention of suicidal behavior. Suicidal patients are routinely excluded from controlled trials, and few studies have targeted such behaviors (Linehan 1997). The general perception is that patients at imminent risk need hospitalization. Although this may be true, the question has never been addressed empirically. Whether patients are well served by this approach or any of the strategies routinely used in clinical practice remains unknown, as described in a recent NIMH report (Pearson et al 2001).

Similarly, although depression is clearly associated with suicidal behavior, it is not clear that reducing the incidence
or severity of depression necessarily reduces risk for suicide. Meta-analytic reviews and reanalyses of data submitted to the Food and Drug Administration (FDA) typically have not found differences between medications and placebo controls in terms of suicides or suicidal acts (Beasley et al 1991; Khan et al 2000; Strorosun et al 2001); however, few of the studies reviewed were designed to explore this issue directly. One recent naturalistic study did suggest that as prescriptions for antidepressant medications increased, suicide rates went down (Isacsson 2000); however, such designs are open to multiple interpretations with respect to cause and effect. We know of no randomized controlled trial in which successful treatment of depression produced a corresponding reduction in suicidal acts. There is surprisingly little evidence for this widely held belief.

On the other hand, psychosocial interventions that target suicidal behaviors appear to reduce risk for both attempts and mortality. Dialectical behavior therapy (DBT), a cognitive–behavioral intervention that seeks to increase tolerance for distressing affects and enhance problem-solving and emotional regulation skills, has been found to reduce the frequency of suicide attempts and subsequent hospitalizations in borderline patients (Linehan et al 1991). Whether this approach can produce similar results in other types of patients remains to be seen, but it has generated considerable interest. Problem-solving therapy has been shown to be effective in the treatment of depressed adolescents (Lerner and Clum 1990) and to reduce suicide attempts among patients with a history of such behavior (Salkovskis et al 1990). The extent to which other effective treatments for depression, such as IPT or CBT, reduce risk for suicide remains unknown. There are indications that making emergency services available without requiring that a person be actively suicidal can reduce risk for suicidal behaviors. Simply maintaining a written correspondence with high-risk patients who refuse treatment was found in one study to reduce rates of suicide (Motto and Bostrom 2001).

The Workgroup recommends that suicidal patients not be routinely excluded from treatment trials when they can be included safely and ethically and that additional studies should be done to evaluate the role of psychosocial interventions for those who are actively suicidal. The NIMH has developed a set of considerations for investigators to use in determining whether to include suicidal patients in controlled trials and for building in appropriate procedural safeguards when they do (see Pearson et al 2001 at http://www.nimh.nih.gov/research/highrisksuicide.cfm#1). Efforts should be made to determine whether suicide is best prevented by interventions aimed at reducing presumed precipitants like depression or alcoholism as opposed to targeting the suicidal behaviors directly. Crisis intervention strategies should be codified in a manual and used to supplement existing interventions. In addition, investigators should be encouraged to employ better measures of suicidality in treatment trials, which could lead to a clearer understanding across trials about which suicidal patients are excluded (for reviews of available measurement resources in children and adolescents and in adults see http://www.nimh.nih.gov/research/suicide.cfm).

New Directions in Intervention Development

The shortcomings just described will be overcome only by developing innovative treatments and refining existing interventions. The Workgroup recommends that NIMH quicken the pace of innovation by channeling research support along three major lines. First, progress in intervention development can be promoted by strengthening linkages between basic research and clinical science. Second, efforts at developing preventive and maintenance interventions must be increased. Third, access to effective interventions should be expanded by means of developing more user-friendly interventions and nontraditional delivery methods.

Treatment Innovation through Basic and Clinical Research

Novel interventions may be created de novo or refined from existing treatments. Innovation often builds on existing knowledge and theory about the processes that initiate and maintain the disorders of interest. This knowledge may come from basic research on normative populations or psychopathology research on clinical populations; efforts to use this information for clinical purposes have come to be called translational research. Similarly, basic research on the change process can be used to test theory and refine existing interventions, as can efforts to examine mechanisms of change within the confines of controlled clinical trials. Finally, innovation can arise from the experience of clinical practitioners. We discuss each in turn.

Basic research as a source of innovation.

Basic research in the areas of cognitive science, neuroscience, and behavioral science (including developmental psychopathology) provides an obvious source of innovation, largely by suggesting possible targets for intervention. This has clearly been the case for the existing evidence-based psychosocial interventions for depression: IPT drew heavily on attachment theory (Weissman et al 2000), and CBT was strongly influenced by social–cognitive theories of emotion and information processing (Beck 1991). It is striking that the two psychosocial interventions with the strongest empirical support so
closely parallel two of the major animal models of depression, separation-loss and learned helplessness (McKinney 1992).

The 2000 report of the National Advisory Mental Health Council’s Behavioral Science Workgroup, Translating Behavioral Science into Action, describes ways in which basic research can inform clinical innovation (see http://www.nimh.nih.gov/bsia/bsiatoc.cfms). Better understanding how people process emotionally relevant information can be used to identify “what” to target. Recent advances in developmental psychopathology that have identified periods of risk for mood disorders and suicide can tell us “when” to intervene. Much has been learned about the structure and function of the nervous system in the last several decades, and the development of imaging technologies allow studies of human neural function in vivo. These advances and others yet to come may be parlayed into new and more powerful psychosocial interventions by linking basic research to intervention development.

For example, we know that the hypothalamic-pituitary-adrenal (HPA) axis plays a role in emotional disorders and that exposure to traumatic life events can produce lasting changes that impair subsequent response to stress (Heim et al 2000; see also the companion article by Davidson and colleagues in this issue). Furthermore, there is evidence that the hippocampus decreases in volume in response to prolonged stress and glucocorticoid exposure (Sapolsky 2000). The hippocampus acts as a brake on the stress response system and also is involved in the regulation of mood and memory. Restoration of hippocampal function has been proposed as a common final pathway that mediates the clinical efficacy of a variety of medications that have their primary effects on different neurotransmitter systems (Duman et al 1997). It may be that psychosocial interventions also have an effect on these underlying neural mechanisms or can be targeted to do so. Animal studies have shown that exercise can enhance hippocampal neurogenesis and enhance learning and memory (Van Praag et al 1999) and that learning to exercise control over aversive events can protect against or reverse their deleterious neurophysiologic effects (Weiss et al 1970). Behavioral activation and cognitive restructuring may play a similar role in humans to reduce distress and prevent the onset of mood disorders (Bell 2001).

There are two broad approach- and withdrawal-related emotion systems that have implications for the emotional disorders and efforts at prevention and treatment (Davidson et al 2000). Approach behaviors have been linked to positive affect in general and dopamine in particular; it has been suggested that bipolar disorder may reflect an underlying instability in this “behavioral activation” system (Depue and Iacono 1989). Withdrawal behavior appears to be more closely tied to negative affect and may be related to norepinephrine and the stress response or “behavioral inhibition” system (Weiss et al 1994).

Research on the structure of affect parallels this growing understanding of the structure and function of these neural systems. For example, Clark and Watson (1991) proposed a tripartite model of anxiety and depression in which both disorders share a common core of negative affect, whereas depression is further distinguished by an absence of positive affect. Barlow and colleagues extended this model and found that it generally corresponds well to the structural relations between depression and the anxiety disorders (Brown et al 1998). Whether this distinction proves helpful in refining interventions remains to be seen. In one such application, CBT has been extended to include attention to positive affect and a sense of well-being (Fava et al 1998).

Cognitive science also suggests a number of targets for intervention development. For example, we know that people with histories of depression think differently under stress or in states of mild distress; they become more negative and rigid in their thinking and have difficulty generating solutions to the problems they face (Ingram et al 1998). These propensities are shaped in part by negative life experiences (Nolen-Hoeksema et al 1992) and both predict risk for symptom onset and appear to mediate the preventive effects observed for CBT (Hollon et al 1992). Work is underway to understand better how these cognitive propensities relate to underlying neural mechanisms (Teasdale et al 1999) and how they are shaped by early interpersonal context (Garber and Flynn 2001).

Research on the mechanisms that underlie interpersonal attachment and vulnerability to disruptions in those bonds may illuminate additional ways to intervene. Interpersonal loss and disappointment can play an important role in the onset and maintenance of depression (Brown and Harris 1978), and criticism from important others (expressed emotion) has been shown to increase the risk for relapse (Hooley and Teasdale 1989). As an example, Hooley and Yurgelun-Todd (2001) are currently using magnetic resonance imaging techniques to explore the brain regions that are activated among recovered depressed patients in response to maternal criticism.

Finally, understanding better the protective mechanisms that allow resilience in the face of life stress may facilitate the development of innovative interventions (Luthar et al 2000). For example, we need to study the development of emotion regulation (Gross and Muñoz 1995). Many of these processes can best be studied in normal populations and pursued in longitudinal designs that track risk. If we can learn more about the mechanisms that underlie these phenomena, we may be able to use this information to
develop new and more effective interventions to prevent and treat depression, bipolar illness, and suicide.

The Workgroup recommends that NIMH foster innovation in intervention development by finding additional ways to encourage and support linkages between basic and intervention research on the mood disorders. We strongly applaud the initiative to fund centers for translational research and endorse the recommendations for supporting such training and research contained in the NIMH report “Translating Behavioral Science into Action.” This is an area that we think is of great importance and one that NIMH already seems to have targeted as important for the future of the field.

RESEARCH ON PSYCHOLOGICAL CHANGE MECHANISMS. Change mechanisms are processes that ameliorate pathology and include both the active ingredients in a given intervention and the processes they mobilize in their targets. Change mechanisms can be studied in both basic research and controlled trials. Basic research can be relatively inexpensive and allows testing hypotheses about strategies that can be used to guide the development of full-scale clinical interventions. For example, research showing that depressed patients became more optimistic and worked harder after initial success served as the impetus for encouraging patients to engineer success experiences and take a structured approach to difficult tasks, both key components of CBT for depression (Beck 1991). Basic research of this kind has great potential and should be encouraged.

More also could be done to use clinical trials to test theories of change to refine and streamline existing interventions. Most interventions are complex packages of procedures that contain multiple components; only some of these components are actually active in the change process. Those active ingredients are presumed to have a causal impact on mechanisms of change within the client (they must if the intervention has an effect), which in turn have an impact on the outcomes of interest. Identifying the active ingredients in a given intervention and the causal mechanisms that mediate their effects can be used to refine the existing approach and to suggest novel innovations.

It is sometimes possible to test theories of change in an experimental fashion by parsing different aspects of the intervention package and making controlled comparisons. As previously described, the finding that the behavioral activation component of CBT did as well as the full treatment package in a dismantling study served as a major impetus for the development of a contextual approach to behavior therapy for depression (Jacobson et al 2001). At other times, it may suffice to measure the different components of an intervention package and relate them to subsequent changes in mechanisms and outcomes. For example, implementing specific cognitive and behavioral strategies early in CBT produced greater change in depression than attending to the quality of the helping alliance, which was more a consequence of change than a cause (DeRubeis and Feeley 1990). Similarly, greater adherence to treatment protocol (talking about relationships) was associated with greater prevention of recurrence in maintenance IPT (Frank et al 1991).

With respect to patient mechanisms, change in expectations (although nonspecific) has been found to precede change in depression in CBT but follows change in depression in medication treatment (DeRubeis et al 1990). On the other hand, changes in explanatory style occurred later in CBT treatment (after the bulk of symptom change), were specific to CBT, and mediated its enduring effects on the prevention of relapse (Hollon et al 1992). These findings suggest that CBT reduces acute distress via one mechanism (disconfirming negative expectations) and prevents subsequent relapse via another (changing explanatory style) in a manner consistent with cognitive theory (Abramson et al 1989).

These studies illustrate how questions of mediation can be addressed in the context of randomized clinical trials. Such efforts are best pursued in designs that incorporate both a less intensive control condition (to rule out third variable causality) and a previously validated, standard reference treatment that operates through different mechanisms (to rule out errors in specifying the direction of causality). Although the methods of causal modeling were first developed to draw inferences when manipulation was not possible, they are even more informative when employed in the context of an experimental design (Holmbeck 1997). Including control conditions is at least as useful in the study of mediation as it is in establishing intervention efficacy. Because temporal antecedence is required to draw a causal inference, it is important to attend to the timing of measurement: treatment components should be measured before mechanisms, and both should be measured before the outcomes they are presumed to affect.

Determining which components in a complex treatment package actually produce change can help refine existing interventions and may suggest new directions not emphasized by existing theory. Once identified, these presumably active ingredients can be altered to test whether they make the interventions more effective. Similarly, identifying the patient mechanisms through which active ingredients exert their effects can refine theory, enhance intervention efficacy, and enrich our understanding of basic processes in normal populations. For example, psychotherapy may effect neurophysiologic change, as preliminary studies are beginning to suggest. IPT appears to produce a pattern of activation in the brain circuitry.
underlying emotion that differs to some extent from that produced by medication treatment (Brody et al. 2001; Martin et al. 2001). Similar studies are underway with respect to CBT. It may be possible to use such studies both to test theories regarding the mediation of change and the basic interrelations among neural, cognitive, and behavioral mechanisms.

There has been a widely shared perception that current NIMH organizational structure and funding patterns have made it difficult for investigators to incorporate research on process and mechanisms in treatment outcome studies. Such difficulties must be resolved. Administrative pressures and the desire to fund more grants limit the size of grants for already costly treatment studies. Consideration should be given to supporting supplemental grants or other means of funding ancillary studies to allow basic science components to be attached to ongoing treatment outcome trials. In addition, NIMH should consider supporting treatment development networks or other initiatives in which active collaboration between basic and intervention researchers is a prerequisite.

**CLINICAL PRACTICE AS A SOURCE OF INNOVATION.** Finally, many of the clinical innovations developed to date have arisen from clinical experience. Cognitive therapy had its origins in Beck’s inability to find evidence of repressed anger in the free associations and dream content of his depressed patients (Beck 1991); DBT arose in part from the problems Linehan encountered in getting existing behavioral approaches to work with suicidal borderline patients (Linehan 1997). The same is true for disorders other than depression, such as Wolpe’s systematic desensitization and Masters and Johnson’s gender therapy, as described in Hayes, Barlow, and Nelson (1999).

Clinical experience can be a potent source of innovation. The context of discovery does not require rules and structure, only intuition and the creative use of information (Popper 1961). People have an intuitive capacity to see connections, even when they are illusory. Such processes are essential to the context of discovery; research methods rarely tell us something new. Rather, their role is to check our propensity to believe things that are not true. Because no one is closer to the immediate phenomena of clinical change than the practicing clinician, efforts should be made to bring these clinicians into the fold, and partnering with a researcher may be needed throughout the process, even at the proposal submission stage. Experienced researchers might set up a typical pathway of empirical studies for a new therapy, beginning with single case studies and moving on to a case series or open trial, and on to a randomized trial if warranted by initial findings. Another useful design is analyses of case records of patients who respond versus those who do not. Such a design can be used to suggest moderators that could then be theoretically grounded and converted into hypotheses suitable for test in controlled studies.

Many effective therapies were first tested in clinical settings using single case studies and case series designs. Classics such as Kazdin (1982) as well as a recent article by Morgan and Morgan (2001) provide compelling accounts of the way in which single case designs, which are eminently suited for use by clinicians, can yield a wealth of valuable information about the process and outcome of treatment. And a recent thoughtful article by Lambert, Hansen, and Finch (2001) describes a methodology they label “patient-focused research,” which uses data collected in clinical practice and monitors the progress of individual patients over the course of treatment. Thus, it may prove possible to harness the creativity of practicing clinicians to develop treatment innovations and take the first steps toward testing their efficacy.

Moreover, some widely used therapies have never been studied in controlled outcome studies. Whether these interventions are truly efficacious remains largely unknown, but each has adherents who believe these treatments have a clinical effect. We recommend that NIMH establish a mechanism to evaluate the efficacy and effectiveness of existing therapies, especially those that have extensive followings, often those developed by charismatic and innovative clinicians. In the case of popular therapies that have been around for a long time, special initiatives may be needed, because the originators of the therapies have little to gain by conducting outcome studies at this point in their careers.

In the case of newer and less well-established therapies, NIMH should try to bring the developers of these therapies into the research fold by establishing a new funding mechanism that would enable clinicians whose therapies meet certain minimum standards to obtain research support. Such a mechanism might include funding for research consultation and to collect data to evaluate the therapies’ efficacy and effectiveness. Active outreach may be needed to bring these clinicians into the fold, and partnering with a researcher may be needed throughout the process, even at the proposal submission stage. Experienced researchers might set up a typical pathway of empirical studies for a new therapy, beginning with single case studies and moving on to a case series or open trial, and on to a randomized trial if warranted by initial findings. Another useful design is analyses of case records of patients who respond versus those who do not. Such a design can be used to suggest moderators that could then be theoretically grounded and converted into hypotheses suitable for test in controlled studies.

Special initiatives for studies of well-established therapies and research partnering mechanisms for less well-established therapies have the potential to shrink the scientist–practitioner gap dramatically and to reduce the numbers of empirically unsupported therapies that are currently so prevalent. An additional step that can be taken along these lines includes providing support to expand the development of research methods suitable for use in applied settings (Hayes et al. 1999). Efforts also should be made to strengthen and broaden clinical researchers’ contact with clinical phenomena by encouraging them to
remain active in clinical work and to consult and supervise in applied settings. Efforts are also needed to strengthen the clinical training provided in many research programs and to tie this clinical training more tightly to students’ research training.

**Developing Preventive and Maintenance Interventions**

The development of preventive interventions and maintenance strategies should be increased and successful strategies tested with greater vigor. Mood disorders often take on a life of their own; some theories even posit that the occurrence of affective distress increases risk for subsequent episodes (Post 1992). Depression has come to be recognized as a chronically recurrent disorder in which the majority of patients will experience multiple episodes across their lifetimes, and clinical practice is evolving toward maintaining such patients on medications indefinitely (APA 2000). Given the costs in human misery and lost productivity, much is to be gained by preventing the onset of the disorder and providing the tools to slow its progression (Muñoz and Ying 1993).

Extending the duration of evidenced-based interventions appears to reduce subsequent risk; both IPT and CBT reduce risk for relapse or recurrence so long as they are continued or maintained (Frank et al 1990; Jarrett et al 2001). This suggests that both do something to suppress symptom expression, much like medications. Moreover, CBT appears to have an enduring effect that lasts beyond the end of treatment (Evans et al 1992; Fava et al 1998; Paykel et al 1999), and the same may be true for MBCT (Teasdale et al 2000) and BA (Hollon 2000; Jacobson et al 1996). This enduring effect appears to be robust regardless of whether the intervention is provided during acute or continuation treatment and with or without medications (Hollon and Shelton 2001). Clearly, some mechanism must be operating that reduces subsequent risk, and additional studies should be directed to determining the nature of that mechanism.

Furthermore, the same emotion regulation strategies that prevent relapse or recurrence in treated patients also appear to prevent initial onset or symptom exacerbation in persons at risk (Gillham et al 2000). Two studies, one in a high school setting (Clarke et al 1995) and one in a health maintenance organization (Clarke et al 2001), have shown that CBT can prevent the onset of diagnosable disorders in at-risk adolescents selected on the basis of having subsyndromal depressive symptoms. In two other studies, CBT reduced subsequent symptom levels, one in a primary care setting (Muñoz et al 1995) and the other among at-risk college students selected on the basis of elevated explanatory style (Seligman et al 1999). These same cognitive behavioral strategies also can be applied in school-based settings (Jaycox et al 1994). These studies suggest that prevention is feasible and ought to be pursued (Muñoz et al, 2002).

With respect to bipolar disorder, brief psychoeducational interventions should be developed for younger persons who have not yet been diagnosed but are at risk because of family history or early-life mood fluctuations. Components of these preventive interventions might include family education about the disorder and its triggers, mood charting, school-based interventions (e.g., modification of the school day to accommodate illness-related sleep disruptions), identification of early warning signs, sleep–wake cycle monitoring, cognitive restructuring, and other tools. Similarly, there is a role for psychosocial interventions with a primary focus of medication adherence, particularly during the maintenance phase. Components might include addressing dysfunctional beliefs about the illness or its medical treatment, the tendency for patients to glamorize the “high” periods, family conflicts pertinent to medication taking, or strategies to enhance memory for dosing patterns (e.g., Cochran 1984; Miklowitz and Goldstein 1997; Newman et al 2001).

Research that leads to a detailed account of how cognitive, behavioral, and affective vulnerabilities influence the onset and prolongation of mood disorders can contribute to the development of effective preventive interventions. For example, adolescence is associated with a striking increase in the incidence of depression (and associated suicide attempts and completions), as well as the emergence of gender differences in depression rates, with female adolescents with depression greatly outnum-

bering their male counterparts (Angold and Rutter 1992). Better understanding of the mechanisms underlying these changes might provide clues to the nature and timing of preventive interventions (Nolen-Hoeksema and Girgus 1994).

An example of the way that an understanding of mechanism can lead to innovative preventive interventions comes from research showing the effects of stress on the neural regulation of mood and behavior across generations (Sapolsky 2000). Exposing pregnant rats to chronic stress results in loss of hippocampal volume in their offspring (Uno et al 1989). If this occurs in human infants of mothers exposed to chronic stress, resulting learning and memory deficits may have an impact on their ability to succeed in school and beyond. Children of depressed parents are known to be at elevated risk for depression and maternal stress during pregnancy, and its impact on brain development may represent one mechanism explaining this elevated risk. Work is underway by one of the authors (RFM) to determine whether preventive psychosocial interventions during pregnancy can reduce maternal stress.
and thereby reduce risk for depression in the mothers and their infants.

Prevention research should test theories about normal development, the course of psychopathology, and change processes that alter the course of mood disorders. Well-designed prevention studies can test whether high- and low-risk groups differ with respect to presumed mechanisms and whether and how interventions change these factors and whether these changes are related to improved mood regulation and reduction in episode incidence. Prevention trials provide an opportunity to test theories regarding the mechanisms that lead to onset and the strategies that avert it.

These efforts often target high-risk populations. Children of depressed parents represent one such high-risk group (Beardslee et al 1998) and children whose parents are suffering from marital distress or bereavement another (Sandler et al 1992). Interventions specifically directed at these groups have shown considerable promise (Beardslee and Gladstone 2001). Children of parents with bipolar disorder represent another high-risk group (Hammen et al 1990), as do children or adolescents who show early evidence of mood fluctuations (Lewinsohn et al 2000). Given the rapid increase in the rates of depression in girls in early adolescence, it may prove useful to target girls in this age range for prevention programs.

Preventive interventions need not be targeted directly at depression to reduce its incidence. For example, exposure to job-search skills and inoculation against setbacks not only resulted in higher levels of reemployment and monthly income, it also reduced levels of depression and the onset of diagnosable depressive episodes among the recently unemployed (Vinokur et al 2000). Similarly, programs designed to increase reading in grade school youngsters also reduced symptoms of depression (Kellam et al 1994).

Because not everyone who falls into these categories will necessarily get depressed and many people who develop depression fall into no known risk category, the ease of identification must not be overstated (Kazdin et al 1997). Still, if carefully implemented, the strategy of targeting people at elevated risk is likely to have merit. Similarly, not all risk factors are specific to depression. Attention also should be paid to general risk factors that predispose children to various disorders (e.g., poverty, social isolation, exposure to violence, and discrimination) and how these have a specific impact on depression (Beardslee and Gladstone 2001). The Institute of Medicine Committee on the Prevention of Mental Disorders identified depression as the most preventable disorder and called for a substantial increase in prevention research in high-risk samples; it is time to heed their call (Muñoz et al 1996).

**Developing More Accessible Psychosocial Interventions**

Many depressed and suicidal patients do not receive efficacious treatment (Young et al 2001). The problem is most severe for members of special populations such as ethnic or racial minorities, individuals with low incomes, people with different sexual orientations, and children and the elderly. Most major cities are already predominantly nonwhite or Latino, as will likely be true for the country as a whole over the next several decades. Nonetheless, members of racial and ethnic minorities are so poorly represented in randomized controlled trials that we know almost nothing about the effectiveness of “evidence-based interventions” in these groups (Bernal and Scharrón-del-Río 2001; US Department of Health and Human Services, 2001).

Efforts should be made to sample populations in a representative fashion, determine whether heterogeneity influences outcomes, and identify the mechanisms responsible. Although this might be done through conventional means, it likely will require adaptations to existing interventions (if not the development of new ones) and the use of nontraditional delivery methods, whether targeted at prevention or treatment. The Workgroup strongly endorses the recommendations of the Clinical Trials and Translation Workgroup for NIMH to place a high priority on extending the empirical validation of interventions to ethnic minority and other special populations and encourages the development of nontraditional delivery methods (see Frank et al, this issue).

**RESEARCH ON TRANSPORTABILITY AS A SOURCE OF INNOVATION.** It is unclear whether interventions efficacious in controlled trials generalize to everyday clinical practice; sometimes they do (Shadish et al 2000), and sometimes they do not (Weisz et al 1992). Factors that influence transportability are in essence moderator variables. If an intervention is efficacious under controlled conditions but less effective in applied settings, is that due to patients, therapists, implementation, or other aspects of the context and setting? Such variability represents an opportunity to explore the processes that lie behind that treatment’s effect (or lack of it). Behind every moderator lies a mediator, and research on transportability can be used to examine those processes (Kazdin 2000).

The transportation of interventions to new populations may require significant adaptations and modifications. A growing literature suggests that interventions for ethnic and minority groups need to be modified in culturally sensitive ways that take into consideration the role of culture and context (Bernal et al 1995). Adapted or culturally enhanced treatments may significantly differ from the original treatments (Kohn et al 2000). For
example, involving families in treatment decisions appears to be especially important when working with Latino populations, and adding a case management component to deal with concrete, real-life problems may be necessary to reduce attrition in low-income, medically ill minority populations (Miranda et al 1996; Organista et al 1994). When treatments must be modified to retain their effects, this provides an opportunity to explore relevant processes and deepen our understanding of the mechanisms involved.

Research also is needed on the factors that influence the ease with which clinicians’ accept novel evidence-based methods. The tour over recommendations to provide psychiatric residents and psychology interns with training in evidence-based treatments suggests just how difficult it may be to change established attitudes about existing clinical practice (Chambless et al 1996). The concept of evidenced-based treatment is new to the field and has encountered considerable resistance among practicing psychotherapists; it is important to make evidence-based treatments more palatable to clinical practitioners if they are to be adopted for routine use. One strategy would be to involve practicing clinicians in the process of innovation and to use their expertise to make these interventions more “user-friendly” from the start. Research focused on increasing the appeal of evidence-based methods to clinicians may lead to new methods of treatment. For example, clinicians often prefer interventions that allow them to individualize treatment for each patient; interventions that meet this preference may be more readily accepted than interventions that do not (Persons 1989).

In addition to attending to the issue of clinicians’ adoption of interventions, the Workgroup recommends that NIMH undertake a variety of other initiatives to encourage the development of evidence-based interventions designed to be readily transportable into clinical settings. Table 1 lists features that would be desirable for an intervention to possess in the interests of being widely accessible and easy to disseminate. One strategy for enhancing such attributes would be to give priority to research designed to develop interventions directly in the clinical settings in which their use is envisioned, so that transportation is not necessary. Intervention development conducted in applied settings and care systems is highly likely to provide an impetus for many innovations.

<table>
<thead>
<tr>
<th>Characteristics of Psychosocial Innovations That Facilitate Dissemination</th>
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<tr>
<td>Produces beneficial effects</td>
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<tr>
<td>Produces enduring effects</td>
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<tr>
<td>Acceptable to patients</td>
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<tr>
<td>Acceptable to clinicians</td>
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<tr>
<td>Straightforward and easy to teach</td>
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<tr>
<td>Implemented by multiple disciplines</td>
</tr>
<tr>
<td>Does not degrade or dilute easily</td>
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<td>Not too expensive</td>
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To successfully carry out research in clinical settings, novel research methodologies, infrastructures, and funding mechanisms will be needed. An outstanding example is the Pennsylvania Practice Research Network (PPRN), an infrastructure developed in Pennsylvania to carry out psychotherapy research in clinical settings (Borkovec et al 2001). The PPRN infrastructure called for participating clinicians to forward the data they collected to an offsite data collection center for scoring and evaluation. Persons (2001) proposed another mechanism for collecting research and clinical data in clinical practice, one in which clinicians themselves scored the data and fed results back into the treatment process. We believe NIMH could support initiatives designed to train clinicians to use web-based evaluation procedures to monitor progress of their patients in clinical practice, draw valid conclusions from their data, and facilitate dissemination of findings to the research and clinical communities. We recommend that NIMH push forward to develop and fund these types of novel mechanisms for the study of psychotherapy in clinical practice settings.

Another promising model for studying whether therapies that have been shown to be efficacious in controlled research are effective in applied settings is the notion of a clinical trial network. National Institutes of Health clinical trials networks have been established for AIDS, cancer, drug abuse, and other disorders. The Clinical Trials Network (CTN) established by the National Institute of Drug Abuse (NIDA) conducts rigorous, multisite studies in community-based clinics that include a wide range of treatment settings and patient populations and accomplishes many collateral goals (see http://www.nida.nih.gov/CTN/research.htm). Effectiveness research is conducted and new interventions are disseminated nationwide. In addition, the network facilitates extensive communication between researchers and clinicians; clinicians frequently suggest modifications to treatments based on their clinical experience using the treatments in the field, and the CTN promotes communication, in both directions, between researchers and clinicians. Clinics are spread throughout 14 national “nodes,” each with a primary research site and principal investigator. Submitted protocols are reviewed by the CTN steering committee, an ad
Table 2. Recommendations for Psychosocial Intervention Development for Mood Disorders

<table>
<thead>
<tr>
<th>Intervention Phase</th>
<th>Target for innovation</th>
<th>Prevention of onset</th>
<th>Treatment</th>
<th>Maintenance</th>
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<tr>
<td>Face-to-face interventions with currently accessible populations</td>
<td>Identify currently accessible groups (e.g., people with insurance) at high imminent risk for clinical episodes and test methods to prevent onset</td>
<td>Increase the effectiveness of interventions for groups that currently come for treatment but do not respond or do not remit fully</td>
<td>Identify patients who, even though they receive state-of-the-art follow-up care, continue to have recurrences, a chronic course, or residual disability</td>
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<tr>
<td>Face-to-face interventions with currently underserved populations</td>
<td>Identify high-risk groups who underuse services (e.g., the poor, the uninsured) and design preventive interventions that will be accessible and acceptable to them</td>
<td>Focus on clinical populations least likely to seek mental health care, more likely to drop out, and least likely to improve</td>
<td>Study patients least likely to have follow-up treatment to determine factors that reduce recurrence, chronicity, and disability For these patients, focus may need to be on treatments that have long-lasting effect; study the factors involved in maintenance of gains after treatment</td>
<td></td>
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<tr>
<td>Nontraditional interventions</td>
<td>Develop and evaluate distance learning approaches to emotion regulation training to reduce incidence of mood disorders</td>
<td>Study the potential of psychosocial interventions delivered in nontraditional means as adjuncts to traditional treatment, or as stand-alone treatments</td>
<td>Once acute treatment is successful, can nontraditional methods be used to help patients monitor mood levels and learn to obtain maintenance interventions early?</td>
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**Description**
- **Face-to-face interventions with currently accessible populations**: Identify currently accessible groups (e.g., people with insurance) at high imminent risk for clinical episodes and test methods to prevent onset.
- **Face-to-face interventions with currently underserved populations**: Identify high-risk groups who underuse services (e.g., the poor, the uninsured) and design preventive interventions that will be accessible and acceptable to them.
- **Nontraditional interventions**: Develop and evaluate distance learning approaches to emotion regulation training to reduce incidence of mood disorders.

**Mechanisms**
- **Face-to-face interventions with currently accessible populations**: Identify modifiable factors related to onset of clinical episodes and test interventions designed to change these factors.
- **Face-to-face interventions with currently underserved populations**: Test interventions designed to prevent onset that address risk factors for these groups; determine whether reduction in incidence is related to changes in risk factors.
- **Nontraditional interventions**: Develop and evaluate distance learning approaches to emotion regulation training to reduce incidence of mood disorders.

**Illustrations**
- **Face-to-face interventions with currently accessible populations**: Conduct prevention trials with high-risk children of depressed parents in HMOs (Clarke et al 2001).
- **Face-to-face interventions with currently underserved populations**: Conduct prevention trials with public-sector primary care patients, including Spanish-speaking patients (Muñoz et al 1995).
- **Nontraditional interventions**: Conduct studies with comorbid patients, suicidal patients, pregnant women, ethnic and linguistic minorities designed to increase utilization and effectiveness and decrease attrition.
Conduct Internet-based studies in which patients in remission can monitor their mood levels and seek help as needed or conduct systematic tests of how to teach these skills most efficiently without face-to-face contact and the treatment effects of doing so.

Conduct studies testing whether phone contact during treatment for depression increases adherence and remission rates (Hunkeler et al. 2000).

Conduct randomized control treatment outcome studies via mail (Munoz et al. 1997) or over the Internet (Stoddard et al. 2001).

Patients who have had one clinical episode are at high risk for another; determine the factors that predict recurrence and the factors that are most likely to protect patients from repeat episodes.

Many psychosocial interventions are based on skill-learning paradigms; conduct studies testing whether either or both interventions significantly affect recurrence rates.

Use emotion regulation research to design practical teaching programs that can be disseminated via mass media; determine whether skills are learned and whether using these skills reduces risk for clinical episodes.

Conduct studies testing whether phone contact during treatment for depression increases adherence and remission rates (Hunkeler et al. 2000).

Conduct randomized control treatment outcome studies via mail (Munoz et al. 1997) or over the Internet (Stoddard et al. 2001).

HMOs, health maintenance organizations.

The targets for innovation are ordered according to the conceptual distance from current practice. The first category is geared to improving effectiveness for current consumers of mental health services for whom existing interventions lack adequate effectiveness. The second category focuses on increasing accessibility to traditional services for populations who do not currently access mental health services sufficiently and adapting existing interventions for these populations to ensure effectiveness. The third category goes beyond the traditional face-to-face methods of mental health service delivery and recommends a systematic evaluation of the potential of mass media and of other methods for the delivery of effective prevention, treatment, and maintenance services to as large a segment of the entire population as possible.
Web-based protocols can be developed to acquaint bipolar patients with the early warning signs of manic episodes (sleep disturbance, irritability, goal-driven behavior). These protocols can also provide access to information about early intervention (treatment with mood stabilizers, family education, or the stabilization of sleep–wake cycles) and to self-monitoring forms that are commonly used in clinical practice (daily mood charts or sleep logs). Self-rated assessment scales can be used to screen widely for bipolar spectrum disorders, as the website of the National Depressive and Manic–Depressive Association is currently doing (Hirschfeld 2001). A similar approach could be used to educate families and friends about suicide risk and coach them in providing crisis intervention. The Web and other nontraditional delivery methods also can be used to reach providers. It can provide training in evidence-based methods, information about the latest research findings, collegial support to clinicians who are leading the way in the provision of evidence-based methods in their professional community, scales useful for monitoring patient progress, clinical database infrastructure, and even consultation on difficult cases.

Research that advances science often can address multiple goals. For example, the presence of non-English-speaking populations could be turned to advantage in a form of “multiple-baseline across languages” design. If a substantial minority in an area speaks Spanish, one could obtain a baseline point prevalence of major depression in the English- and Spanish-speaking population, then begin a Spanish-language media campaign (via radio, Internet, television, or newspapers) to teach individuals to regulate their mood using cognitive behavioral and interpersonal strategies. The Spanish-language campaign might be assumed to “pass through” the non-Spanish speakers without affecting them. Depression levels and incidence of major depressive episodes then could be reassessed and compared between the English- and the Spanish-speaking populations. The campaign then could continue in Spanish and also be launched in English and outcomes again assessed. Hypothetically, both symptoms and diagnosable episodes should be reduced after the first interval only in the Spanish-speaking population, with comparable changes occurring after the second interval in the English-speaking population.

It is useful to conceptualize the development of new psychosocial interventions in terms of “market segmentation.” By developing a variety of alternative delivery methods, we should be able to tailor interventions for increasing segments of the population in need, including those in rural areas and non-English-speakers. None of these methods will reach everyone and none will be universally effective, but together they can expand prevention and treatment of mood disorders to a larger proportion of the population and provide a framework for prioritizing resources (Christensen et al 1978). The Workgroup strongly recommends that the NIMH develop initiatives to support research on interventions that employ innovative service delivery methods.

DEVELOPING ADJUNCTIVE INTERVENTIONS AS A SOURCE OF INNOVATION. Adjunctive interventions can play an important role in assisting patients with mood disorders, even if not considered primary treatments for the basic disorder. For example, adjunctive interventions might be targeted at reducing associated dysfunction or providing social support. In particular, they might be directed at enhancing adherence to evidence-based interventions. In this latter regard, the Workgroup commends and endorses the goals expressed in NIMH’s program announcement on treatment adherence research.

One example of the type of adjunctive intervention that deserves to be pursued is motivational interviewing (MI; Miller and Rollnick 2002). This intervention is designed to assist patients in resolving the ambivalence associated with early stages of readiness to change (Prochaska et al 1992) and thereby initiate and adhere to behavior change. Typically, MI is brief (one or two sessions), client-centered, and compatible with a variety of approaches to psychotherapy. Despite its theoretical appeal and widespread use in the areas of substance abuse or behavioral medicine, it has yet to be applied to the mood disorders. It has great potential as an adjunct to existing interventions (including medication treatment), and we encourage systematic exploration of that possibility.

Recommendations for Research Priorities

In summary, the Workgroup recommends three priorities to advance psychosocial intervention development over the next decades. Each should be pursued in a manner that tests theories about the mechanisms of change. We recommend that NIMH increase its support for psychosocial intervention development research with a particular focus on the following:

1. Development of new and more effective interventions to treat a wider range of patients. This might best be accomplished by linking intervention development with basic research on the mechanisms of disorder and clinical research on the mechanisms of change. We strongly endorse the recent proposal to create centers for translational research and recommend that NIMH develop a specialized initiative to attract new scholars to this area and to rapidly test new targets implicated by basic research. Specifically, we recommend that the NIMH 1) sponsor conferences in which young investigators generate proposals for
translational research that are reviewed by senior figures in the field (as is currently being done with respect to borderline personality disorder); 2) provide administrative grants modeled on minority supplements to place young investigators with a background in basic research in clinical research settings (and vice versa) for the purpose of doing translational research; 3) issue a request for proposals to develop interventions that target possible mechanisms suggested by basic research and to explore the active ingredients and underlying mechanisms of change in evidence-based interventions; and 4) provide administrative supplements for the purpose of studying treatment impact on depression and functional capacity in patients with other psychiatric and medical disorders.

2. Development of interventions that prevent onset and recurrence to reduce both the incidence and the prevalence of depression and bipolar disorder. This might best be accomplished by linking intervention development with research in developmental psychopathology and personality development to identify the optimal times and optimal targets for effective intervention. Specifically, we recommend that NIMH 1) adopt a strategy similar to that used by the Small Business Innovative Research (SBIR) grants in which investigators who first demonstrate “proof of concept” with respect to identifying groups at high imminent risk and feasibility of preventive interventions are then put on a “fast track” for funding for a randomized prevention trial; 2) provide administrative supplements to explore transgenerational processes and the effects of interventions targeted at related considerations such as maternal health care, parenting skills, or vocational or academic difficulties on the subsequent development of depression and bipolar disorder in high-risk children; and 3) issue a request for proposals for studies of the prevention of onset in high-risk samples (e.g., adolescent girls or pregnant women) and the prevention of recurrence in recovered patient samples, populations for whom evidence of successful prevention already exists but cannot as yet be considered conclusive.

3. Development of user-friendly interventions and non-traditional delivery methods to increase access to evidence-based interventions, especially among underserved special populations. This might best be done by including both patients and practitioners in the treatment development process and by studying the mechanisms that underlie moderating factors. We strongly endorse recent efforts to support research on transportability that bridges controlled research to clinical practice and specifically recommend that NIMH 1) establish a Clinical Trials Network like that pioneered by NIDA to conduct effectiveness research in clinical settings and support the development of practice research networks; 2) extend funding for “proof of concept” studies with “fast track” extensions to test the feasibility and effectiveness of using novel media such as the Internet to deliver psychosocial interventions; and 3) provide administrative supplements to clinical trials to reach minority populations and to adapt the interventions provided to suit their needs.

Table 2 presents specific strategies for implementing these recommendations. The columns represent the three phases of intervention: 1) prevention of onset, 2) treatment, and 3) maintenance. The rows are divided into three key targets for innovation: 1) traditional (face-to-face) interventions with populations already using mental health services, but who do not respond adequately to existing treatments; 2) traditional (face-to-face) interventions with populations who do not currently avail themselves of mental health services to increase treatment acceptance, adherence, and effectiveness for these groups (U.S. Department of Health and Human Services, 2001); and 3) nontraditional interventions that go beyond the usual face-to-face delivery system and that test the limits of communitywide interventions, distance learning, and other means of conveying evidence-based preventive, treatment, and maintenance services. For each of the cells of the table, a description is provided of the focus defined by these factors, the mechanisms that will lead to progress, and illustrations of existing or potential studies that would yield innovative psychosocial interventions. It is important to approach these endeavors from a theoretical perspective and to examine the mediators and moderators that are actually involved. It also is timely to use advances in basic research and clinical science to enhance existing interventions and develop novel innovations, both for prevention and treatment. Finally, much can be done to increase access to effective interventions among underserved populations and to increase the adoption of such interventions by clinical practitioners, particularly via the use of nontraditional delivery methods.

The Workgroup thanks Dr. Karen Babich and Ms. Joan Cole of NIMH for their assistance in many aspects of the preparation of this report.

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

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