onset of an episode of depression. The most impressive piece of evidence linking loss to subsequent depression is the finding that loss of a parent before age 11 places adults at a higher than usual risk of depression. Some investigators have postulated that early childhood losses or separations actually sensitize neuronal receptor sites in the brain, thereby producing a vulnerability to mood disorders in adulthood. Persons who grow up with that enhanced vulnerability may be highly sensitive to images or ideas linked to depressive states, so that an episode of depression may be precipitated without requiring a catastrophic external loss. Chronic stress or deprivation of environmental origin may produce alterations in the catecholaminergic system in response to stimulation from the corticotropin-releasing hormone-adrenocorticotropic hormone (ACTH) axis. The end result of the changes may be the clinical picture of depression.

The effects of psychosocial influences on neurophysiological factors have been amply demonstrated in primate research. Infant squirrel monkeys who are separated from their mothers experience long-lasting and, in some cases, permanent neurobiological changes. The changes include lasting alterations in the sensitivity of noradrenergic receptors, changes in hypothalamic serotonin secretion, and persistently elevated plasma cortisol levels. The sensitivity and the number of brain opiate receptors are also significantly affected by repeated separations. Some of the changes are reversible if the infant monkeys are reunited with their mothers or siblings; other changes are not. Moreover, the separations appear to be more or less damaging during certain developmental periods, possibly because of the correlation with myelinization in the nervous system.

In the ensuing discussion of psychodynamic factors in the etiology of depression, the reader must keep in mind that psychological influences work in concert with genetic vulnerability and neurophysiological alterations to produce the characteristic clinical picture of depression. Those characteristics include psychomotor retardation, sleep changes, loss of appetite, diminished sex drive, anhedonia, loss of energy, inappropriate guilt feelings, and suicidal ideation. Similarly, comprehensive treatment planning must take into account both the psychodynamic factors and the alterations of neurotransmitters.

One of the most sophisticated efforts to define the relative contributions of psychological vulnerability, genetics, and environmental stressors in major depressive disorder was a prediction study involving female twins. Multiple assessments of 680 female-female twin pairs of known zygosity were made over time, and the findings allowed the investigators to develop an etiological model to predict major depressive episodes. One of the most influential predictors was the presence of recent stressful events. Genetic factors were also important in prediction of depression. Two other factors, neuroticism and interpersonal relations, also played a substantial etiological role. Neuroticism seemed to contribute in part by reducing the level of social support for an individual. Interpersonal dimensions of social support, recent difficulties, and parental warmth all were involved in predicting a major depressive episode.

PSYCHODYNAMIC THEORIES OF DEPRESSION

Anger turned inward A common finding in depressed patients is profound self-depreciation. Sigmund Freud, in his classic 1917 paper "Mourning and Melancholia," attributed that self-reproach to anger turned inward, which he related to object loss. The object loss may or may not be real. A fantasied loss may be sufficient to trigger a severe depression. Moreover, the patient may actually be unaware of any specific feelings of loss in light of the fact that the fantasied loss may be entirely unconscious.

Freud drew an analogy between serious melancholic states and normal grief. Both may be time-limited, but Freud cited two principal differences. In cases of *grief*, there is an *actual* object loss in external reality; in *depression* the lost object is more likely to be *emotional* than real. The second difference is that persons with depression experience profound loss of self-esteem, but the self-regard of persons engaged in a mourning process is not diminished.

The observational differences between grief and depression were pivotal in Freud's theory. He reasoned that one way of dealing with the loss of a beloved person is to become like the person. Freud defined that process as *introjection*, a defense mechanism central to the psychodynamics of depression, in which the patient internalizes the lost object so that it becomes an internal presence. Freud later noted that introjection is the only way that the ego can give up a valued and loved object.

Because depressed persons perceive the departed love object as having abandoned them, feelings of hatred and anger are intermingled with feelings of love. Freud suggested that ambivalence of that nature, involving the coexistence of love and hate, is instrumental in the psychodynamics of depression. As a result of introjecting the lost object, the negative part of the depressed patient's ambivalence—the hatred and anger—is directed inward and results in the pathognomonic picture of self-reproach. In that manner a suicidal act may have the unconscious meaning of murder.

Karl Abraham, one of Freud's early colleagues, shared Freud's view of depression but also extended and elaborated it further. Abraham viewed the process of introjection as a defense mechanism that takes two forms. First, he thought that the introjection of the original love object is the basis for building one's ego-ideal, so that the role of the conscience is eventually taken over by the introjected object. In that conceptualization much of pathological self-criticism is seen as emanating from the introjected love object. In the second form of introjection, more in keeping with Freud's idea, the content of self-reproach is merciless criticism directed at the object. In other words, Abraham viewed the two processes of introjection as instrumental in the creation of the superego. Abraham also linked depression to early fixations at the anal and the oral levels of psychosexual development. He viewed oral sadistic tendencies as the primary source of self-punishment in depressed patients, and he inferred that inadequate mothering during the oral stage of development was involved.

The psychodynamic understanding of depression defined by Freud and expanded by Abraham is known as the classical view of depression. That theory involves four key points: (1) Disturbances in the infant-mother relationship during the oral phase (the first 12 to 18 months of life) predispose to subsequent vulnerability to depression. (2) Depression can be linked to real or imagined object loss. (3) Introjection of the departed object is a defense mechanism invoked to deal with the distress connected with the object loss. (4) Because the lost object is regarded with a mixture of love and hate, feelings of anger are directed inward at the self.

Depressive position Although Melanie Klein understood depression as involving the expression of aggression toward loved ones, much as Freud did, the developmental theory on which her view was based is quite different from Freudian theory. During the first year of life, Klein believed, the infant progresses from the paranoid-schizoid position to the depressive position. In the first few months of life, according to Klein, the

infant projects highly destructive fantasies into its mother and then becomes terrified of the mother as a sadistic persecutor. That terrifying "bad" mother is kept separate from the loving, nurturing "good" mother through the defense mechanism of splitting. In that manner the infant's blissful feeding experience remains uncontaminated and undisturbed by persecutory fears of attack by the "bad" mother. In the course of normal development, according to Klein, the positive and the negative images of the mother are integrated into a more ambivalent view. In other words, the infant recognizes that the "bad" mother it fears and hates is the same mother as the "good" mother it loves and adores. The recognition that one can hurt loved ones is the essence of the depressive position.

Klein connected clinical depression with an inability to successfully negotiate the depressive position of childhood. She regarded depressed persons as fixated or stuck at a developmental level in which they are extraordinarily concerned that loved good objects have been destroyed by the greed and destructiveness they have directed at them. In the absence of those good objects, depressed persons feel persecuted by the hated bad objects. In short, Klein's view was that depressed patients are longing or pining for the lost love objects while being persecuted by bad objects. In that theoretical framework the feelings of self-depreciation are linked to the fear that one's good parents have been transformed into violent persecutors as a result of one's own destructive tendencies. Also, the bad internal objects are internalized into the superego, which then makes sadistic demands on the patient. Hence, in the Kleinian view, the self-reproaches experienced by depressed patients are directed against the self and internal impulses, rather than toward an introjected object, as in Freud's view.

Tension between ideals and reality Whereas most psychodynamic theories of depression incorporate the superego as a significant part of the conceptual understanding, Edward Bibring viewed depression as tension arising from within the ego itself, rather than between the ego and the superego. According to Bibring, the ego has three highly invested narcissistic aspirations—to be good and loving, to be superior or strong, and to be loved and worthy. Those ideals are held up as standards of conduct. Depression sets in when a person becomes aware of the discrepancy between those ideals and reality. Helplessness and powerlessness result from the feeling that one cannot measure up to such high standards. Any blow to the self-esteem or any frustration of the strivings toward those aspirations precipitates depression. Bibring's theory, unlike Freud's and Klein's, does not regard aggression as playing a primary role in depression. The depressed person may ultimately experience anger turned inward, resulting from the awareness of helplessness; however, such expressions of aggression are secondary, rather than primary. The essence of depression, in Bibring's view, is a primary affective state arising within the ego and is based on the tension between what one would like to be and what one is.

Ego as victim of superego Edith Jacobson compared the state of depression to a situation in which the ego is a powerless, helpless child, victimized by the superego, which becomes the equivalent of a sadistic and powerful mother who takes delight in torturing the child. Like Freud, Jacobson assumed that depressed persons have identified with ambivalently regarded lost love objects. The self is experienced as identified with the negative aspects of the object, and ultimately the sadistic qualities of the lost love object are transformed into the cruel superego. Hence, depressed persons feel that they are at the mercy of a sadistic internal tormentor that is unrelenting in its victimization. Jacobson also noted that the boundary between self and object may disappear, resulting in a fusion of the bad self with the bad object.

Dominant other Silvano Arieti studied the psychodynamic underpinnings of depression in severely ill patients who were unresponsive to most somatic treatments. He observed a common psychological theme in those patients that involved living for someone else, rather than for themselves. He referred to the person for whom depressed patients live as the dominant other. In most cases the dominant other is the spouse or a parent, but Arieti also noted that sometimes a principle, an ideal, or an organization serves a similar psychodynamic function. In such cases he referred to the entity as the dominant ideology or the dominant goal.

Depression often sets in when patients realize that the person for whom they have been living is never going to respond in a manner that will meet their expectations. The goal of their lives is regarded as unattainable, and a profound feeling of helplessness sets in. In Arieti's conceptualization of depression, he stressed a marked rigidity in the thinking of depressed persons, so that any alternative to living for the dominant other or the dominant ideology is viewed as unacceptable and even unthinkable. Depressed patients feel locked into an inflexible perspective on how they should live their lives and how gratification or fulfillment can be obtained. Even though they are depressed because living for someone or something other than themselves has been a failure, they nevertheless feel paralyzed and unable to shift their approach to life. If the dominant other will not respond to them in the way they have longed for, they feel that life is worthless, and that rigidity is often involved in a decision that suicide is the only alternative.

CASE EXAMPLE A 19-year-old college student consulted a psychiatrist after one semester in school. He told the psychiatrist that he was depressed and discouraged with college and with himself. College was not what he had expected, and he had not performed up to his expectations. He was seriously questioning whether he should return for the second semester, and he had a sense of hopelessness about changing his feelings. Suicidal thoughts had occasionally crossed his mind, although he was not planning to act on them. His sleep was disturbed by awakening in the middle of the night and ruminating about what he should do. He felt a significant diminution in his energy level, and he commented that things he used to find enjoyable no longer gave him pleasure.

The patient attended a prestigious college on the West Coast, but he indicated that he had actually wanted to get into Harvard. His application to Harvard had resulted in his being placed on the waiting list, but he had not been accepted. The psychiatrist he consulted commented that the college he had chosen to attend was certainly a highly regarded one. The patient responded, "It's not Harvard." When the psychiatrist asked the patient how he had done academically during the first semester, the patient appeared embarrassed and replied, "I only got a 3.25 grade-point average—one A and three Bs." The psychiatrist asked him why he seemed embarrassed to reveal such a solid academic record. The patient explained that he had wanted to make the dean's list but that he had fallen short of it, since the list required a 3.5 grade-point average.

The psychiatrist asked the patient if he hoped to be in a different situation after one semester of college. The patient's answer revealed that he had an extraordinarily high internal expectation of himself. He had wanted to be "a star," a straight-A student at Harvard. He explained that his father had gone to Harvard, and he hoped that, by being a standout there, he would finally achieve the praise and recognition from his father that he had always longed for but had never received. His father seemed disappointed that his son had not been accepted to Harvard, and the patient was convinced that his father was ashamed of his son for not making the dean's list.

EXPLANATION The above case example illustrates the psychodynamic theories of both Arieti and Bibring. The patient was living his life for a dominant other—his father. He tried to per-

Alkermes, Ex. 1060

form beyond his abilities to extract an approving and loving response from his father that was never forthcoming. That longed-for response was rigidly construed as the only thing that mattered in life; even though he was succeeding at a highly competitive college, his success did not result in his feeling good about himself. Moreover, the patient's depression can also be linked to his awareness of the disparity between his idealized expectations of himself and the reality of his situation, as described by Bibring. Being a straight-A student at Harvard was his own aspiration; the reality was that he was a B+ student at a college that did not measure up to Harvard.

The vignette also reflects two other key elements in the psychodynamic etiology of depression. First, in accord with the psychoanalytic notion of multiple causation, more than one psychodynamic theory may be pertinent in understanding an individual patient's depression. Clearly, both the dominant other and the tension between ideals and realities were significant determinants in causing the patient's depression. Second, the precipitating factors that produce depression do not have to be catastrophic events involving obvious external disasters. To a casual observer the college student had no apparent reason to be depressed, since he was performing successfully at a highly regarded college. Nonetheless, the *intrapsychic meaning* of his academic performance was such that the patient felt hopeless and despairing as a result. In assessing the psychodynamic factors in depression, clinicians must always attend to idiosyncratic personal meanings of events to fully understand the effects they have on the patient. Otherwise, clinicians run the risk of responding in the same unempathic manner that often characterizes the responses of family members. In the absence of objective evidence of any disastrous events in the depressed person's life, loved ones often react by saying: "You have no reason to be depressed. Everything is going so well in your life."

Selfobject failure The ego and the superego do not figure in Heinz Kohut's conceptualization of depression. Kohut's theory, known as self psychology, rests on the assumption that the developing self has specific needs that must be met by parents to give the child a positive sense of self-esteem and self-cohesion and that similar responses are required from others throughout the course of the life cycle. He referred to those needs as mirroring, twinship, and idealization. The *mirroring* responses required by the self are equated with the gleam in the mother's eye when the child exhibitionistically shows off for the mother. Admiration, validation, and affirmation are responses that are included under the category of mirroring. *Twinship* responses refer to the child's need to be like others. A small boy who is outside playing with his toy lawn mower while his father is mowing the lawn is meeting important psychological needs in asserting his commonality with his father. Finally, the need for *idealization* is an important aspect of the development of the self. Children who grow up with parents they can respect and idealize develop healthy standards of conduct and morality.

Kohut referred to those three needs collectively as selfobject needs. In other words, the responses demanded from others are required by the self, and the needs of the object as a separate person are not taken into account. The other person serves as an object who meets the needs of the self. Selfobject needs essentially refer to certain functions that persons in the environment provide, rather than to those persons themselves. Kohut felt that selfobject responses continue to be needed throughout life and are as necessary for emotional health as oxygen is for physical health. Within that conceptual framework, depression involves the failure of selfobjects in the environment to provide the self of the depressed person with mirroring, twinship, or idealizing responses necessary for the self to feel whole and sustained. The massive loss of self-esteem seen in depression is regarded by Kohut and the self psychologists as a serious disruption of the self-selfobject connection or bond.

Depression as affect and compromise formation Among contemporary ego psychologists a widely held view is that depression is not truly a psychiatric disorder or illness. Instead, depression is regarded as an affect reflecting conflict and compromise formation. Charles Brenner, the principal architect of that view, suggested that concern about such childhood calamities as object loss, loss of love, castration, and punishment are associated with two kinds of unpleasure. One form of unpleasure is anxiety, which involves an *anticipated* calamity or danger. The other form of unpleasure, depressive affect, involves a calamity that has *already happened*. That theory of depressive affect differs sharply from the classical views of Freud and Abraham. Brenner pointed out that depression is not always related to object loss or to oral wishes. He also asserted that identification with a lost object is found in some depressed persons but not in all and that anger turned inward is a *result* of depression, rather than a cause. Depressive affect, in Brenner's view, can be linked to any of the childhood calamities, rather than uniquely to object loss. People can experience depressive affect because they feel unloved, because they feel castrated, or because they feel punished in a variety of ways. Depressive affect is a normal and universal part of the human condition.

A critical feature in Brenner's formulation is the idea of compromise formation, in which a symptom is viewed as simultaneously expressing an unconscious wish or drive and a defense against that wish or drive. A particular compromise formation may be more or less successful in eradicating depressive affect in the same manner as it may succeed to varying degrees in dealing with anxiety. A dog phobia, for example, is a symptomatic compromise formation that succeeds in eliminating anxiety as long as dogs are avoided. Similarly, certain forms of compromise formation may eradicate depressive affect while others do not.

The central point of Brenner's psychodynamic theory is that depressive affect is a universal feature in every pathological conflict, whether it is apparent on the surface or buried in the depths of the compromise formation. Depressive affect is a universal factor in all cases of psychiatric illness. From that standpoint, Brenner believed that classifying certain forms of mental illness as depression simply because depressive affect is part of the conscious symptoms does not make sense. The conscious experience of depression provides information about the efficacy and the nature of a patient's defensive maneuvers and compromise formations, in Brenner's view, but it does not reveal much about the underlying causes of the patient's illness.

Early deprivation Several investigators have noted that consistent, loving, nurturant parental involvement appears to have some value in preventing the development of depression. Conversely, separation from parents early in life or the actual loss of a parent may predispose one to depression. Edith Zetzel observed that adverse experiences in the formative years of childhood, particularly those involving separation and loss, make it difficult for children to tolerate depressive affects without resorting to primitive defensive operations. If caretakers fail to assist children in identifying and tolerating painful feelings

that result from an adverse life experience, the child will grow up with inadequate coping mechanisms. That impaired adaptation may contribute to the subsequent development of depression.

Empirical research has provided some corroboration for the view that early deprivation is relevant to the cause of depression. René Spitz demonstrated that infants separated from their mothers during the second six months of life have overt signs of depression. In some cases the infants in Spitz's studies wasted away and died in response to the separations. Margaret Mahler and her colleagues, who studied the interactions between normal and abnormal mother-infant pairs, found that children's emotional dependence on their parents is instrumental in the development of their capacity to grieve and mourn. That capacity, in turn, influences children's feelings of self-esteem and helplessness. Although the development of depression may involve genetic and constitutional factors, as well as environmental stressors, most theorists agree that the early relationship between child and parent plays a significant role in causing depression.

Premorbid personality factors A comprehensive psychodynamic understanding of depression must include premorbid personality factors in the equation. All persons may become depressed, given sufficient environmental stress, but certain personality types or traits appear to dispose one to depression. For example, the harsh, perfectionistic superego characteristic of persons with obsessive-compulsive personality disorder may lead them to feel that they are always falling short of their own excessive expectations of themselves. As noted earlier, that intrapsychic constellation may be critical in the development of a major depressive episode. Similarly, Axis II personality disorders involving dependent yearnings for care—such as dependent, histrionic, and borderline personality disorders—may also be more vulnerable to depression. Those personality disorders that use projection and other externalizing defense mechanisms, such as antisocial and paranoid personality disorders, are less likely to decompensate into depression. No particular premorbid personality type has been associated with the development of bipolar disorder.

Evidence is accumulating that an Axis II diagnosis of a personality disorder may complicate the course and treatment of depression. Depressed patients with personality disorders generally have poorer outcomes in the area of social functioning than those without personality disorders. Furthermore, residual depressive symptoms are more likely to present in recovering depressed patients who have an Axis II diagnosis. Psychoanalytic clinicians have observed that personality factors frequently serve to maintain a depressed state once it has occurred. In clinical practice the complicating factors of a comorbid personality disorder diagnosis are quite common. One study found that 42 percent of persons with major depressive disorder and 51 percent of patients with dysthymic disorder have an accompanying Axis II diagnosis.

CHARACTEROLOGICAL DEPRESSION Many patients encountered in clinical practice report feelings of depression even though they lack symptoms of a well-defined Axis I disorder, such as major depressive episode. Many of those patients have a primary diagnosis of a personality disorder on Axis II and experience characterological depression, a feeling of pervasive loneliness or emptiness associated with the perception that others are not meeting one's emotional needs. They can be distinguished from patients with an Axis I diagnosis of major depressive episode by the absence of vegetative symptoms (such as psychomotor retardation, loss of libido, diminished appetite, lack of energy, and sleep disturbance) and by the presence of certain qualitative features of their complaint of depression. Loneliness, emptiness, and boredom are often chronic complaints in characterological depression but are much less common in Axis I illnesses. In addition, a conscious sense of rage at not having their needs met may be present. The patients often describe childhood experiences in which they felt deprived of appropriate emotional nurturance from their parents. As a result, they continue to seek parental substitutes in adult life.

Characterological depression is differentiated from Axis II personality disorders by the fact that it is an affective state occurring within the context of certain personality disorders, rather than a constellation of traits forming an overarching personality type.

A 29-year-old woman came to psychotherapy complaining that she was "empty" inside and "needed to be filled up" by a positive experience with a psychotherapist. She said that, while she was growing up, her mother never had time for her and that her mother loved her two sisters more than her. The patient had had a series of romantic relationships with men, but she never felt that she was getting the kind of attention and love that she needed from any of them. The men often ended the relationship because they felt that she was too demanding and that they could not possibly meet all her needs. Her last therapist had "given up" on her because he, too, felt that he was unable to be of help to her. The patient also indicated that she had called her previous therapist almost every night because she would begin to feel lonely and need his reassurance that he still cared. She feared that she had turned off her therapist by being too demanding. She also described several angry outbursts directed at him when he would not talk with her for lengthy periods of time on the phone during the evening. She wondered if her outbursts made him hate her.

The patient had taken four different antidepressive medications with no improvement. She did not meet the diagnostic criteria for an Axis I dysthymic disorder or major depressive episode. However, she did have characteristics in keeping with two different Axis II diagnoses—dependent personality disorder and borderline personality disorder.

OTHER CLINICAL ENTITIES In addition to the existence of characterological depression in the presence of other Axis II personality disorders, another clinical entity is described by psychoanalysts as depressive personality or depressive character. That disorder may be a form of chronic depression closely related to the Axis I diagnosis of dysthymic disorder. Persons suffering from the disorder exhibit the following symptoms: helplessness; chronic feelings of guilt; relationships characterized by dependency; persistent low self-esteem; an inclination to be self-punitive, self-denying, and hypercritical; and a conviction that things are hopeless and will never change. Patients with that character structure do not allow themselves to have any form of gratification in life because of disturbed relationships in childhood with parents or parental substitutes.

A related form of characterological depression has been labeled depressive-masochistic personality disorder by Otto Kernberg. Patients with the disorder are characterized by an extremely demanding superego that results in humorless, overly conscientious, self-critical tendencies. The patients have excessive needs for approval, love, and acceptance from others, and they unconsciously cause others to feel guilty because of their inability to meet the patient's demands. The consequences of that pattern of interaction are further feelings of rejection because others do not want to be part of a relationship in which they never meet the expectations of the patient. People with depressive-masochistic personalities are also characterologically prone to turn anger inward to avoid any expression of aggression and anger toward others.

Clinicians must remember that depression spans the entire spectrum of pathology and health. In addition to being a discrete

Alkermes, Ex. 1060

psychiatric disorder, depression refers to an emotional state that can be present in normal persons at certain times, as well as in persons with characterological or psychotic conditions. Moreover, simply because the patient does not have sufficient symptoms to be given an Axis I diagnosis of a mood disorder does not mean that the depression is benign. In one study, employees with minor forms of depression that did not meet Axis I criteria had 51 percent more disability days than did persons with a diagnosis of major depressive episode.

MANIA

Even though the standard treatment of bipolar disorder is pharmacological, a psychodynamic understanding of patients with mania is of value in the overall treatment and management of bipolar disorder. Genetic vulnerability and biochemical abnormalities are clearly involved in the illness, but psychological factors have repeatedly been observed to play roles in the precipitation of manic episodes. One 10-year follow-up study identified two different groups of treatment failures in a cohort of patients with bipolar disorder. One group of patients were shown to relapse because the treating psychiatrist had failed to increase the lithium (Eskalith) dose in response to increased physiological activation before the onset of a manic episode. In the other group of treatment failures, psychological issues that were clearly involved in precipitating manic episodes had not been given appropriate attention by the responsible psychiatrists, and manic episodes had resulted from the stress of those psychological factors.

Patients with bipolar disorder have been studied from the perspective of ongoing psychoanalysis and psychoanalytic psychotherapy, and those clinical investigations have revealed specific psychodynamic factors at work in the onset of manic episodes. In one series of patients, unconscious sexual urges and fantasies seemed to overpower ego defense mechanisms, leading to a clinical picture of hypersexuality and other symptoms of mania. Increasing the lithium dosage resulted in a decline of the sexual behavior and a reinstitution of the ego defense mechanisms that were present before the manic episode. In the course of continued psychotherapeutic or psychoanalytic treatment, those patients became consciously aware of their unconscious sexual desires and of the defenses brought to bear to deal with those desires. That conscious awareness enabled the patients to identify early warning signals of increased sexual impulses, so that future manic episodes could be avoided by increasing the lithium dose.

Those studies reflect how a psychodynamic understanding of patients with bipolar disorder may be crucial to the effective treatment of the disorder. Most manic patients cannot make use of psychotherapy interventions in the midst of a full-blown manic episode because the essence of mania is a denial of psychological problems. However, after the patient has become euthymic as a result of pharmacological stabilization, psychotherapeutic interventions may have value both in preventing subsequent episodes and in dealing with the feelings of shame and guilt associated with embarrassing behavior that took place during the manic episode.

PSYCHODYNAMIC THEORIES OF MANIA The psychodynamic understanding of mania is usefully applied to clinical instances of hypomania because the differences between the two entities are quantitative, rather than qualitative. Just as mania and depression have been linked from a neurophysiological standpoint, they are similarly connected from a psychodynamic perspective.

Karl Abraham Most theories of mania view manic episodes as defensive against underlying depression. Karl Abraham, for example, believed that manic episodes may reflect an inability to tolerate childhood depression in reaction to a developmental tragedy, such as the loss of a parent. The manic state, in Abraham's view, is understood as a way of removing the shackles of a tyrannical superego through the merger of the ego and the superego. Self-criticism is then replaced by euphoric self-satisfaction.

Bertram Lewin Bertram Lewin regarded the hypomanic patient's ego as a purified pleasure ego. The defense mechanism of denial is appropriated by the ego to disregard unpleasant perceptions and affects, as well as distressing psychic realities that may result in self-punishment or self-criticism.

Melanie Klein Melanie Klein also viewed mania and hypomania as defensive reactions to depression, but she linked the mechanism to the depressive position, rather than to an overriding of the superego. The essence of the depressive position is intense anxiety that one's own aggression has resulted in the destruction of important love objects, such as parents. In Klein's own words, "Persecution (by 'bad' objects) and the characteristic defenses against it, on the one hand, and pining for the loved ('good') object, on the other, constitute the depressive position." She thought that manic defenses are necessary both to control and master the dangerous bad objects and to restore and save the loved good objects.

Those manic defenses include omnipotence, denial, idealization, and contempt. *Omnipotence* serves to deny the need for good objects, to delude oneself into feelings of self-containment and grandiosity, and to help one feel insulated and protected from assault by internal persecutors. *Idealization and denial* work together in such a way that idealization of self and others serves to deny any destructiveness or aggression in relationships. The euphoric disposition of the manic or hypomanic patient reflects the tendency to gloss over any unpleasant aspects of reality and to treat everything with a sense of humor and a striking disregard for the tragic dimensions of reality, even if the situation is tragic. Idealization, however, may rapidly give way to *contempt*, which is also linked to denial because it is a way of disregarding the importance of love objects and, therefore, denying the concern that damage has been done to them and reparation is needed. Moreover, the manic patient can then minimize any distressing feelings of sorrow or regret that may arise in connection with concerns about having destroyed love objects.

Klein also observed that a wish to triumph over parents is often an integral part of the manic defensive posture. She noted that a frequent childhood fantasy is to reverse the child-parent relationship and that the fantasy produces feelings of guilt and anxieties of a depressive nature related to the wish to destroy and replace the parents. Feelings of depression may develop after a job promotion or other professional success because the person's unconscious wish to triumph over and to surpass one's parents has been fulfilled.

The Kleinian conceptualization of mania as defensive against feelings of depression is useful in understanding the phenomenon of dysphoria in manic patients when depression breaks through a manic episode, requiring a resurgence of manic denial. That formulation is also useful in understanding the commonly observed phenomenon of elation after the death of a loved one.

Alkermes, Ex. 1060

A patient received a phone call that informed him of his mother's death. Rather than feeling grief-stricken or shocked, he noted a sense of expansiveness and power. As he discussed the odd reaction with his psychotherapist, he was able to recognize that the high feeling he experienced was related to a sense that he was finally liberated from feelings of slavish dependence on a tyrannical mother.

TREATMENT The psychodynamic theory of Klein also informs psychotherapeutic approaches to bipolar-disorder patients. Because manic defenses are evoked by difficulties in working through the depressive position, the psychotherapist must assist the patient in integrating the loving and aggressive sides of both object representation and self-representation within. The process of integration facilitates the work of mourning. An auspicious moment for that form of therapeutic work may be after a manic episode, when patients feel remorseful about the damage they have done to others and to their own reputations by ill-advised behavior. Klein observed that, through a positive relationship with a therapeutic figure, patients may be able to restore the lost love objects by the internalization of the therapist and thereby lessen the fear of persecution from the bad objects. Manic defenses are less important then because the need for them has profoundly changed.

Other Theories Other views of mania include Bibring's conceptualization that manic elation is essentially a compensatory reaction secondary to severe depression or an unconscious fulfillment of a person's narcissistic aspirations to be loved, worthy, superior, and virtually flawless. Jacobson understood mania as a transformation of the sadistic superego figure from a punitive tormentor into a loving and forgiving object who is thoroughly idealized. This dramatically altered superego is then projected into persons in the outside world with whom the manic patient establishes idealized relationships that are free from any negative characteristics, such as hatred and anger.

CLINICAL IMPLICATIONS The overthrow of the superego characteristic of manic states manifests itself clinically as lack of conscientiousness, disregard for laws or rules of conduct, and hypersexuality.

A 45-year-old dentist in the throes of a manic episode was admitted to a psychiatric hospital. The psychiatry resident who was on duty attempted to take a history of the patient, who refused to cooperate in any way with the examination. Instead, he told jokes, most of which contained sexual innuendoes, and tried to engage the female resident in seductive banter. When a male nurse arrived at the scene to assist with the admission, the patient suggested that the resident could have sex with him while the nurse watched. He denied having any problems that required hospitalization and said that his wife had forced him to come to the hospital because she was a prude and did not like any of his sexual demands. He said he had the largest penis in the city and that he had to fight off women who were dying to sleep with him.

Some manic patients induce a sense of giddiness in clinicians, so that serious and even tragic dimensions of the clinical situation are minimized or glossed over. Also, the grandiose and expansive sense of self is often an obvious compensatory reaction to feelings of profoundly low self-esteem. As in the case of the manic dentist, patients may attempt to convince others that they have extraordinary sexual prowess or that they are besieged by admirers; such attempts are ways of dealing with feelings of sexual inadequacy or loneliness. Some manic patients write novels or "scientific" treatises that are hundreds of pages long and characterize their creative products as brilliant works of genius. When others read them and do not understand them, the patients suggest that other people lack the intelligence to comprehend their sophisticated thinking.

OTHER PSYCHOLOGICAL THEORIES

ADOLF MEYER Meyer viewed depression as a person's reaction to a distressing life experience, such as a financial setback, the loss of a job, the death of a loved one, or a serious physical illness. He believed that depression must always be understood in the context of the patient's life history, as an event that has psychic causality.

KAREN HORNEY Horney believed that children raised by parents who are rejecting and unloving are prone to feelings of insecurity and loneliness. In her view, children need to be loved but fear criticism and rejection, which makes them susceptible to feelings of depression and helplessness.

SANDOR RADO Rado linked depression to a profound feeling of helplessness. He believed that anhedonia, the inability to experience pleasure, is a central phenomenon in depression that develops when persons are not aware of their capacities or are unable to provide feelings of emotional self-gratification. Rado connected severe depression with a punitive superego that punishes the patient for unconscious hostility toward a deceased loved one.

JOHN BOWLBY Bowlby saw depression from an ethological perspective that emphasized disturbances of the mother-infant attachment bond. He believed that separations of infants from mothers (or other caretakers) early in life lead to feelings of depression and hopelessness that may in some cases continue throughout the life cycle.

HARRY STACK SULLIVAN Although Sullivan concentrated his efforts on schizophrenia more than on mood disorders, his interpersonal perspective applies to both. He thought that adverse interactions between persons and their psychosocial environments were critical to the development of depression.

COGNITIVE-BEHAVIORAL THEORY According to the theory developed by Aaron Beck, depression results from specific cognitive distortions that are present in persons prone to depression. Those distortions are referred to as *depressogenic schemata*, which are cognitive templates that perceive both internal and external data in ways that are altered by early experiences. Those schemata are associated with four systematic errors in logic: overgeneralization, magnification of negative events with a simultaneous minimization of positive events, arbitrary inference, and selective abstraction.

LEARNED HELPLESSNESS The learned helplessness theory of depression connects depressive phenomena to the experience of uncontrollable events. For example, when dogs in a laboratory were exposed to electrical shocks from which they could not escape, they showed certain behaviors that differentiated them from dogs who had not been exposed to such uncontrollable events. After exposure to the shocks, they would not cross a barrier to stop the flow of electric shock when put in a new learning situation. According to the learned helplessness theory, the dogs learned that outcomes were independent of responses, so they had both cognitive motivational deficit (meaning they would not make attempts to escape the shock) and emotional deficit (indicating a decreased reactivity to the shock). In the reformulated view of learned helplessness as applied to human depression, internal causal explanations are thought to produce a loss of self-esteem after adverse external events. Behaviorists who subscribe to the theory stress that

Alkermes, Ex. 1060

improvement of depression is contingent on the patient's learning a sense of control and mastery of the environment.

SUGGESTED CROSS-REFERENCES

Further discussion of psychoanalytic theory can be found in Section 6.1. For additional material on characterological depression, see the discussion of borderline personality disorder in Chapter 25.

REFERENCES

Abraham K: Notes on the psycho-analytical investigation and treatment of manic-depressive insanity and allied conditions. In *Selected Papers of Karl Abraham, M.D.*, p 137. Basic Books, New York, 1953.

American Psychiatric Association: Practice guidelines for major depressive disorder in adults. Am J Psychiatry (Suppl) *150:* 126, 1993.

*Arieti S: Psychotherapy of severe depression. Am J Psychiatry *134:* 864, 1977.

*Bibring E: The mechanism of depression. In *Affective Disorders: Psychoanalytic Contributions to Their Study*, P. Greenacre, editor, p 13. International Universities Press, New York, 1953.

*Brenner C: A psychoanalytic perspective on depression. J Am Psychoanal Assoc *39:* 25, 1991.

Broadhead W E, Blazer D G, George L K, Tse C K: Depression, disability days, and days off from work in a prospective epidemiologic survey. JAMA *264:* 2524, 1990.

Coe C L, Glass J C, Wiener S G, Levine S: Behavioral but not physiological adaptation to repeated separation in mother and infant primates. Psychoneuroendocrinology *8:* 401, 1983.

Coe C L, Mendoza S P, Smotherman W P, Levine S: Mother-infant attachment in the squirrel monkey: Adrenal responses to separation. Behav Biol *22:* 256, 1978.

Coe C L, Wiener S G, Rosenberg L T, Levine S: Endocrine and immune responses to separation and maternal loss in nonhuman primates. In *The Psychobiology of Attachment and Separation*, M Reite, T Field, editors, p 163. Academic Press, Orlando, 1985.

Depression Guideline Panel: *Depression in Primary Care*, vol 2, *Treatment of Major Depression*. US Department of Health and Human Services, Rockville, MD, 1993.

Feinstein S C, Wolpert E A: Juvenile manic-depressive illness: Clinical and therapeutic considerations. J Am Acad Child Psychiatry *12:* 123, 1973.

Freud S: The ego and the id. In *Standard Edition of the Complete Psychological Works of Sigmund Freud*, vol 19, p 3. Hogarth Press, London, 1961.

*Freud S: Mourning and melancholia. In *Standard Edition of the Complete Psychological Works of Sigmund Freud*, vol 14, p 237. Hogarth Press, London, 1963.

Gabbard G O: *Psychodynamic Psychiatry in Clinical Practice: The DSM-IV Edition*. American Psychiatric Press, Washington, 1994.

Gabbard G O: Psychodynamic psychiatry in the decade of the brain. Am J. Psychiatry *149:* 991, 1992.

Gold P W, Goodwin F K, Chrousos G P: Clinical and biochemical manifestations of depression: Relation to the neurobiology of stress, part I. N Engl J Med *319:* 348, 1988.

Gold PW, Goodwin F K, Chrousos G P: Clinical and biochemical manifestations of depression: Relation to the neurobiology of stress, part II. N Engl J Med *319:* 413, 1988.

Jacobson E: Psychotic identifications. In *Depression: Comparative Studies of Normal, Neurotic, and Psychotic Conditions*, p 242. International Universities Press, New York, 1971.

Jacobson E: Transference problems in depressives. In *Depression: Comparative Studies of Normal, Neurotic, and Psychotic Conditions*, p 284. International Universities Press, New York, 1971.

Kendler K S, Kessler R C, Neale M C, Heath A C, Eaves L J: The prediction of major depression in women: Toward an integrated etiological model. Am J Psychiatry *150:* 1139, 1993.

*Klein M: Mourning and its relation to manic-depressive states. In *Love, Guilt, and Reparation and Other Works 1921–1945*, p 344. Free Press, New York, 1975.

Klerman G L, Weissman M M, editors: *New Applications of Interpersonal Therapy*. American Psychiatric Press, Washington, 1993.

Kohut H: *The Analysis of the Self: A Systematic Approach to the Psychoanalytic Approach of Narcissistic Personality Disorders*. International Universities Press, New York, 1971.

Kohut H: *How Does Analysis Cure?* A Goldberg, editor. University of Chicago Press, Chicago, 1984.

Marin D B, Kocsis J H, Frances A J: Personality disorders in dysthymia. J Per Dis *7:* 223, 1993.

Miller M D, Frank E, Cornes C: Applying interpersonal psychotherapy to bereavement-related depression following loss of a spouse in late life. J Psychother Prac Res *3:* 149, 1994.

Lewin B D: *The Psychoanalysis of Elation*. Norton, New York, 1950.

Loeb F F, Loeb L R: Psychoanalytic observations on the effect of lithium on manic attacks. J Am Psychoanal Assoc *35:* 877, 1987.

Phillips K A, Gunderson J G, Hirschfeld R M A, Smith L E: A review of the depressive personality. Am J Psychiatry *147:* 830, 1990.

Slavney P R: The mind-brain problem, epistemology, and psychiatric education. Acad Psychiatry *17:* 59, 1993.

Suomi S J: The development of affect in rhesus monkeys. In *The Psychobiology of Affective Development*, N Fox, R Davidson, editors, p 119. Erlbaum, Hillsdale, NJ, 1984.

Suomi S J: Early stress and adult emotional reactivity in Rhesus monkeys. In *Childhood Environment and Adult Disease: Symposium No. 156*, Ciba Foundation Symposium Staff, editors, p 171. Wiley, Chichester, England, 1991.

16.6 MOOD DISORDERS: CLINICAL FEATURES

HAGOP S. AKISKAL, M.D.

HETEROGENEITY OF MOOD DISORDERS

NOSOLOGY Mood disorders are characterized by pervasive dysregulation of mood and psychomotor activity as well as by related biorhythmic disturbances. The rubric of affective disorder—which in some European classifications also subsumes morbid anxiety states—increasingly is being replaced by the nosologically more delimited concept of mood disorder. Thus the term "mood disorder" is now the preferred term in both the World Health Organization's 10th revision of the *International Classification of Diseases and Related Problems* (ICD-10, 1992) and the American Psychiatric Association's (APA) fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV, 1994) for bipolar disorder (with manic or hypomanic and depressive episodes) and major depressive disorders and their respective attenuated variants known as cyclothymic and dysthymic disorders.

Conditions that in earlier editions of those manuals were categorized as endogenous depression, involutional melancholia, and psychotic depressive reaction have been incorporated into major depressive disorder, whereas depressive neurosis has been largely absorbed by dysthymic disorders. Although the neurotic-endogenous distinction has been officially deleted, the term "melancholic features" is now used as a qualifying phrase for those major depressive disorders where biological concomitants predominate. While both the American and international classifications recognize the common occurrence of mixed anxiety-depressions, it is unresolved as to whether they should be classified with mood disorders or with anxiety disorders. It is equally uncertain how to classify the classic neurasthenic conditions, which have reemerged under the name "chronic fatigue syndrome."

DESTIGMATIZATION The reshuffling and reclassification of various affective conditions into the mood disorders section of the third edition of DSM (DSM-III) and DSM-IV has, on balance, led to considerable broadening of their boundaries. That

reflects, in part, new developments in pharmacotherapy that have resulted in considerable alleviation of suffering for persons with classic mood disorders. As a result many persons with recurrent mood disorders who would have been otherwise disabled are now able to lead productive lives. Those gratifying results have, in turn, helped to destigmatize that group of disorders. Destigmatization has been further facilitated by published self-revelations of famous persons with depressive disorder and bipolar disorder.

SPECTRUM OF MOOD DISORDERS As often happens when new therapeutic interventions prove successful, the past decade has witnessed an increased readiness to diagnose mood disorders—and their variants—even where clinical features are atypical. Those developments should not be dismissed as mere therapeutic fad, however. External validating strategies, such as familial-genetic studies and prospective follow-up, can now be used to buttress the broadened concept of mood disorders. New research comparing monozygotic and dizygotic twins has demonstrated that the genetic potential to mood disorders embraces entities that extend beyond the narrow concept of endogenous depression (melancholia in DSM-IV) to subsume a larger variety of depressions, including many affected persons in the community who have never received psychiatric treatment. Although such data might seem counterintuitive to those who would restrict depression to a core primary biological disease, they suggest that the constitutional predisposition for mood dysregulation occurs in as many as one of every three persons. That ratio is similar to the proportion of those who develop a full depressive disorder following bereavement or to that of rhesus monkeys developing depressivelike behavior following a separation paradigm. Those figures, in turn, suggest that many subjects possess protective factors against major depressive breakdowns; alternatively, such data suggest that other factors mediate which person with emotional distress will progress to a clinical case. A great deal thus might be learned about the nature of pathological affective processes by studying self-limiting affective conditions on the border of mood disorders.

The suffering and dysfunction resulting from mood disorders are among the most common reasons advanced for consulting psychiatrists and other physicians. All great physicians of the past, beginning with Hippocrates, have devoted considerable space in their general medical texts to the clinical characterization of such disorders. Those classic texts provided detailed clinical portrayals of both melancholia and mania, as well as their cyclic alterations in the same patient. Greek physicians recognized a broad spectrum of affective disturbances, ranging from the relatively mild temperamental forms (which in the official nosology is represented by dysthymic disorder and cyclothymic disorder) to the more severe illnesses (including what today is considered mood disorder with mood-congruent and mood-incongruent psychotic features). The ancients were also aware of the intimate relation of morbid states of fear to melancholia. Finally, they noted that melancholia and certain physical diseases shared seasonal incidence, and described the common occurrence of alcohol indulgence, especially in those prone to mania.

BOUNDARIES The boundaries between temperament (personality) and mood disorder, grief and melancholia, anxiety and depressive states, depressive and bipolar disorders, mood-congruent and mood-incongruent psychotic features, and other (schizophrenic) psychotic conditions are still unresolved. Since the earliest descriptions in ancient medical treatise, mood disorders have been known to be highly comorbid with alcohol use and somatic disease. These trends continue to be true today, with the addition of substance use disorders.

AFFECTS, MOODS, TEMPERAMENTS, AND MORBID MOOD STATES

ETHOLOGICAL CONSIDERATIONS Affects and moods refer to different aspects of emotion. Affect is communicated through facial expression, vocal inflection, gestures, and posture, and, according to current ethological research, is intended to move people to appraise whether a person is satisfied, distressed, disgusted, or in danger. Thus joy, sadness, anger, and fear are basic affects that serve a communicative function in humans and other primates, as well as many mammalian species.

Affects tend to be short-lived expressions, reflecting momentary emotional contingencies. Moods convey sustained emotions; their more enduring nature means that they are experienced long enough to be felt inwardly. Moods are made manifest in subtle ways, and their accurate assessment often requires empathic understanding by the interviewer. The words that subjects use to describe their inner emotions may or may not coincide with the technical terms used by researchers or clinicians. Furthermore, the inward emotion and the prevailing affective tone may conflict. That conflict could be due to deliberate simulation (that is, the subject does not wish to reveal his or her inner emotion), or it could be the result of a pathological lesion or process that is affecting the emotions and their neural substrates. Thus evaluating moods and affective expression requires considerable experience.

SADNESS AND JOY The normal emotions of sadness and joy are part of everyday life and should be differentiated from major depressive disorder and mania. Sadness, or normal depression, is a universal human response to defeat, disappointment, or other adversities. The response may be adaptive, in an evolutionary sense, by permitting withdrawal to conserve inner resources, or it might signal the need for support from significant others.

Transient depressive periods also occur as reactions to certain holidays or anniversaries, as well as during the premenstrual phase and the first week postpartum. Termed, respectively, holiday blues, anniversary reactions, premenstrual dysphoric disorder (see Section 15.4) and maternity blues, the conditions are not in themselves psychopathological, but those predisposed to mood disorder may develop clinical depression during such times.

In view of the higher prevalence of depression in women, premenstrual affective changes—tension, irritability, hostility, and labile mood—have received much attention. The attempt to establish a late-luteal-phase dysphoric disorder has neglected the not uncommon occurrence of premenstrual eutonia, increased energy, and sexual drive. Those mixed affective manifestations tend to point toward a biphasic phenomenon. Available data do not support the existence of a distinct premenstrual mood disorder. Rather, women with severe premenstrual complaints appear to have higher rates of lifetime major mood disorders. Furthermore, such events as epileptic attacks, panic states, and the perpetration of violent crimes might, in some instances, be associated with the premenstrual phase. Those considerations suggest the hypothesis that psychobiological changes occurring premenstrually exacerbate, in a nonspecific way, a large spectrum of neuropsychiatric disorders to which the women are otherwise predisposed. In other words, the exag-

Alkermes, Ex. 1060

gerated premenstrual variability in emotional equilibrium is unlikely to be the primary factor or cause of those neuropsychiatric manifestations.

GRIEF Also known as normal bereavement, grief is considered to be the prototype of reactive depression, and occurs in response to significant separations and losses, such as death, divorce, romantic disappointment, leaving familiar environments, forced emigration, or civilian catastrophes. (Unfortunately, DSM-IV tends to limit the concept of normal grief to loss due to death.) In addition to depressed affect appropriate to the loss, bereavement reactions are characterized by the prominence of sympathetic arousal and restlessness, believed to represent, from an evolutionary perspective, physiological and behavioral mechanisms to facilitate the search for the lost object. Like other adversities, bereavement and loss do not generally seem to cause depressive disorder, except in those predisposed to mood disorder.

ELATION The positive emotion of elation is popularly linked to success and achievement. However, paradoxical depressions may also follow such positive events, possibly because of the increased responsibilities that often have to be faced alone. Elation is conceptualized psychodynamically as a defense against depression or as a denial of the pain of loss, as exemplified by the so-called maniacal grief, a rare form of bereavement reaction in which elated hyperactivity may replace the expected grief.

Other pseudomanic states include the brief energetic and unusually lucid periods encountered in dying patients or in those who need to take superhuman action in the face of unusual duress, both of which have been conceptualized as flights into health. It is also conceivable that in predisposed persons those reactions might be the prelude to a genuine manic episode. Given such predisposition, sleep deprivation (which commonly accompanies major stressors) might represent one of the intermediary mechanisms between stressor and adverse clinical outcome.

AFFECTIVE TEMPERAMENTS Another mediating factor between normal and pathological moods is temperament. Most persons have a characteristic pattern of basal affective oscillations that defines their temperament. For instance, some are easily moved to tears by sad or happy circumstances, whereas others tend to remain placid. Normally, oscillations in affective tone are relatively minor, tend to resonate with day-to-day events, and do not interfere with functioning. Some exhibit greater variability of emotional responses whereby, with no obvious provocation, the person alternates between normal mood and sadness or elation, or both. They tend to cluster into basic temperamental types: the depressive temperament (where the person easily swings into the sad direction), the hyperthymic temperament (where the person is naturally inclined toward cheerful moods), and the cyclothymic temperament (where the person swings between cheerful and sad moods). All three temperaments typically have an early onset and tend to persist throughout life.

An examination of the traits associated with those temperaments can provide the rationale for Ernst Kretschmer's hypothesis about the social functions they served. Thus, the person with a depressive temperament (Table 16.6-1) is hard-working, dependable, and suitable for jobs that require long periods of devotion to meticulous detail. Some such persons shoulder the burdens of existence without experiencing its pleasures. The hyperthymic temperament (Table 16.6-1), endowed with high levels of energy, extraversion, and humor, will assume leadership positions in society or excel in the performing arts or entertainment. In talented persons the cycloid temperament, which alternates between sadness and elation, could provide the inspiration and the intensity needed for composing music, painting, or writing poetry. The danger with such temperaments is that they could swing too far in one or the other direction, or in both directions. Such substances as alcohol, caffeine, and other stimulants when used by those persons might further destabilize their affect regulation.

Temperaments then are best regarded as variations of normal emotional expressiveness, which might continue throughout life without significant impairment, or they might be accentuated in the teenage and early adult years, and become manifest as a dysthymic disorder or a cyclothymic disorder with its attendant interpersonal, academic, and vocational problems. Finally, they might be the point of departure for major mood disorders.

MORBID MOOD STATES Mood disorders are morbid mood states characterized by the following features.

Pathological mood change Pathological moods are distinguished from their normal counterparts by being out of proportion to any concurrent stressor or situation; being unresponsive to reassurance; being sustained for weeks, months, and sometimes years; and having a pervasive effect on the person, such that judgment is seriously influenced by the mood.

Endoreactive moods Major depression and mania are diagnosed respectively, when, sadness or elation is overly intense and continues beyond the expected impact of a stressful life event; indeed, the morbid mood might arise without apparent or significant life stress. Thus the pathological process in mood disorders is in part defined by the ease with which an intense emotional state is released, and especially by its tendency to

TABLE 16.6-1
Attributes of Depressive and Hyperthymic Temperaments

Depressive	Hyperthymic
1. Gloomy, incapable of fun, complaining	1. Cheerful and exuberant
2. Humorless	2. Articulate and jocular
3. Skeptical, pessimistic, and given to brooding	3. Overoptimistic and carefree
4. Guilt-prone, low self-esteem, and preoccupied with inadequacy or failure	4. Overconfident, self-assured, boastful, and grandiose
5. Introverted with restricted social life	5. Extroverted and people seeking
6. Sluggish, living a life out of action	6. High energy level; full of plans and improvident activities
7. Few interests, but which, nonetheless, can be pursued with relative constancy	7. Versatile, with broad interests
8. Passive	8. Overinvolved and meddlesome
9. Reliable, dependable, and devoted	9. Uninhibited and stimulus seeking
10. Habitual long sleeper (more than 10 hours a night)	10. Habitual short sleeper (less than six hours a night)

Alkermes, Ex. 1060

persist autonomously even when the offending stressor is no longer operative. Rather than being endogenous (that is, occurring in the absence of precipitants), mood disorders are best conceptualized as endoreactive (that is, once released, they tend to persist autonomously). The homeostatic dyscontrol of mood, which is part of a more pervasive mood dysregulation, resists reversal to the habitual or baseline affective tone. DSM-IV, which tends to disparage theory and adhere to a descriptive level of operationalization, gives insufficient weight to this fundamental characteristic of mood disorders.

Syndromal illness In a more descriptive vein what sets mood disorders apart from their normal emotional counterparts is the clustering of signs and symptoms into discrete syndromes that typically recur on an episodic basis or pursue a course of intermittent chronicity. Such cyclicity—and in some cases regular recurrence known as periodicity—represents other signs of mood dysregulation particularly relevant to bipolar disorder.

Impairment Normative reactions to adversity and stress, including biological stress, typically consist of transient admixtures of anxiety and dysphoria that are best captured under the DSM-IV rubric of adjustment disorder with mixed emotional features. That is, the self-limiting reactions are best qualified broadly as normal affective states that produce little, if any, impairment in the main areas of functioning.

Although anxiety, irritability, and anger do occur in various types of mood disorders, it is pathologically sustained mood states of depression and elation that characterize those disorders. Morbid mood states (mood disorders) then consist of protracted emotional reactions that deepen or escalate, respectively, into clinical depression or mania, with a tendency to recur or to evolve, in as many as a third of cases, into chronicity. The contribution of temperamental peculiarities to such outcomes should be apparent. The impaired functioning characteristic of mood disorders is thus based on a combination of factors, which include severity, autonomy, recurrence, and chronicity of the clinical features.

To recapitulate, dysregulation in mood disorders can take different forms. It could become manifest as a single severe episode that persists autonomously for months and sometimes for years, or it might recur with episodes of varying severity, years apart or in rapid succession, and with or without interepisodic remission. In general, the earlier the age at onset, the more likely it is that there will be recurrences, especially those that are bipolar in nature. Thus, depending on the course of the illness, impairment could be state dependent, occurring during an episode, or it could extend into the interepisodic period. National Institute of Mental Health (NIMH) estimates suggest that, on the average, a woman with bipolar disorder spends 12 years in florid episodes (often hospitalized), loses 14 years from a productive career and motherhood, and has her life curtailed by 9 years.

Recent observations have also revealed another pattern of impairment. In dysthymic disorder and cyclothymic disorder, which represent an intensification of temperamental instability, impairment is not due to the severity of the mood disturbance per se, but to the cumulative impact of the dysregulation beginning in the juvenile or early adult years and continuing unabated or intermittently over long periods; hence the frequent confusion with character pathology. Here the impairment is more subtle but nonetheless pervasive. Persons with cyclothymic disorder tend to be perpetual dilettantes whereas those with dysthymic disorder often lead morose and colorless lives.

PSYCHOPATHOLOGY AND CLINICAL PRESENTATION

DEPRESSIVE SYNDROME Like other illnesses, depressive disorder clusters into signs and symptoms that constitute what DSM-IV and ICD-10 term major depressive episode (Table 16.6-2). Those criteria attempt to set an operational threshold for depressive disorder based on a specified number of items and their temporal patterns. It is only after taking an in-depth phenomenological approach that a clinician can ascertain the presence of a depressive disorder. The DSM-IV diagnostic criteria for major depressive disorder (Tables 16.6-3 and 16.6-4) provide only a general guide. Disturbances in all four spheres—mood, psychomotor activity, cognitive, and vegetative—should be ordinarily present for a definitive diagnosis of major depressive disorder, although that is not specified in DSM-IV.

Mood disturbances Mood change, usually considered the sine qua non of morbid depression, becomes manifest in a variety of disturbances, including (1) painful arousal, (2) hypersensitivity to unpleasant events, (3) insensitivity to pleasant events, (4) insensitivity to unpleasant events, (5) reduced anticipatory pleasure, (6) anhedonia or reduced consummatory pleasure, (7) affective blunting, and (8) apathy. The phenomenology and psychometric properties of that broad range of mood distur-

TABLE 16.6-2
Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.
   (1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
   (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
   (3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
   (4) insomnia or hypersomnia nearly every day
   (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
   (6) fatigue or loss of energy nearly every day
   (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
   (8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
   (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms do not meet criteria for a mixed episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

Alkermes, Ex. 1060

TABLE 16.6-3
Diagnostic Criteria for Major Depressive Disorder, Single Episode

A. Presence of a single major depressive episode.
B. The major depressive episode is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
C. There has never been a manic episode, a mixed episode, or a hypomanic episode. **Note:** This exclusion does not apply if all of the manic-like, mixed-like, or hypomaniclike episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

Specify (for current or most recent episode):
Severity/psychotic/remission specifiers
Chronic
With catatonic features
With melancholic features
With atypical features
With postpartum onset

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-4
Diagnostic Criteria for Major Depressive Disorder, Recurrent

A. Presence of two or more major depressive episodes.
Note: To be considered separate episodes, there must be an interval of at least two consecutive months in which criteria are not met for a major depressive episode.
B. The major depressive episodes are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
C. There has never been a manic episode, a mixed episode, or a hypomanic episode. **Note:** This exclusion does not apply if all of the maniclike, mixed-like, or hypomaniclike episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

Specify (for current or most recent episode):
Severity/psychotic/remission specifiers
Chronic
With catatonic features
With melancholic features
With atypical features
With postpartum onset

Specify:
Longitudinal course specifiers (with and without interepisode recovery)
With seasonal pattern

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

bances are under investigation at the Salpêtrière Hospital in Paris. The focus here will be primarily on painfully aroused mood (depression) and diminished capacity for pleasure (anhedonia), two mood disturbances given selective weight in DSM-IV and ICD-IO.

DEPRESSED MOOD The term "depressed mood" refers to negative affective arousal, variously described as depressed, anguished, mournful, irritable, or anxious. Those terms tend to banalize a morbidly painful emotion that is typically experienced as worse than any physical pain. There is thus a physical quality to depressed mood, which in the extreme is indescribably painful. Even when not so severe, depressive suffering is qualitatively distinct from its neurotic counterparts, taking the form of groundless apprehensions with severe inner turmoil and torment. That description is particularly apt for middle-aged and elderly persons, who were once considered to be suffering from involutional melancholia. The sustained nature of the mood permits no respite, although it tends to be less intense in the evening. Suicide may represent an attempt to find deliverance from such unrelenting psychic torment: death can be experienced as comforting.

Patients with a milder form of the malady typically seen in primary care settings might deny experiencing mournful moods and instead complain of physical agony in the form of headache, epigastric pain, precordial distress, and so on, in the absence of any evidence of physical illness. Such conditions have been described as *depressio sine depressione*, or masked depression. In such cases, commonly observed in older patients, the physician should corroborate the presence of mood disturbance by the depressed affect in the patient's facial expression, voice, and overall appearance.

ANHEDONIA AND LOSS OF INTEREST Paradoxically, the heightened perception of pain in many persons with depressive disorder is accompanied by an inability to experience normal emotions. Patients exhibiting the disturbance may lose the capacity to cry, a deficit that is reversed as the depression is lifting.

In evaluating anhedonia it is not enough to inquire whether the patient has lost the sense of pleasure; the clinician must document that the patient has actually given up previously enjoyed pastimes. When mild, anhedonia evidences with decreased interest in life. Later, patients complain that they have lost all interest in things that gave them pleasure. In the extreme they lose their feelings for their children or spouses, who once were a source of joy. Thus the hedonic deficit in clinical depression might represent a special instance of a more pervasive inability to experience emotions.

Some patients emotionally cut off from others, experience depersonalization, and the world seems strange to them (derealization). The impact of the loss of emotional resonance can be so pervasive that patients may surrender values and beliefs that had previously given meaning to their lives. For instance, a member of the clergy might present with the complaint that he or she no longer believes in the work, that he or she has lost God. The inability of the person with depressive disorder to experience normal emotions—commonly observed among young depressed patients—is different from the schizophrenic patient's flat affect in that the loss of emotions is itself experienced as painful, that is, the patient suffers immensely from the inability to experience emotions.

Psychomotor disturbances In depression refer to psychomotor changes consisting of abnormalities in the motor expression of mental activity.

AGITATION Although agitation (pressured speech, restlessness, wringing of hands, and pulling of hair) is the more readily observed abnormality, it appears less specific to the illness than does retardation (slowing of psychomotor activity). Psychophysiological studies have documented that such slowing often coexists with agitation.

PSYCHOMOTOR RETARDATION Underlying many of the deficits seen in clinical depression, some authorities believe psychomotor retardation to be the core or primary pathology in mood disorders. Morbid depression—what patients describe as being "down"—can be understood in terms of extreme psychomotor slowing. The patient experiences inertia, being unable to act physically and mentally. Recent brain imaging research that has revealed subcortical (extrapyramidal system) disturbances in mood disorders tends to support the centrality of psychomotor dysfunction in these disorders.

Alkermes, Ex. 1060

Long neglected in psychopathological research, psychomotor retardation has now been measured with precision. In the Salpêtrière Retardation Scale special emphasis is placed on the following disturbances: (1) paucity of spontaneous movements; (2) slumped posture with downcast gaze; (3) overwhelming fatigue—patients complain that "everything is an effort"; (4) reduced flow and amplitude of speech and increased latency of responses, often giving rise to monosyllabic speech; (5) a subjective feeling that time is passing slowly or has stopped; (6) poor concentration and forgetfulness; (7) painful rumination—thinking that dwells on a few (usually unpleasant) topics; and (8) indecisiveness, which refers to an inability to make simple decisions.

DSM-IV places greater emphasis on the more easily observable objective or physical aspects of retardation. For the patient, however, the subjective sense of slowing is often its more pervasive and disabling aspect. That psychological dimension of retardation is most reliably elicited from depressed persons with good verbal skills.

Ms. A., a 34-year-old literature professor, presented to a mood clinic with the following complaint: "I am in a daze, confused, disoriented, staring. My thoughts do not flow, my mind is arrested . . . I seem to lack any sense of direction, purpose . . . I have such an inertia, I cannot assert myself. I cannot fight, I have no will."

A patient with lesser linguistic sophistication would simply complain of an inability to perform household chores or a difficulty in concentrating on his or her studies. Such psychomotor deficits in turn underlie depressed patients' diminished efficiency or their inability to work.

PSEUDODEMENTIA AND STUPOR In elderly persons the slowing of mental functions can be so pronounced that the patient may experience memory difficulties, disorientation, and confusion. In young persons psychomotor slowing is sometimes so extreme that the patient might slide into a stupor, unable to participate even in such basic biological functions as feeding himself or herself; such an episode often represents the precursor of bipolar disorder, which later declares itself by mania. (In the author's view, it is terminologically and historically misleading to label those phenomena as catatonic features, as stipulated by DSM-IV.) Today depressive disorder is diagnosed in its earlier stages, and subtle degrees of stupor are much more likely to be encountered clinically, as illustrated by the following vignette:

A 20-year-old male college student seen in the emergency room spoke of "being stuck—as if I have fallen into a black hole and can't get out." Further evaluation revealed that the patient was speaking metaphorically of his total loss of initiative and drive, and as having been engulfed by the disease process. To a clinician without the requisite phenomenological training, such a patient might be considered bizarre, and perhaps even psychotic. Yet the patient responded dramatically to fluoxetine (Prozac) and in two weeks was back in school.

Cognitive disturbances According to the cognitive view of depression, negative evaluations of the self, the world, and the future are central to understanding depressed mood and behavior. It is equally likely, however, that the depressed mood colors perceptions of the self and others or that disturbed psychomotor activity leads to negative self-evaluations. Therefore, it is best to approach cognitive changes in depression empirically as key clinical manifestations of depression. Clinically those faulty thinking patterns become manifest as follows: (1) ideas of deprivation and loss; (2) low self-esteem and self-confidence; (3) self-reproach and pathological guilt; (4) helplessness, hopelessness, and pessimism; and (5) recurrent thoughts of death and suicide.

The essential characteristic of depressive thinking is that the sufferer views everything in an extremely negative light. The self-accusations are typically unjustified or are blown out of proportion, as in the case of a middle-aged woman who was tormented by guilt because as a child she had not repaid 5 cents she had borrowed from a classmate. Some of the thoughts may verge on the delusional. For instance, an internationally renowned scientist complained that he was "nothing." Such self-evaluations, which indicate an extremely low image of self, might nonetheless reflect an accurate perception of the impairment due to psychomotor retardation.

MOOD-CONGRUENT PSYCHOTIC FEATURES In depressive disorder with psychotic features negative thinking acquires grossly delusional proportions, being maintained with such conviction that the thoughts are not amenable to change by evidence to the contrary. Classically, delusional thinking in depression derives from humankind's four basic insecurities, those regarding health, financial status, moral worth, and relationship to others. Thus severely depressed patients may have delusions of worthlessness and sinfulness, reference, and persecution. They believe they are being singled out for their past mistakes and that everyone is aware of their errors. Persecutory ideation in depression is often *prosecutory* in nature in that it derives from the belief that the person deserves punishment for such transgressions. A severely depressed man may feel so incompetent in all areas of functioning, including the sexual sphere, that he may suspect his wife of having an affair (delusion of infidelity).

Other depressed persons believe that they have lost all their money and that their children will starve (delusions of poverty); or that they harbor an occult illness, such as cancer or the acquired immune deficiency syndrome (AIDS) (delusions of ill health); or that parts of their bodies are missing (nihilistic delusions). In more severe illness the patient might feel that the world has changed, that calamity and destruction await everyone. In rare instances a parent with such delusions might kill his or her young children, to save them from moral or physical decay, and then commit suicide. Finally, a minority of depressed persons may have fleeting auditory or visual hallucinations with extremely unpleasant content along the lines of their delusions (for example, hearing accusatory voices or seeing themselves in coffins or graveyards). All of those psychotic experiences are genuine affective delusions or hallucinations. They are mood congruent in the sense that they are phenomenologically understandable in light of the prevailing pathological mood.

The DSM-IV criteria for severity-psychotic-remission specifiers for current (or most recent) major depressive episode, including mood-congruent and mood-incongruent psychotic features, appear in Table 16.6-5.

MOOD-INCONGRUENT PSYCHOTIC FEATURES It is possible that so-called first-rank or Schneiderian-type symptoms could arise in the setting of a major depressive episode.

A 42-year-old civil servant said she was so paralyzed by depression that she felt that she had no personal initiative and volition left; she believed some malignant force had taken over her actions, and that it would comment on every action that she would undertake. The patient fully recovered with thymoleptic medication. There is no reason to believe that the feelings of somatic passivity and running commentary were indicative of a schizophrenic process.

Thus with proper phenomenological probing, certain classes of apparently mood-incongruent psychotic experiences listed in DSM-IV, can be understood as arising from the pathological mood and the profound changes in psychomotor activity that

Alkermes, Ex. 1060

TABLE 16.6-5
Criteria for Severity/Psychotic/Remission Specifiers for Current (or Most Recent) Major Depressive Episode

Note: Code in fifth digit. Can be applied to the most recent major depressive episode in major depressive disorder and to a major depressive episode in bipolar I or II disorder only if it is the most recent type of mood episode.

Mild: Few, if any, symptoms in excess of those required to make the diagnosis and symptoms result in only minor impairment in occupational functioning or in usual social activities or relationships with others.
Moderate: Symptoms or functional impairment between "mild" and "severe."
Severe without psychotic features: Several symptoms in excess of those required to make the diagnosis, **and** symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.
Severe with psychotic features: Delusions or hallucinations. If possible, specify whether the psychotic features are mood-congruent or mood-incongruent:
- **Mood-congruent psychotic features:** Delusions or hallucinations whose content is entirely consistent with the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment.
- **Mood-incongruent psychotic features:** Delusions or hallucinations whose content does not involve typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. Included are such symptoms as persecutory delusions (not directly related to depressive themes), thought insertion, thought broadcasting, and delusions of control.

In partial remission: Symptoms of a major depressive episode are present but full criteria are not met, or there is a period without any significant symptoms of a major depressive episode lasting less than two months following the end of the major depressive episode. (If the major depressive episode was superimposed on dysthymic disorder, the diagnosis of dysthymic disorder alone is given once the full criteria for a major depressive episode are no longer met.)
In full remission: During the past two months, no significant signs or symptoms of the disturbance were present.
Unspecified.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

accompany them. (In other instances, the clinician must search history of alcohol and/or substance use disorder or withdrawal as putative explanation for mood-incongruence in psychotic depression.)

HOPELESSNESS AND SUICIDE Given that most, if not all, clinically depressed patients find themselves locked in the private hell of their negative thoughts, it is not surprising that up to 15 percent of untreated or inadequately treated patients give up hope that they will ever recover and so kill themselves. The suicide attempt is not, however, undertaken in the depth of melancholia. One severely depressed patient, when asked if she had any suicide plans, replied, "Doctor, I don't exist—I am already dead."

Thus the risk of suicide is less pronounced during acute severe depression. Emil Kraepelin has observed that it is when psychomotor activity is improving, and yet mood and thinking are still dark, that the patient is most likely to muster the requisite energy to commit the suicidal act. Profound hopelessness on mental status evaluation should alert the clinician to the possibility of such an outcome.

There is no basis for the common belief that inquiring about suicide would provoke such behavior. On the contrary, the patient is often relieved that the physician is aware of the magnitude of his or her suffering. Suicidal ideation is commonly expressed indirectly, such as in a wish not to wake up. Some depressed persons are tormented with suicidal obsessions in the sense that they are constantly resisting unwanted urges or impulses to destroy themselves. Others might yield to such urges passively, as by careless driving or by walking among high-speed traffic. A third group will harbor elaborate plans, carefully preparing their will and taking out insurance. Such deliberate planning indicates a very high suicidal risk. The examples are not exhaustive, however, but are meant to remind clinicians in charge of depressed patients to be always alert to the possibility of suicide.

Vegetative disturbances The Greeks believed that depression was a somatic illness and ascribed it to black bile, and hence the term "melancholia." The mood change in depressive disorder is accompanied by measurable alterations of biorhythms that implicate limbic-diencephalic dysfunction. Once the changes occur, they tend to become autonomous of the environment throughout much of the episode, which means that they do not respond to interpersonal feedback of a pleasant and upbeat nature. The biological concomitants of melancholia include profound reductions in appetite, sleep, and sexual functioning, as well as alterations of other circadian rhythms, especially morning worsening of mood and psychomotor performances. Those disturbances are central to the DSM-IV concept of melancholia (Table 16.6-6), a form of depression in which such biological concomitants predominate. In a smaller subgroup of depressed persons, there is a reversal of the vegetative and circadian functions whereby there are increases in appetite and sleep—and sometimes in sexual functioning—along with an evening worsening of mood; in that atypical pattern (Table 16.6-7), now recognized in DSM-IV, patients often exhibit mood reactivity and sensitivity to rejection.

ANOREXIA AND WEIGHT LOSS Among the most reliable somatic indicators of depressive disorder are anorexia and weight loss. In addition to the presumed hypothalamic disturbance of depression, anorexia might be secondary to blunted olfactory or taste sensations or a decreased enjoyment of food, or, rarely, it might be due to a delusional belief that the food has been poisoned.

If weight loss is severe, especially after the age of 40, the psychiatrist should first rule out, through appropriate medical consultation, the likelihood of an occult malignancy. Inanition, especially in elderly persons, can lead to malnutrition and electrolyte disturbances, which represent medical emergencies.

TABLE 16.6-6
Criteria for Melancholic Features Specifier

Specify if:
With melancholic features (can be applied to the current or most recent major depressive episode in major depressive disorder and to a major depressive episode in bipolar I or bipolar II disorder only if it is the most recent type of mood episode)

A. Either of the following, occurring during the most severe period of the current episode:
   (1) loss of pleasure in all, or almost all, activities
   (2) lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens)
B. Three (or more) of the following:
   (1) distinct quality of depressed mood (i.e., the depressed mood is experienced as distinctly different from the kind of feeling experienced after the death of a loved one)
   (2) depression regularly worse in the morning
   (3) early morning awakening (at least two hours before usual time of awakening)
   (4) marked psychomotor retardation or agitation
   (5) significant anorexia or weight loss
   (6) excessive or inappropriate guilt

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

Alkermes, Ex. 1060

TABLE 16.6-7
Criteria for Atypical Features Specifier

Specify if:
With atypical features (can be applied when these features predominate during the most recent two weeks of a major depressive episode in major depressive disorder or in bipolar I or bipolar II disorder when the major depressive episode is the most recent type of mood episode, or when these features predominate during the most recent two years of dysthymic disorder)
A. Mood reactivity (i.e., mood brightens in response to actual or potential positive events)
B. Two (or more) of the following features:
(1) significant weight gain or increase in appetite
(2) hypersomnia
(3) leaden paralysis (i.e., heavy, leaden feelings in arms or legs)
(4) long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment
C. Criteria are not met for with melancholic features or with catatonic features during the same episode.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

WEIGHT GAIN Overeating, decreased activity, or both may result in weight gain. In middle-aged patients it may aggravate preexisting diabetes, hypertension, or coronary artery disease. In younger patients, especially women, weight problems may conform to a bulimic pattern. That is sometimes the expression of the depressive phase of a bipolar disorder with infrequent hypomanic periods (bipolar II disorder). It does not mean, however, that all bulimia nervosa is the result of a mood disorder.

INSOMNIA Sleep disturbance, a cardinal sign of depression, often becomes manifest in insomnia that is characterized by multiple awakenings, especially in the early hours of the morning, rather than by difficulty falling asleep. The light sleep of a depressed person, in part a reflection of the painful arousal of the disorder in general, tends to prolong the depressive agony over 24 hours. Thus deep stages of sleep (3 and 4) are either decreased or deficient. The attempt to overcome the problem by drinking alcohol may initially meet with success, but ultimately will lead to an aggravation of the insomnia. That also is true for sedative-hypnotic agents, which are often prescribed by the busy general practitioner who has not spent enough time in diagnosing the depressive condition. Sedatives, including alcohol, while effective in reducing the number of awakenings in the short term, are not effective in the long run because of a further diminution of stage 3 and stage 4 sleep. They are not antidepressants and tend to prolong the depression.

HYPERSOMNIA Young depressed persons, especially those with bipolar tendencies, often complain of hypersomnia, and will have difficulty getting up in the morning.

Kevin, a 15-year-old boy, was referred to a sleep center to rule out narcolepsy. His main complaints were fatigue, boredom, and a need to sleep all the time. Although he had always been somewhat slow to get going in the morning, he now could not get out of bed to go to school. That alarmed his mother, prompting the sleep consultation. Formerly a B student, he had been failing most of his courses in the six months before referral. Psychological counseling, predicated on the premise that his family's recent move from another city had led to Kevin's isolation, had not been beneficial. He had also received an extensive neurological and general medical workup, with negative results. He slept 12 to 15 hours a day, but denied cataplexy, sleep paralysis, and hypnagogic hallucinations. During the interview he denied being depressed, but admitted that he had lost interest in everything except his pet. He had no drive, participated in no activities, and had gained 30 pounds in six months. He believed he was brain damaged and wondered whether it was worth living like that. The question of committing suicide disturbed him as it was contrary to his religious beliefs. In view of the findings he was prescribed desipramine (Norpramin) in a dosage that was gradually increased to 200 mg a day over three weeks. Not only did the desipramine reverse the presenting complaints, but it pushed him to the brink of a manic episode.

The affective nature of the disorder in such patients often goes unrecognized, and their slothful behavior and tendency to slumber may be ascribed to laziness.

CIRCADIAN DYSREGULATION Many circadian functions, such as temperature regulation and cortisol rhythms, are disrupted in major depressive disorder. Disturbances of sleep rhythms, however, have received the greatest research focus. Whether suffering from insomnia or hypersomnia, nearly two thirds of patients with depressive disorder exhibit a shortening of rapid-eye-movement (REM) latency, the period from the onset of sleep to the first REM period. That abnormality is observed throughout the depressive episode and, in persons with recurrent depression, may be seen in relatively euthymic periods as well. Their occurrence in the well relatives of the affectively ill suggests that circadian abnormalities might precede the psychological manifestations of the disorder. Other REM abnormalities include longer REM periods and increased density of eye movements in the first third of the night.

There are little data on the consistency of sleep electroencephalogram (EEG) abnormalities in patients examined from episode to episode. However, clinical experience suggests that the same patient observed over time (even during the same episode) may exhibit insomnia and morning worsening of mood and activity at one period of the disorder and hypersomnia extending to late morning hours at another period. In either case persons with depressive disorder are characteristically tired in the morning, which means that even prolonged sleep is not refreshing for them. The propensity to exhibit such divergent patterns of sleep disturbance is more likely in bipolar illness. Patients with major depressive disorder tend to exhibit insomnia in a more stereotypical fashion, episode after episode; despite extreme fatigue, even with thymoleptic medication, they rarely oversleep. Such fatigue coexisting with negative affective arousal is exhausting.

SEASONALITY Another biorhythmic disturbance in mood disorders is seasonal (especially autumn-winter) accentuation or precipitation of depression; many, if not most, of those patients experience hypomania in the spring and thus should be classified as having bipolar II disorder. In the fall and winter the patients complain of fatigue, tend to crave sugars, and overeat and oversleep. The hypersomnia in some of those patients is associated with delayed (rather than short) REM latencies. Such data suggest that circadian abnormalities in depressive disorders are characterized by dysregulation rather than by mere phase advance. The DSM-IV criteria for seasonal pattern specifier are listed in Table 16.6-8.

SEXUAL DYSFUNCTION Decreased sexual desire is seen in both depressed men and women. In addition, some women experience a temporary interruption of their menses. Depressed women are typically unresponsive to lovemaking or are disinclined to participate in it, a situation that could lead to marital conflict; psychotherapists may mistakenly ascribe the depression to the marital conflict, resulting in unnecessarily zealous psychotherapeutic attention to conjugal issues. A decrease in or loss of libido in men often results in erectile failure, which may prompt endocrinological or urological consultation. Again, depression may be ascribed to the sexual dysfunction rather than the reverse, and definitive treatment may be delayed due to the physician's focus on the sexual complaint. Some men with depressive disorder have even been subjected to permanent

penile implants before having received a more definitive treatment for their depression.

Among a small subgroup of persons with depressive disorder, there may be increased sexual drive of a compulsive nature. Such patients tend to have other atypical features as well, and hence the symptom of increased sexual drive can be considered the fifth reverse vegetative sign in those patients (after evening or morning worsening of mood, initial insomnia, hypersomnia, and weight gain). In other depressed persons, increased sexual drive may indicate a mixed episode in bipolar disorder.

MANIC SYNDROME As with clinical depression, the psychopathology of mania can be conveniently discussed under mood, psychomotor, circadian, and cognitive disturbances. The clinical features of mania are generally the opposite of those of depression. Thus instead of lowered mood, thinking, activity, and self-esteem, there is elevated mood, a rush of ideas, psychomotor acceleration, and grandiosity. Despite those contrasts the two disorders also share such symptoms as irritability, anger, insomnia, and agitation; an excess of such symptoms suggests a mixed phase or mixed state of mania and depression occurring simultaneously. Manic and mixed manic episodes represent the hallmark of what was once termed manic-depressive psychosis and currently are recognized as bipolar I disorder.

Although milder degrees of mania (hypomania) can contribute to success in business, leadership roles, and the arts, recurrences of even mild manic symptomatology could be disruptive. The elated mood tends to produce overoptimism concerning abilities, and coupled with the impulsivity characteristic of mania, could lead to disaster. Thus accurate and early diagnosis is paramount.

Classic mania—as formulated in the DSM-IV operationalization of manic episode (Table 16.6-9)—is relatively easy to recognize. However, misdiagnosis is still common in North American practice, with clinicians' confusing severe mania with schizophrenia and its milder variants with normality or with narcissistic or sociopathic disorders. As with the misdiagnosis of depressive disorder, such errors in clinical judgment are often attributable to a lack of familiarity with the phenomenology of the classic illness. Again, DSM-IV criteria provide only a guideline. The actual diagnosis requires empathic understanding. The manic patient lifts the observer's mood, makes the person smile and even laugh, and can be irritating as well. The patient's speech is fast, and may even appear loose, but it also can be witty. Finally, the behavior is often dramatic, expansive, and jesting. The overall gestalt experienced in the presence of such patients is emotionally and qualitatively distinct from that of persons with schizophrenia. Those considerations become clearer when clinicians familiarize themselves with the psychopathology of mania in the area of mood, behavior, and thinking.

TABLE 16.6-8
Criteria for Seasonal Pattern Specifier

Specify if:
With seasonal pattern (can be applied to the pattern of major depressive episodes in bipolar I disorder, bipolar II disorder, or major depressive disorder, recurrent)

A. There has been a regular temporal relationship between the onset of major depressive episodes in bipolar I or bipolar II disorder or major depressive disorder, recurrent, and a particular time of the year (e.g., regular appearance of the major depressive episode in the fall or winter).
Note: Do not include cases in which there is an obvious effect of seasonal-related psychosocial stressors (e.g., regularly being unemployed every winter).
B. Full remissions (or a change from depression to mania or hypomania) also occur at a characteristic time of the year (e.g., depression disappears in the spring).
C. In the last two years, two major depressive episodes have occurred that demonstrate the temporal seasonal relationships defined in criteria A and B, and no nonseasonal major depressive episodes have occurred during that same period.
D. Seasonal major depressive episodes (as described above) substantially outnumber the nonseasonal major depressive episodes that may have occurred over the person's lifetime.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-9
Criteria for Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week (or any duration if hospitalization is necessary).
B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
(1) inflated self-esteem or grandiosity
(2) decreased need for sleep (e.g., feels rested after only three hours of sleep)
(3) more talkative than usual or pressure to keep talking
(4) flight of ideas or subjective experience that thoughts are racing
(5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
(6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
C. The symptoms do not meet criteria for a mixed episode.
D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).
Note: Maniclike episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar I disorder.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

Mood elevation The mood in mania is classically one of elation, euphoria, and jubilation, typically associated with laughing, punning, and gesturing.

Mood lability and irritability The prevailing positive mood in mania is not stable, and momentary tearfulness is common. Also, for many patients the high is so excessive that it is actually dysphoric. When opposed, the patient can become extremely irritable and hostile. Thus lability and irritable hostility are as much features of the manic mood as are the elated mood.

Psychomotor acceleration Accelerated psychomotor activity, the hallmark of mania, is characterized by an overabundance of energy and activity and by rapid and pressured speech. Subjectively, the patient experiences an unusual sense of physical well-being (eutonia).

FLIGHT OF IDEAS Thinking processes are accelerated, experienced as flight of ideas, and thinking and perception are unusually sharp. The patient may speak with such pressure that it is difficult to follow the associations; such clang associations are often based on rhyming or chance perceptions, and could flow with lightning rapidity. The pressure to speak may continue despite the development of hoarseness.

Alkermes, Ex. 1060

IMPULSIVE BEHAVIOR Manic patients are typically impulsive, disinhibited, and meddlesome. They are intrusive in their increased involvement with other persons, leading to friction with family members, friends, and colleagues. They are distractible and move quickly, not only from one thought to another, but from one person to another, showing heightened interest in every new activity that strikes their fancy. They are indefatigable and engage in various activities in which they usually display poor social judgment. Examples include preaching or dancing in the street; abuse of long distance calling; buying new cars, hundreds of records, expensive jewelry, or other unnecessary items; impulsive marriages; engaging in risky business ventures; gambling; and sudden aimless trips. Such pursuits can lead to personal and financial ruin.

DELIRIOUS MANIA An extremely severe expression of mania (also known as Bell's mania), delirious mania involves frenzied physical activity that continues unabated, leading to a medical emergency that is life threatening; that complication, the manic counterpart of stupor, is rare, however. (There is no need to invoke here the concept of catatonic features [Table 16.6-10], as advocated by DSM-IV. The DSM-IV position is terminologically confusing and phenomenologically imprecise.)

Vegetative disturbances Such disturbances are more difficult to evaluate in mania as compared with depression.

HYPOSOMNIA The cardinal sign is decreased need for sleep—the patient sleeps for only few hours but feels energetic on awakening. Some patients may actually go sleepless for several days. That practice could lead to a dangerous escalation of manic activity, which might continue despite signs of physical exhaustion.

INATTENTION TO NUTRITION There does not seem to be a clinically significant level of appetite disturbance as such, but weight loss may occur because of increased activity and neglect of nutritional needs.

SEXUAL EXCESSES The sexual appetite is typically increased and may lead to sexual indiscretion. Married women with previously unblemished sexual lives may associate with men below their social status. Men typically overindulge in alcohol, frequenting bars and visiting prostitutes on whom they squander their savings. The sexual misadventures of manic patients result in marital disasters, and hence the multiple separations or divorces that are almost pathognomonic of the disorder. Such sexual impulsivity is even more problematic now, in view of the AIDS epidemic.

TABLE 16.6-10
Criteria for Catatonic Features Specifier

Specify if:
With catatonic features (can be applied to the current or most recent major depressive episode, manic episode, or mixed episode in major depressive disorder, bipolar I disorder, or bipolar II disorder)
The clinical picture is dominated by at least two of the following:
(1) motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor
(2) excessive motor activity (that is apparently purposeless and not influenced by external stimuli)
(3) extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism
(4) peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing
(5) echolalia or echopraxia

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

Cognitive distortions Manic thinking is overly positive, optimistic, and expansive.

GRANDIOSITY, LACK OF INSIGHT, AND DELUSION FORMATION The patient presents an inflated self-esteem and a grandiose sense of confidence and achievements. Behind that façade, however, there may be a vague and painful recognition that the positive self-concepts do not represent reality. However, such insight, if present at all, is transient, and manic patients are notoriously refractory to self-examination and insight. Denial and lack of insight, cardinal psychological derangements of mania, are not listed in the DSM-IV criteria for manic episode or bipolar disorders. It is because of their lack of insight that manic patients engage in activities that harm them and their loved ones. It also explains, in part, their noncompliance with medication regimens during the manic phase. Finally, because of their lack of insight, manic experiences can easily acquire delusional proportions. Those include delusions of exceptional mental and physical fitness and exceptional talent; delusions of wealth, aristocratic ancestry, or other grandiose identity; delusions of assistance (that is, well-placed persons or supernatural powers are assisting in their endeavors); or delusions of reference and persecution, based on the belief that enemies are observing or following them out of jealousy at their special abilities. At the height of mania patients may even see visions or hear voices congruent with their euphoric mood and grandiose self-image; for instance, they might see images of heaven or hear cherubs chanting songs to praise them. (The denial characteristic of mania—and the frequently psychotic nature of episodes—means that clinicians must routinely obtain diagnostic information about past episodes from significant others.)

MOOD-INCONGRUENT MANIC PSYCHOSIS Psychosis in the setting of mania is typically mood congruent. The sense of physical well-being and mental alacrity is so extraordinary that it is understandable why manic persons believe that they possess superior powers or perhaps are great scientists or famous reformers. Moreover, their senses are so vivid that reality appears richer and more exotic, and can be easily transformed into a vision; likewise, their thoughts are so rapid and vibrant that they feel they can hear them. Thus certain first-rank Schneiderian-type symptoms, which have been traditionally considered mood incongruent, can be understood phenomenologically to arise from the powerful mental experiences of mania.

Mr. Z., a 37-year-old engineer, had experienced three manic episodes for which he had been hospitalized; all three episodes were preceded by several weeks of moderate psychomotor retardation. Although each time he had responded to lithium (Eskalith, Lithobid), once outside the hospital, he had been reluctant to take it and eventually refused to do so. Now that he was euthymic, following his third and most disruptive episode during which he had badly beaten his wife, he said that he could better explain how he felt when manic. Mania, he felt, was "like God implanted in him," so he could serve as "testimony to man's communication with God." He elaborated as follows: "Ordinary mortals will never, never understand the supreme manic state which I'm privileged to experience every few years. It is so vivid, so intense, so compelling. When I feel that way, there can be no other explanation: To be manic is, ultimately, to be God. God himself must be supermanic: I can feel it, when mania enters through my left brain like laser beams, transforming my sluggish thoughts, recharging them, galvanizing them. My thoughts acquire such momentum, they rush out of my head, to explain the true nature of mania to psychiatrists and all others concerned. That's why I will never accept lithium—to do so is to obstruct the divinity in me." Although he was on the brink of divorce, he would not yield to his wife's plea to go back on lithium.

Alkermes, Ex. 1060

The vignette illustrates the possibility that even some of the most psychotic experiences in mania represent explanatory delusions, the patient's attempt to make sense of the mania. The DSM-IV criteria for severity-psychotic-remission specifiers for manic episode (Table 16.6-11) are more concerned with operational rigor than phenomenological sophistication needed to understand such core manic experiences. (Some manic patients abuse alcohol and stimulants in order to enhance their mental state and, therefore, mood-incongruence can sometimes be explained on that basis.)

Mania versus hypomania Nonpsychotic and nondisruptive variants of mania are much more common and are recognized by DSM-IV as hypomanic episodes (Table 16.6-12). Diagnostically, it is important to obtain information from others who have observed the patient: the experience is often pleasant and the subject may either be unaware of it or tend to deny it. Although DSM-IV states that treatment-emergent hypomania does not count towards a diagnosis of bipolarity, prospective observations have shown that all such episodes are followed eventually by spontanious hypomania.

DIAGNOSIS AND CLINICAL SUBTYPES

The classification of mood disorders in DSM-IV subsumes a large variety of patients seen in private and public, ambulatory, and inpatient settings. The main demarcation in that large clinical terrain is that between bipolar and depressive (unipolar) disorders. Thus bipolar disorder ranges from the classic manic and depressive episodes of psychotic intensity (bipolar I) through recurrent major depressive episodes, hypomanic episodes (bipolar II disorder), and cyclothymic mood swings. Likewise, depressive disorders include those with psychotic severity, melancholia, atypical features, and dysthymic variants.

The distinction between major and specific attenuated subtypes depends on the disorder's depth and duration. In dysthymic disorder and cyclothymic disorder a partial mood syndrome—consisting of subdepressive features in the former and subdepressive and hypomanic features in the latter—is maintained, either intermittently or continuously, for at least two years. The onset is typically in adolescence or childhood, and most persons with those attenuated diagnoses seen in young adulthood have had low-grade mood symptoms for 5 to 10 years. Major mood disorders, which on the average begin much later in life, require the presence of either a full manic episode or a full depressive episode—sustained for at least one or two weeks, respectively—and an episodic course, typically permitting recovery or remission from episodes. DSM-IV recognizes that nearly 20 percent of persons with major depressive disorders fail to achieve full symptomatic recovery and, therefore, should be qualified as chronic (Table 16.6-13) or in partial remission (Table 16.6-15). They will no longer be considered dysthymic, as was the misleading convention in the DSM-III.

DICHOTOMY OR CONTINUUM? Although, in the extreme, bipolar and depressive (unipolar) disorders are discriminable clinically and therapeutically (Table 16.6-14), clinical observations testify to a vast area of overlap between those extremes.

TABLE 16.6-11
Criteria for Severity/Psychotic/Remission Specifiers for Current (or Most Recent) Manic Episode

Note: Code in fifth digit. Can be applied to a manic episode in bipolar I disorder only if it is the most recent type of mood episode.
Mild: Minimum symptom criteria are met for a manic episode.
Moderate: Extreme increase in activity or impairment in judgment.
Severe without psychotic features: Almost continual supervision required to prevent physical harm to self or others.
Severe with psychotic features: Delusions or hallucinations. If possible, specify whether the psychotic features are mood-congruent or mood-incongruent:
- **Mood-congruent psychotic features:** Delusions or hallucinations whose content is entirely consistent with the typical manic themes of inflated worth, power, knowledge, identity, or special relationship to a deity or famous person.
- **Mood-incongruent psychotic features:** Delusions or hallucinations whose content does not involve typical manic themes of inflated worth, power, knowledge, identity, or special relationship to a deity or famous person. Included are such symptoms as persecutory delusions (not directly related to grandiose ideas or themes), thought insertion, and delusions of being controlled.

In partial remission: Symptoms of a manic episode are present but full criteria are not met, or there is a period without any significant symptoms of a manic episode lasting less than two months following the end of the manic episode.
In full remission: During the past two months no significant signs or symptoms of the disturbance were present.
Unspecified.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-12
Criteria for Hypomanic Episode

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least four days, that is clearly different from the usual nondepressed mood.
B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
   (1) inflated self-esteem or grandiosity
   (2) decreased need for sleep (e.g., feels rested after only three hours of sleep)
   (3) more talkative than usual or pressure to keep talking
   (4) flight of ideas or subjective experience that thoughts are racing
   (5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
   (6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
   (7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.
D. The disturbance in mood and the change in functioning are observable by others.
E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.
F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Hypomaniclike episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar II disorder.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-13
Criteria for Chronic Specifier

Specify if:
Chronic (can be applied to the current or most recent major depressive episode in major depressive disorder and to a major depressive episode in bipolar I or II disorder only if it is the most recent type of mood episode)
Full criteria for a major depressive episode have been met continuously for at least the past two years.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

Alkermes, Ex. 1060

TABLE 16.6-14
Differentiating Characteristics of Bipolar and Unipolar Depressions

	Bipolar	Unipolar
History of mania or hypomania (definitional)	Yes	No
Temperament—personality	Cyclothymic—extroverted	Dysthymic—introverted
Sex ratio	Equal	More women than men
Age of onset	Teens, 20s, and 30s	30s, 40s, 50s
Postpartum episodes	More common	Less common
Onset of episode	Often abrupt	More insidious
Number of episodes	Numerous	Fewer
Duration of episode	Three to six months	Three to twelve months
Psychomotor activity	Retardation > agitation	Agitation > retardation
Sleep	Hypersomnia > insomnia	Insomnia > hypersomnia
Family history		
Bipolar	Yes	±
Unipolar	Yes	Yes
Alcoholism	±	Yes
Pharmacological response		
Cyclic antidepressants	Induce hypomania-mania	±
Lithium carbonate	Acute antidepressant effects	Ineffective

TABLE 16.6-15
Course Specifiers That Apply to Mood Disorders

	With/ Without Interepisode Recovery	Seasonal Pattern	Rapid Cycling
Major depressive disorder, single episode			
Major depressive disorder, recurrent	X	X	
Dysthymic disorder			
Bipolar I disorder, single manic episode			
Bipolar I disorder, most recent episode hypomanic	X	X	X
Bipolar I disorder, most recent episode manic	X	X	X
Bipolar I disorder, most recent episode mixed	X	X	X
Bipolar I disorder, most recent episode depressed	X	X	X
Bipolar I disorder, most recent episode unspecified	X	X	X
Bipolar II disorder, hypomanic	X	X	X
Bipolar II disorder, depressed	X	X	X
Cyclothymic disorder			

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-16
Criteria for Longitudinal Course Specifiers

Specify if (can be applied to recurrent major depressive disorder or bipolar I or II disorder):

With full interepisode recovery: if full remission is attained between the two most recent mood episodes

Without full interepisode recovery: if full remission is not attained between the two most recent mood episodes

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

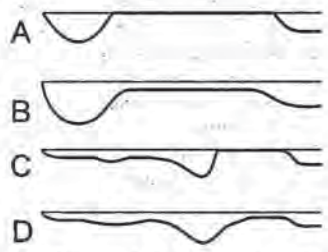

FIGURE 16.6-1 *The four graphs depict prototypical courses.* (A) *The course of major depressive disorder, recurrent, in which there is no antecedent dysthymic disorder and there is a period of full remission between the episodes. That pattern predicts the best future prognosis.* (B) *The course of major depressive disorder, recurrent, in which there is no antecedent dysthymic disorder but in which prominent symptoms persist between the two most recent episodes—that is, no more than partial remission is attained.* (C) *shows the rare pattern (present in fewer than 3 percent of persons with major depressive disorder) of major depressive disorder, recurrent, with antecedent dysthymic disorder but with full interepisode recovery between the two most recent episodes.* (D) *The course of major depressive disorder, recurrent, in which there is antecedent dysthymic disorder and in which there is no period of full remission between the two most recent episodes. This pattern, commonly referred to as double depression, is seen in about 20–25 percent of persons with major depressive disorder. (Figure from DSM-IV,* Diagnostic and Statistical Manual of Mental Disorders, *ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.)*

Thus the distinctions between the various affective subtypes are not as hard and fast as DSM-IV attempts to portray. For instance, full-blown bipolar disorder can be superimposed on cyclothymic disorder which tends to persist after the resolution of manic or major depressive episodes. Even more common is major depressive disorder complicating cyclothymic disorder. Likewise, recent evidence indicates that dysthymic disorder may precede major depressive disorder in as many as a third of cases. Moreover, one of four persons with major depressive disorder subsequently develop hypomanic or manic episodes and so should be reclassified as having bipolar disorder. Finally, unexpected crossing from dysthymic disorder to manic episodes has also been described, suggesting that some forms of dysthymic disorder are subaffective precursors of bipolar disorder. Such observations are in line with Kraepelin's historic attempt to bring all mood disorders under one rubric.

Undoubtedly, heterogeneity exists in the realm of mood disorders. What the foregoing observations suggest, however, is that a large chunk of the unipolar terrain might be pseudo-unipolar—to wit, soft bipolar. The clinical significance of those considerations lies in the fact that many of the DSM-IV subtypes of mood disorders are not pure entities, and that considerable overlap and switches in polarity take place. They also provide some rationale, for instance, as to why lithium (or lith-

Alkermes, Ex. 1060

ium augmentation) may be effective in some apparently unipolar depressions; such patients do not experience spontaneous hypomanic episodes, but instead often exhibit a high baseline level of hyperthymia. Finally, there seems to be an emerging consensus that persons with bipolar disorders whose premorbid adjustment and interepisodic adjustment are cyclothymic are at risk for antidepressant-induced rapid cycling, defined as a rapid succession of major episodes with few or no intervals of freedom. Those considerations further testify to the wisdom of supplementing major mood diagnoses with temperamental attributes. DSM-IV makes subtle or oblique hints concerning that.

The course specifiers that apply to DSM-IV mood disorders are listed in Table 16.6-15. The DSM-IV criteria for longitudinal course specifiers are presented in Table 16.6-16. Four prototypical courses of depressive disorders are shown in Figure 16.6-1. Those course specifiers and patterns do not represent an exhaustive list.

DEPRESSIVE DISORDERS

The broad category of depressive disorders includes major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified (NOS) (Table 16.6-17).

MAJOR DEPRESSIVE DISORDER Episodes usually begin over a prodromal period of weeks to months. The DSM-IV diagnosis of major depressive disorder requires (1) dysphoric mood or decreased interest in usual activities and (2) at least four additional classic depressive signs and symptoms, (3) which must be sustained for at least two weeks, and (4) cannot be explained by a process known to cause depressive symptoms, such as normal bereavement or certain physical conditions commonly associated with depression.

Nature of comorbid physical disease Those considerations raise the question of whether major depressive disorder should be limited to depressions of unknown etiology (for example, those without documented physical causes). The DSM-IV approach has basically taken the position that whenever the etiology is known, the condition should be diagnosed as mood disorder due to a general medical condition, which must be specified (Table 16.6-18) or substance-induced mood disorder (Table 16.6-19). The problem with that approach lies in the fact that many common medical factors associated with depression—for example, use of reserpine—do not seem to be causative in the etiological sense but rather are triggering agents in otherwise predisposed persons. That is analogous to the situation with life events, which no longer are used in making distinctions between subtypes of depression. A more troubling implication is that major depressive disorders without demonstrable physical disease are not medical or otherwise biological. There appears to be no reliable or valid way in which a clinician can decide that a depressive condition is due to a specified medical condition. For that reason it is generally more practical to diagnose the depressive disorder on Axis I and to specify the contributing physical condition on Axis III. In brief, the designation "due to a general medical condition" is both cumbersome and redundant. It is the author's position that major depressive disorder represents a syndrome which is the final common pathway of multifactorial interacting factors, and should be diagnosed irrespective of presumed etiology.

Diagnostic threshold Another question concerning the DSM-IV definition of major depressive disorders relates to the threshold at which a constellation of depressive features can be said to constitute a condition distinct from the ordinary blues. According to the current definition it is sufficient for a person to experience, in response to a setback, a lowering of the spirits, self-doubt, difficulty in sleeping and concentration, and

TABLE 16.6-17
Diagnostic Criteria for Depressive Disorder Not Otherwise Specified

The depressive disorder not otherwise specified category includes disorders with depressive features that do not meet the criteria for major depressive disorder, dysthymic disorder, adjustment disorder with depressed mood, or adjustment disorder with mixed anxiety and depressed mood. Sometimes depressive symptoms can present as part of an anxiety disorder not otherwise specified. Examples of depressive disorder not otherwise specified include

1. Premenstrual dysphoric disorder: in most menstrual cycles during the past year, symptoms (e.g., markedly depressed mood, marked anxiety, marked affective lability, decreased interest in activities) regularly occurred during the last week of the luteal phase (and remitted within a few days of the onset of menses). These symptoms must be severe enough to markedly interfere with work, school, or usual activities and be entirely absent for at least one week postmenses.
2. Minor depressive disorder: episodes of at least two weeks of depressive symptoms but with fewer than the five items required for major depressive disorder.
3. Recurrent brief depressive disorder: depressive episodes lasting from two days up to two weeks, occurring at least once a month for 12 months (not associated with the menstrual cycle).
4. Postpsychotic depressive disorder of schizophrenia: a major depressive episode that occurs during the residual phase of schizophrenia.
5. A major depressive episode superimposed on delusional disorder, psychotic disorder not otherwise specified, or the active phase of schizophrenia.
6. Situations in which the clinician has concluded that a depressive disorder is present but is unable to determine whether it is primary, due to a general medical condition, or substance induced.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-18
Diagnostic Criteria for Mood Disorder Due to a General Medical Condition

A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either (or both) of the following:
   (1) depressed mood or markedly diminished interest or pleasure in all, or almost all, activities
   (2) elevated, expansive, or irritable mood
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.
C. The disturbance is not better accounted for by another mental disorder (e.g., adjustment disorder with depressed mood in response to the stress of having a general medical condition).
D. The disturbance does not occur exclusively during the course of a delirium.
E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify type:
With depressive features: if the predominant mood is depressed but the full criteria are not met for a major depressive episode
With major depressivelike episode: if the full criteria are met (except criterion D) for a major depressive episode
With manic features: if the predominant mood is elevated, euphoric, or irritable
With mixed features: if the symptoms of both mania and depression are present but neither predominates
Coding note: Include the name of the general medical condition on axis I, e.g., mood disorder due to hypothyroidism, with depressive features; also code the general medical condition on axis III.
Coding note: If depressive symptoms occur as part of a preexisting dementia, indicate the depressive symptoms by coding the appropriate subtype of the dementia if one is available, e.g., dementia of the Alzheimer's type, with late onset, with depressed mood.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

Alkermes, Ex. 1060

TABLE 16.6-19
Diagnostic Criteria for Substance-Induced Mood Disorder

A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either (or both) of the following:
   (1) depressed mood or markedly diminished interest or pleasure in all, or almost all, activities
   (2) elevated, expansive, or irritable mood
B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):
   (1) the symptoms in criterion A developed during, or within a month of, substance intoxication or withdrawal
   (2) medication use is etiologically related to the disturbance
C. The disturbance is not better accounted for by a mood disorder that is not substance induced. Evidence that the symptoms are better accounted for by a mood disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent non-substance-induced mood disorder (e.g., a history of recurrent major depressive episodes).
D. The disturbance does not occur exclusively during the course of a delirium.
E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the mood symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

Code [Specific Substance]-Induced Mood Disorder:
(alcohol; amphetamine [or amphetaminelike substance]; cocaine; hallucinogen; inhalant; opioid; phencyclidine [or phencyclidinelike substance]; sedative, hypnotic, or anxiolytic; other [or unknown] substance)

Specify type:
With depressive features: if the predominant mood is depressed
With manic features: if the predominant mood is elevated, euphoric, or irritable
With mixed features: if symptoms of both mania and depression are present and neither predominates

Specify if:
With onset during intoxication: if the criteria are met for intoxication with the substance and the symptoms develop during the intoxication syndrome
With onset during withdrawal: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, a withdrawal syndrome

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

decreased sexual interest for 14 days to qualify for a diagnosis of a major depressive disorder of mild intensity. Some authorities would consider such a condition to represent instead a minor depression, probably no more than an adjustment disorder. It would appear that criteria other than signs and symptoms and duration would be necessary to differentiate a depressive disorder from adjustment reactions to life situations. The presence of the following characteristics might assist in such a differentiation.

1. By definition a major depressive disorder should be incapacitating. Previously, much attention had been paid to the interpersonal consequences of depression. Recent evidence indicates that measurable deficits in work performance are often early manifestations. Afflicted persons are also unable to benefit from taking leisure time, and hence the futility of prescribing vacations.

2. Depressive disorder is usually perceived as a break from a person's usual or premorbid self, which can be so striking that the sufferer may feel as though he or she is losing his or her mind. The important point is that both the patient and significant others can usually relate the onset of the illness to a given month or quarter of a year, which is not true, for instance, for dysthymic disorder.

3. Depressive disorder is often experienced by the sufferer as qualitatively distinct from grief or other understandable reactions to loss or adversity. William James described it as follows:

> There is a pitch of unhappiness so great that the goods of nature may be entirely forgotten, and all sentiment of their existence vanish from the mental field. For this extremity of passion to be reached, something more is needed than [adversity] . . . the individual must in his own person become the prey of pathological melancholy . . . such sensitiveness and susceptibility of mental pain is a rare occurrence where the nervous constitution is entirely normal: one seldom finds it in a healthy subject even where he is the victim of the most atrocious cruelties of outward fortune . . . it is an . . . active anguish, a sort of psychical neuroglia wholly unknown to healthy life.

Two additional features, when present, would further validate the diagnosis of major depressive disorder.

4. Recurrence—especially periodicity or regular seasonal occurrence.

5. Consecutive-generation family history of mood disorder—especially when a large number of family members are afflicted with depression or mood disorder—is characteristic of clinical depression. For instance, in one study in which minor or neurotic depressive persons were prospectively followed, it was found that such pedigrees predicted the development of major episodes. DSM-IV makes no provision for considering such familial factors in diagnostic decisions. In clinical practice those factors often do influence diagnostic decisions.

Single episode and recurrent subtypes About a third of all major depressive episodes do not recur. Such patients tend to be older, they are less likely to have a positive family history for mood disorders, and the course of the disorder is more protracted (one to two years). Patients with major depressive disorder, single episode (Table 16.6-3), should be distinguished from those experiencing their first episodes of major depressive disorder, recurrent (Table 16.6-4). The latter group tends to be younger, and the disorder is more likely to have been preceded by a depressive temperament or dysthymic disorder.

Research has also established that recurrent major depressive disorders are more familial than are their single-episode counterparts. The average length of episodes is six months, whereas the mean interval between episodes tends to vary (typically years). The mean number of major episodes over a lifetime, according to retrospective and prospective studies, is five to six, as contrasted with an average number of eight to nine major episodes in bipolar disorder.

Melancholic features In DSM-III the neurotic-endogenous distinction was deleted. Neurotic depression was absorbed by dysthymic disorder and the major depressive disorders that complicate it; endogenous depression became melancholic features, a qualifying phrase for those major depressive disorders in which anhedonia, guilt, and psychomotor-vegetative disturbances dominate the clinical picture (Table 16.6-6). DSM-IV has retained those conventions.

Although the foregoing conventions have received much criticism, they are based on solid data from independent studies in the United States and Germany. Thus neurotic depression, defined as a reactive (that is, precipitated) nonpsychotic depression of mild to moderate intensity with predominant anxiety and characterologic pathology, does not seem to constitute a distinct nosological entity. Although such a presentation is com-

TABLE 16.6-20
Three- to Four-Year Prospective Follow-up in Neurotic Depressions ($N = 100$)

Diagnosis and Outcome	N*
Manic episode	4
Hypomanic episode	14
Psychotic depression	21
Endogenous depression	36
Episodic course	42
Unstable characterological features	24
Social invalidism	35
Suicide	3

*The total exceeds 100 because more than one outcome was possible in each patient.

Table from H Akiskal, A Bitar, V Puzantian, T Rosenthal, P Walker. The nosological status of neurotic depression: A prospective 3-to-4 year examination in light of the primary-secondary and unipolar-bipolar dichotomies. Arch Gen Psychiatry *35:* 756, 1978. Used with permission.

mon in clinical practice, the prospective follow-up course of those patients is heterogeneous (Table 16.6-20). The progression of a precipitated, relatively mild depression (reactive illness) to severe psychotic depression—or one with a melancholic autonomy—during prospective observation suggested that so-called endogenous depressions may have their onset in milder depressions, that neurotic and psychotic depressions do not necessarily refer to distinct disorders but to disorders that differ in severity, and that the presence of precipitating stress carries little diagnostic weight in differentiating subtypes of depression (although the absence of such stress might be used to support a melancholic level of major depressive disorder).

At the heart of the concept of morbid depression is its autonomy from stresses that may have precipitated it and its general unresponsiveness to other environmental input. That is embodied in Donald Klein's concept of endogenomorphic depression, which could be precipitated and mild (endoreactive, as discussed earlier) while exhibiting disturbances of hedonic mechanisms refractory to current interpersonal contexts. Many authorities believe that autonomy dictates the need to use somatic approaches to reverse the maladaptive autonomy and restore response to interpersonal feedback; that is, psychotherapeutic approaches are deemed largely ineffective until the autonomy is somatically lysed.

Given the somatic connotation of the ancient concept of melancholia, the (APA) classification has officially adopted it as the preferred nosological term for the revised concept of endogeneity, and hence the prominence of the vegetative and biorhythmic features accorded to it in both DSM-III and DSM-IV. However, the APA diagnostic schema risks confusing endogeneity with another classic concept of mood disorder, that of involutional melancholia.

Psychotic features About 15 percent of major depressive disorders, usually those with melancholic features, develop into delusional depressions. In young persons they tend to be retarded, even stuporous, and are best considered as initial episodes of bipolar disorder. When psychotic depression develops for the first time after the age of 50, it often presents with severe agitation, delusional guilt, hypochondriacal preoccupations, early-morning awakening, and weight loss. The premorbid adjustment of those patients has classically been characterized as obsessoid. Their mournful-anxious mood and agitation are autonomous, being refractory to psychological interventions, and they endure great suffering. Except for the fact that the frequency of episodes is generally in the range of one to two in late-onset (so-called involutional) depressions, they represent the closest approximation to the DSM-IV melancholia. In view of Kraepelin's postulation of a cerebral basis for such cases, it is of interest that ventricular enlargement and white matter opacities have been reported in psychotic depressions. Their etiological specificity for persons with late-onset psychotic depression has been controversial, however, given similar findings in younger (more bipolar) persons with psychotic depression. Brain imaging findings tend to be correlated with the neurocognitive deficits observed in psychotic depressions. Those features do not seem to define a distinct depressive subtype, but one of greater severity. Finally, despite attempts to suggest a neurochemical uniqueness, based largely on the need for antipsychotic treatment in the acute phase of many of those patients, familial and other external validators have failed to support psychotic depression as a separate entity, and hence the decision in DSM-IV to use psychotic features merely as a specifier for major depressive episode (Table 16.6-5). Emerging data, nonetheless, might eventually force a change in this convention. For instance, William Coryell and collaborators in the National Institute of Mental Health (NIMH) collaborative study of depression have shown psychotic depression to be the most consistent unipolar subtype across episodes.

Chronic depression The symptom profile in chronic depressions is usually one of low-grade intensity rather than one of severe syndromal chronicity. Severe depressive disorder in its psychotic forms is so agonizing that the sufferer is at risk of committing suicide before the disorder has a chance to become chronic. More commonly, the psychotic symptoms respond to medication or to electroconvulsive therapy (ECT), but residual depressive symptoms may linger for a long time. In other persons with chronic depressions the chronicity arises from more mundane (nonpsychotic) major depressive episodes, depressive residua following one or several clinical episodes that fail to remit fully. Thus instead of the customary remission within a year, the patients are ill for years. The level of depression varies, fluctuating between syndromal illness and milder symptoms. The patients often show a sense of resignation, a generalized fear of an inability to cope, adherence to rigid routines, and inhibited communication.

Rather than exhibiting a frankly depressive mood, many persons with chronic depression suffer from deficits in their ability to enjoy leisure and display an attitude of irritable moroseness. Those leisure deficits and the irritable humor tend to affect their conjugal lives: their marriages are typically in a state of chronic deadlock, leading neither to divorce nor to reconciliation. In other patients the residual phase is dominated by somatic features, such as sleep and other vegetative or autonomic irregularities. Thus self-treatment with ethanol or iatrogenic benzodiazepine dependence is commonly observed. That those interpersonal, conjugal, and autonomic manifestations represent unresolved depression is shown by persistent sleep EEG—especially REM and delta phase—abnormalities that are indistinguishable from their acute counterparts.

Failure to recover from major depressive disorder is associated with increased familial loading for depression, disabled spouses, deaths of immediate family members, concurrent disabling medical disease, use of depressant antihypertensive agents, and excessive use of alcohol and sedative-hypnotic agents. Social support is often eroded in persons with residual depression, through either the death or the illness of significant others. Therefore, a thorough medical evaluation and socially supportive interventions should be essential ingredients of the overall approach to those patients.

Interpersonal disturbances in such patients are usually secondary to the distortions produced by long-standing depression.

Alkermes, Ex. 1060

Therefore, observed pathological characterological changes—clinging or hostile dependence, demandingness, touchiness, pessimism, and low self-esteem—are best considered as constituting postdepressive personality changes. There exists a dangerous stereotypical thinking that because a patient has not responded adequately to standard treatments (the illness has become chronic), there must be a characterological substrate to the disorder. The long duration of the disorder often leads to the patient's identification with the failing functions of depression, producing the self-image of being a depressed person. Such a self-image itself represents a malignant cognitive manifestation of the depressive disorder and dictates vigorous treatment targeted at the mood disorder.

The DSM-IV criteria for chronic specifier appear in Table 16.6-14.

DYSTHYMIC DISORDER Dysthymic disorder (Table 16.6-21) is distinguished from depressive disorder by the fact that it is not a sequel to well-defined major depressive episodes. Instead, in the most typical cases, patients complain that they have always been depressed. Thus most cases are of early onset, beginning in childhood or adolescence, and certainly by the time the persons reach their 20s. A late-onset subtype is much less prevalent and has not been well characterized clinically, but has been identified largely through epidemiological studies in the community among middle-aged and geriatric populations.

TABLE 16.6-21
Diagnostic Criteria for Dysthymic Disorder

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least two years. **Note:** In children and adolescents, mood can be irritable and duration must be at least one year.
B. Presence, while depressed, of two (or more) of the following:
   (1) poor appetite or overeating
   (2) insomnia or hypersomnia
   (3) low energy or fatigue
   (4) low self-esteem
   (5) poor concentration or difficulty making decisions
   (6) feelings of hopelessness
C. During the two-year period (one year for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than two months at a time.
D. No major depressive episode has been present during the first two years of the disturbance (one year for children and adolescents); i.e., the disturbance is not better accounted for by chronic major depressive disorder, or major depressive disorder, in partial remission.
   Note: There may have been a previous major depressive episode provided there was a full remission (no significant signs or symptoms for two months) before development of the dysthymic disorder. In addition, after the initial two years (one year in children or adolescents) of dysthymic disorder, there may be superimposed episodes of major depressive disorder, in which case both diagnoses may be given when the criteria are met for a major depressive episode.
E. There has never been a manic episode, a mixed episode, or a hypomanic episode, and criteria have never been met for cyclothymic disorder.
F. The disturbance does not occur exclusively during the course of a chronic psychotic disorder, such as schizophrenia or delusional disorder.
G. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:
Early onset: if onset is before age 21 years
Late onset: if onset is age 21 years or older
Specify (for most recent two years of Dysthymic Disorder):
With atypical features

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

Although the dysthymic disorder category in DSM-IV can occur as a secondary complication of other psychiatric disorders, the core concept of dysthymic disorder refers to a subaffective disorder with the following characteristics: (1) low-grade chronicity for at least two years, (2) insidious onset with origin often in childhood or adolescence, and (3) persistent or intermittent course. Although not part of the formal definition of dysthymic disorder, the family history is typically replete with both depressive and bipolar disorders, which is one of the more robust findings supporting its link to primary mood disorder.

Social adjustment Dysthymic disorder is typically an ambulatory disorder compatible with relatively stable social functioning. However, the stability is precarious; recent data have documented that many of the patients invest whatever energy they have in work, leaving none for leisure and family or social activities, which results in the characteristic marital friction. Those empirical findings on the work orientation of persons with dysthymic disorder echo earlier formulations in the German and Japanese literature. For instance, Kraepelin described such persons as follows: "Life with its activity is a burden which they habitually bear with dutiful self-denial without being compensated by the pleasure(s) of existence."

It has been suggested that the dedication to work on the part of persons with dysthymic disorder represents an overcompensation in that it is a defense against their battle with disorganization and inertia. Nevertheless, Kretschmer suggested that such persons are the backbone of society, dedicating their lives to jobs that require dependability and great attention to detail. Epidemiological studies have demonstrated that some persons with protracted dysthymic complaints, extending over many years, have never experienced clear-cut depressive episodes. Some of them may seek outpatient counseling and psychotherapy for existential depressions, with feelings of being empty and of lacking any joy in life outside their work. Such persons have been described as leading monocategorical existences. Others present clinically because of an intensification of their low-grade dysphoria into major depressive disorder.

Course An insidious onset of depression dating back to late childhood or the teens, preceding any superimposed major depressive episodes by years, or even decades, represents the most typical developmental background of dysthymic disorder. A return to the low-grade depressive pattern is the rule following recovery from superimposed major depressive episodes, if any, and hence the designation "double depression" as a prominent DSM-IV course pattern for depressive illness. That pattern is commonly seen in clinical practice and consists of the baseline dysthymic disorder fluctuating in and out of depressive episodes.

Patients with dysthymic disorder often complain of having been depressed since birth or of feeling depressed all the time. They seem to view themselves as belonging to an aristocracy of suffering. Those descriptions of chronic gloominess in the absence of more objective signs of depression earn such patients the label of characterological depression. The description is further reinforced by the fluctuating depressive picture that merges imperceptibly with the patient's habitual self, and thus the uncertainty as to whether dysthymic disorder belongs in Axis I or in Axis II.

Clinical picture The profile of dysthymic disorder overlaps with that of major depressive disorder, but differs from it in that symptoms tend to outnumber signs (more subjective than objective depression). Thus marked disturbances in appetite and libido are uncharacteristic, and psychomotor agitation or retar-

dation is not observed. All of that translates into a depression that is attenuated in symptomatology. However, subtle endogenous features not uncommonly are observed: psychomotor inertia, lethargy, and anhedonia that are characteristically worse in the morning. Because patients presenting clinically often fluctuate in and out of a major depressive episode, the core DSM-IV criteria for dysthymic disorder tend to emphasize vegetative dysfunction, whereas the alternative criterion B for dysthymic disorder (Table 16.6-22) in a DSM-IV appendix lists cognitive symptoms.

Although dysthymic disorder as defined here represents a more restricted concept than does its parent, neurotic depression, it is still quite heterogeneous. Anxiety is not a necessary part of its clinical picture, yet dysthymic disorder is often diagnosed in patients with anxiety and neurotic disorders. That clinical situation is perhaps to be regarded as a secondary or anxious dysthymic disorder or even as a general neurotic syndrome. For greater operational clarity it is best to restrict dysthymic disorder to a primary disorder, one that cannot be explained by another psychiatric disorder. The essential features of such primary dysthymic disorder include habitual gloom, brooding, lack of joy in life, and preoccupation with inadequacy. Dysthymic disorder then is best characterized as long-standing fluctuating low-grade depression, experienced as part of the habitual self and representing an accentuation of traits observed in the depressive temperament (Table 16.6-1). Thus dysthymic disorder can be viewed as a more symptomatic form of that temperament (introduced in a DSM-IV appendix as a depressive personality disorder [see Chapter 25]). Sleep EEG data indicate that many persons with dysthymic disorder at baseline exhibit the sleep patterns of those with acute major depressive disorder, providing further support to the constitutional nature of the disorder. Yet further evidence for that position comes from studies demonstrating high rates of familial affective disorder in dysthymic disorder and depressive temperament or depressive personality.

The clinical picture of dysthymic disorder thus is varied, with some patients proceeding to major depressive disorder, whereas in others the pathology becomes manifest largely at the personality level. In contrast with these continuously morbid dysthymic conditions, community studies have revealed intermittent forms of dysthymiclike manifestations. Some have been considered recurrent brief depressive disorder (Table 16.6-23), in a DSM-IV appendix, because they do not meet the duration criterion for major depressive disorder, while pursuing a protracted intermittent course like that of dysthymic disorder; the group includes persons who make frequent suicide attempts. In so-called minor depressive disorder (Table 16.6-24), observed in primary care settings, the depression is subthreshold in that it is milder than major depression and yet is not protracted enough to be considered dysthymic. Those varied manifestations of depression argue for a continuum model (Figure 16.6-2) as originally envisaged by Kraepelin. Judd and collaborators have recently suggested that subthreshold depressive symptoms—without necessarily meeting the criterion for mood change, might actually represent the most common expressions of depressive disorders. From such a base, individuals predisposed to depressive illness, would fluctuate in and out of the various DSM-IV subtypes of depressive disorders.

Prospective studies on children with dysthymic disorder have demonstrated that they frequently experience major depressive episodes, some of which progress to hypomanic episodes, manic episodes, or mixed episodes (Tables 16.6-25 and 16.6-26) during puberty or adolescence. Persons with dysthymic disorder presenting clinically as adults more often pursue a unipolar course, which can be disabling without treatment.

TABLE 16.6-22
Alternative Research Criterion B for Dysthymic Disorder

B. Presence, while depressed, of three (or more) of the following:
   (1) low self-esteem or self-confidence, or feelings of inadequacy
   (2) feelings of pessimism, despair, or hopelessness
   (3) generalized loss of interest or pleasure
   (4) social withdrawal
   (5) chronic fatigue or tiredness
   (6) feelings of guilt, brooding about the past
   (7) subjective feelings of irritability or excessive anger
   (8) decreased activity, effectiveness, or productivity
   (9) difficulty in thinking, reflected by poor concentration, poor memory, or indecisiveness

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-23
Research Criteria for Recurrent Brief Depressive Disorder

A. Criteria, except for duration, are met for a major depressive episode.
B. The depressive periods in criterion A last at least two days but less than two weeks.
C. The depressive periods occur at least once a month for 12 consecutive months and are not associated with the menstrual cycle.
D. The periods of depressed mood cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
F. There has never been a major depressive episode, and criteria are not met for dysthymic disorder.
G. There has never been a manic episode, a mixed episode, or a hypomanic episode, and criteria are not met for cyclothymic disorder. **Note:** This exclusion does not apply if all of the manic-, mixed-, or hypomaniclike episodes are substance or treatment induced.
H. The mood disturbance does not occur exclusively during schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, or psychotic disorder not otherwise specified.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-24
Research Criteria for Minor Depressive Disorder

A. A mood disturbance, defined as follows:
   (1) at least two (but less than five) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (a) or (b):
      (a) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
      (b) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
      (c) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
      (d) insomnia or hypersomnia nearly every day
      (e) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
      (f) fatigue or loss of energy nearly every day
      (g) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
      (h) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

Alkermes, Ex. 1060

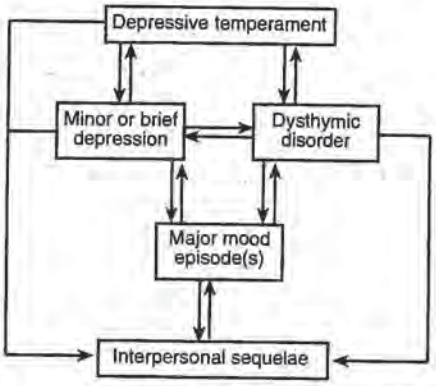

FIGURE 16.6-2 *Relation of various depressive conditions supporting a spectrum concept. (Figure from H S Akiskal: Dysthymia; Clinical and external validity. Acta Psychiatr Scand 89 (Suppl): 19, 1994. Used with permission.)*

TABLE 16.6-25
Criteria for Mixed Episode

A. The criteria are met both for a manic episode and for a major depressive episode (except for duration) nearly every day during at least a one-week period.
B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Mixedlike episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar I disorder.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-26
Criteria for Severity/Psychotic/Remission Specifiers for Current (or Most Recent) Mixed Episode

Note: Code in fifth digit. Can be applied to a mixed episode in bipolar I disorder only if it is the most recent type of mood episode.

Mild: No more than minimum symptom criteria are met for both a manic episode and a major depressive episode.
Moderate: Symptoms or functional impairment between "mild" and "severe."
Severe without psychotic features: Almost continual supervision required to prevent physical harm to self or others.
Severe with psychotic features: Delusions or hallucinations. If possible, specify whether the psychotic features are mood-congruent or mood-incongruent:
Mood-congruent psychotic features: Delusions or hallucinations whose content is entirely consistent with the typical manic or depressive themes.
Mood-incongruent psychotic features: Delusions or hallucinations whose content does not involve typical manic or depressive themes. Included are such symptoms as persecutory delusions (not directly related to grandiose or depressive themes), thought insertion, and delusions of being controlled.
In partial remission: Symptoms of a mixed episode are present but full criteria are not met, or there is a period without any significant symptoms of a Mixed Episode lasting less than two months following the end of the mixed episode.
In full remission: During the past two months, no significant signs or symptoms of the disturbance were present.
Unspecified.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

A 27-year-old, male grade-school teacher presented with the chief complaint that life was a painful duty and that it had always lacked luster for him. He said he felt enveloped by a sense of gloom that was nearly always with him. Although he was respected by his peers, he felt, he said, "like a grotesque failure, a self-concept I have had since childhood." He stated that he merely performed his responsibilities as a teacher, and that he had never derived any pleasure from anything he had done in life. He said he had never had any romantic feeling: sexual activity, in which he had engaged with two different women, had been one of pleasureless orgasm. He said he felt empty, going though life without any sense of direction, ambition, or passion, a realization that itself was tormenting. He had bought a pistol, to put an end to what he called his useless existence, but did not carry his suicide out, believing that it would hurt his students and the small community in which he lived.

Patients with dysthymic disorder who present clinically as adults rarely develop mania. However, when treated with antidepressants some of them may develop brief hypomanic switches that typically disappear when the antidepressant dose is decreased. DSM-IV would not allow the occurrence of such switches in dysthymia; yet systematic clinical observation have verified their occurrence in as many as a third of dysthymic patients. In that special subgroup of persons with dysthymic disorder the family histories are often positive for bipolar disorder. Such patients represent a clinical bridge between depressive disorder and bipolar II disorders.

BIPOLAR DISORDERS

Four bipolar disorders are included in DSM-IV: bipolar I (manic-depressive) disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder NOS (Table 16.6-27).

BIPOLAR I DISORDER Typically beginning in the teenage years, the 20s, or the 30s, the first episode could be manic, depressive, or mixed. One common mode of onset is mild retarded depression, or hypersomnia, for a few weeks or months, which then switches into a manic episode. Others begin with a severely psychotic manic episode that presents schizophreniform features; it is only when a more classic manic episode occurs that the affective nature of the disorder is clarified. In a third group several depressive episodes take place before the first manic episode. A careful history taken from significant others will often reveal dysthymic or cyclothymic traits that antedated the frank onset of major episodes by several years. In DSM-IV there are six ways to subcategorize bipolar I patients: single manic episode (Table 16.6-28), most recent episode hypomanic (Table 16.6-29), most recent episode manic (Table 16.6-30), most recent episode mixed (Table 16.6-31) most recent episode depressed (Table 16.6-32) and most recent

TABLE 16.6-27
Diagnostic Criteria for Bipolar Disorder Not Otherwise Specified

The bipolar disorder not otherwise specified category includes disorders with bipolar features that do not meet criteria for any specific bipolar disorder. Examples include
1. Very rapid alternation (over days) between manic symptoms and depressive symptoms that do not meet minimal duration criteria for a manic episode or a major depressive episode
2. Recurrent hypomanic episodes without intercurrent depressive symptoms
3. A manic or mixed episode superimposed on delusional disorder, residual schizophrenia, or psychotic disorder not otherwise specified
4. Situations in which the clinician has concluded that a bipolar disorder is present but is unable to determine whether it is primary, due to a general medical condition, or substance induced

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

Alkermes, Ex. 1060

TABLE 16.6-28
Diagnostic Criteria for Bipolar I Disorder, Single Manic Episode

A. Presence of only one manic episode and no past major depressive episodes.
   Note: Recurrence is defined as either a change in polarity from depression or an interval of at least two months without manic symptoms.
B. The manic episode is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.

Specify if:
Mixed: if symptoms meet criteria for a mixed episode
Specify (for current or most recent episode):
Severity/psychotic/remission specifiers
With catatonic features
With postpartum onset

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-29
Diagnostic Criteria for Bipolar I Disorder, Most Recent Episode Hypomanic

A. Currently (or most recently) in a hypomanic episode.
B. There has previously been at least one manic episode or mixed episode.
C. The mood symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The mood episodes in criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.

Specify:
Longitudinal course specifiers (with and without interepisode recovery)
With seasonal pattern (applies only to the pattern of major depressive episodes)
With rapid cycling

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

episode unspecified (Table 16.6-33). According to DSM-IV, bipolar I disorder, Single manic episode, is used to describe patients who are having a first episode of mania (most such patients eventually develop depressive episodes). The remaining subcategorization is used to specify the nature of the current or most recent episode in patients who have had recurrent mood episodes. For clinicians and researchers alike it is more meaningful to chart a patient's course in color over time—for example, red rectangles for manic, blue for depressive, and violet for mixed episodes; hypomanic, dysthymic and cyclothymic periods can be drawn in the appropriate colors on a smaller scale between the major episodes. Life events, biologic stressors, and treatment can be indicated by arrows on the time axis. This approach, championed by Kraepelin, is routinely used in mood clinics.

On the average, manic episodes predominate in youth and depressive episodes in the later years. Although the overall sex ratio is about one to one, men on the average undergo more manic episodes and women experience more mixed and depressive episodes. Bipolar I disorder in children is not as rare as previously thought; however, most reported cases are boys, and mixed-manic (dysphoric-explosive) presentations are the most common mode.

Manic phase Mania, typically begins acutely over a period of one to two weeks; more sudden onsets have also been described. The DSM-IV criteria (Table 16.6-9) stipulate (1) a

TABLE 16.6-30
Diagnostic Criteria for Bipolar I Disorder, Most Recent Episode Manic

A. Currently (or most recently) in a manic episode.
B. There has previously been at least one major depressive episode, manic episode, or mixed episode.
C. The mood episodes in criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.

Specify (for current or most recent episode):
Severity/psychotic/remission specifiers
With catatonic features
With postpartum onset
Specify:
Longitudinal course specifiers (with and without interepisode recovery)
With seasonal pattern (applies only to the pattern of major depressive episodes)
With rapid cycling

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-31
Diagnostic Criteria for Bipolar I Disorder, Most Recent Episode Mixed

A. Currently (or most recently) in a Mixed Episode.
B. There has previously been at least one Major Depressive Episode, Manic Episode, or Mixed Episode.
C. The mood episodes in criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.

Specify (for current or most recent episode):
Severity/psychotic/remission specifiers
With catatonic features
With postpartum onset
Specify:
Longitudinal course specifiers (with and without interepisode recovery)
With seasonal pattern (applies only to the pattern of Major Depressive Episodes)
With rapid cycling

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-32
Diagnostic Criteria for Bipolar I Disorder, Most Recent Episode Depressed

A. Currently (or most recently) in a major depressive episode.
B. There has previously been at least one manic episode or mixed episode.
C. The mood episodes in criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.

Specify (for current or most recent episode):
Severity/psychotic/remission specifiers
Chronic
With catatonic features
With melancholic features
With atypical features
With postpartum onset
Specify:
Longitudinal course specifiers (with and without interepisode recovery)
With seasonal pattern (applies only to the pattern of major depressive episodes)
With rapid cycling

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-33
Diagnostic Criteria for Bipolar I Disorder, Most Recent Episode Unspecified

A. Criteria, except for duration, are currently (or most recently) met for a manic, a hypomanic, a mixed, or a major depressive episode.
B. There has previously been at least one manic episode or mixed episode.
C. The mood symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The mood symptoms in criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
E. The mood symptoms in criteria A and B are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Specify:
Longitudinal course specifiers (with and without interepisode recovery)
With seasonal pattern (applies only to the pattern of major depressive episodes)
With rapid cycling

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

distinct period that represents a break from premorbid functioning, (2) a duration of at least one week, (3) an elevated or irritable mood, (4) at least three to four classic manic signs and symptoms, and (5) the absence of any physical factors that could account for the clinical picture. The irritable mood in mania can deteriorate to cantankerous behavior, especially when the person is rebuffed. Such patients are among the most aggressive seen in the emergency room. Extreme psychotic disorganization, a common presentation of mania, further contributes to the aggression. Alcohol use, which is observed in at least 50 percent of bipolar I patients (typically in the manic phase), further disinhibits the patient and might lead to a dangerous frenzy. Such patients may attack loved ones and hurt them physically. So-called crimes of passion have been committed by patients harboring delusions of infidelity on the part of spouses or lovers, usually when under the influence of alcohol.

The genesis of delusional and hallucinatory, even first-rank, psychotic experiences in mania have already been described. Recent research has also documented that most types of formal thought disorders are common to both schizophrenic and mood psychoses: only poverty of speech content (vagueness) emerges as significantly more common in schizophrenia. Finally, posturing and negativism have been shown to occur in mania (and, in the author's view, do not warrant the designation of catatonic features as advocated by DSM-IV). Although not specifically mentioned in the DSM-IV definition, confusion, even pseudodemented presentations, can occur in mania.

Mania is most commonly expressed as a phase of bipolar I disorder, which has strong genetic determinants. Available evidence does not permit separating recurrent mania without depressive episodes as a distinct nosological entity from that form.

Secondary mania Although there is some suggestion that postpartum mania without depression is distinct from familial bipolar I disorder, in which both depressive and manic episodes can sometimes occur in the postpartum period, the evidence for a distinct puerperal mania is not compelling at this time (hence the decision in DSM-IV to use postpartum-onset as a specifier, rather than a separate mood disorder subtype [see Section 15.4]). It has also been known for some time that mania without prior bipolarity can arise in the setting of such somatic illnesses as influenza, thyrotoxicosis, systemic lupus erythematosus or its treatment with steroids, rheumatic chorea, multiple sclerosis, Huntington's disease, cerebrovascular disorder, diencephalic and third ventricular tumors, head trauma, complex partial seizures, and most recently, AIDS. The family history is reportedly low in such cases, suggesting a relatively low genetic predisposition and thus a lower risk of recurrence. The patients do not easily fit into the DSM-IV category of mood disorder due to a general medical condition (Table 16.6-18) because most of the conditions appear to be cerebral.

Less well-defined forms of mania are the so-called reactive manias. Personal loss and bereavement are hypothesized to be triggering factors, and the reaction is conceptualized in psychodynamic terms as a denial of loss. Although such explanations may be plausible in individual cases, no systematic data are available to suggest that the patients differ in family history from persons with other manias. The same is generally true for depressed patients who switch to hypomania or mania after the abuse of stimulant drugs, treatment with antidepressants, or sleep deprivation; in all of those situations a bipolar diathesis is usually manifest, either in a family history of mania or in spontaneous excited episodes during prospective observation. First-onset manic episodes have also been seen in persons who abstained from alcohol after one or two decades of abuse and who evolved into having classic bipolar I disorder.

Chronic mania DSM-IV does not specifically address the diagnostic questions posed by the 5 percent of bipolar I patients characterized by a chronic manic course. That course most commonly represents deterioration of course dominated by recurrent manic episodes. Noncompliance with pharmacological treatment is the rule. Recurrent excitement is personally reinforcing, subjective distress is minimal, and insight is seriously impaired; therefore, the patient sees no reason to adhere to treatment. Episodic or chronic alcohol abuse, which is prevalent in such patients, has been suggested as a contributory cause of the chronicity. Some authorities consider comorbid cerebral pathology to be responsible for nonrecovery from manic excitements occurring in late life.

Grandiose delusions, such as delusions of inventive genius or aristocratic birth, are not uncommon in chronic mania, and may lead to the mistaken diagnosis of paranoid schizophrenia. Because of their social deterioration, Kraepelin had subsumed such patients under the category "manic dementia." Nonschizoid premorbid adjustment and a family history of bipolar I disorder, as well as the absence of flagrant formal thought disorder, can be marshaled in establishing the affective basis of those poor-prognosis manic states.

Mixed phase Momentary tearfulness, depressed mood, and even suicidal ideation are commonly observed at the height of mania or during the transition from mania to retarded depression. Another common mixed feature is racing thoughts in the context of a retarded depression. Those transient labile periods, which occur in most bipolar I patients, must be contrasted with the mixed episodes experienced by 30 to 40 percent of patients in the long-term course of bipolar I disorder.

The mixed episodes proper (Table 16.6-25)—variously referred to as mixed mania or dysphoric mania—are characterized by dysphorically excited moods, anger, panic attacks, pressured speech, agitation, suicidal ideation, severe insomnia, grandiosity, and hypersexuality, as well as by persecutory delusions and confusion. Mixed states, when of mild to moderate intensity, could be misdiagnosed as major depressive disorder,

Alkermes, Ex. 1060

or as atypical or neurotic depression, whereas severely psychotic forms that involve hallucinations and Schneiderian symptoms, can be misdiagnosed as schizoaffective disorder, or even schizophrenia. A correct diagnosis is mandatory for proper management because most classes of antidepressants may further aggravate the mixed pathology of those patients, whereas antipsychotics could exacerbate the depressive component. Thus misdiagnosis and inappropriate treatment can prolong the patient's suffering, leading to a protracted course over many months. That is especially likely to happen when the patient is nondelusional and the clinical picture is confused with agitated depressive disorder, and the patient is subjected to aggressive antidepressant therapy.

Depressive phase Psychomotor retardation, with or without hypersomnia, is the hallmark of the depressive phase of bipolar I disorder. Symptoms typically begin over a period of several weeks, although sudden onsets over one or two days are also seen. Although bipolar depressive episodes do not always acquire full-blown melancholic features, the autonomy of the episodes is a fundamental characteristic. Delusional and hallucinatory experiences are less common in the depressive phase of bipolar I disorder as compared with the manic and mixed phases. Stupor is the more common mode of psychotic presentation of bipolar depression, particularly in adolescents and young adults, where the mistaken diagnosis of catatonic stupor is often made. Pseudodemented organic presentations appear to be the counterpart of stupor in the elderly.

CYCLOTHYMIC DISORDER An attenuated bipolar disorder that typically begins insidiously before the age of 21, it is characterized by alternating short cycles of subsyndromal depression and hypomania (Table 16.6-34). That list, which reflects findings from the author's research, is more explicit than are the DSM-IV criteria (Table 16.6-35). The course of cyclothymia is continuous or intermittent, with infrequent periods of euthymia. Shifts in mood are typically endoreactive, such as suddenly falling in love or feeling profoundly dejected without adequate cause. Circadian cycles seem to play a role in the sudden mood changes, such as the person's going to sleep in good spirits and waking up early with suicidal urges.

In these ambulatory patients mood swings are overshadowed by the chaos that such swings produce in their personal lives. Repeated marital failures or romantic breakups are common, due to interpersonal friction and episodic promiscuous behavior. Uneven performance at school and work is another common characteristic. Thus persons with cyclothymic disorder are dilettantes: they show great promise in many areas, but rarely are able to bring any of their efforts to fruition. Their lives are often a string of improvident activities. Geographical instability is a characteristic feature: easily attracted to a new location, a new job, or a new love partner, they soon lose interest and leave in dissatisfaction. Polysubstance abuse, a complication occurring in 50 percent of such persons, is often an attempt at self-treatment.

TABLE 16.6-34
Clinical Features of Cyclothymic Disorder

Biphasic dysregulation characterized by abrupt endoreactive shifts from one phase to the other, each phase lasting for few days at a time, with infrequent euthymia.

Behavioral manifestations:
- Hypersomnia versus decreased need for sleep
- Introverted self-absorption versus uninhibited people seeking
- Taciturn versus talkative
- Unexplained tearfulness versus buoyant jocularity
- Psychomotor inertia versus restless pursuit of activities

Subjective manifestations:
- Lethargy and somatic discomfort versus eutonia
- Dulling of senses versus keen perceptions
- Slow-witted versus sharpened thinking
- Shaky self-esteem alternating between low self-confidence and overconfidence
- Pessimistic brooding versus optimism and carefree attitudes

Summarized from H S Akiskal, M Khani, A Scott-Strauss: Cyclothymic temperamental disorders. Psychiatr Clin North Am 2: 527, 1979.

TABLE 16.6-35
Diagnostic Criteria for Cyclothymic Disorder

A. For at least two years, the presence of numerous periods with hypomanic symptoms and numerous periods with depressive symptoms that do not meet criteria for a major depressive episode. **Note:** In children and adolescents, the duration must be at least one year.
B. During the above two-year period (one year in children and adolescents), the person has not been without the symptoms in criterion A for more than two months at a time.
C. No major depressive episode, manic episode, or mixed episode has been present during the first two years of the disturbance.
Note: After the initial two years (one year in children and adolescents) of cyclothymic disorder, there may be superimposed manic or mixed episodes (in which case both bipolar I disorder and cyclothymic disorder may be diagnosed) or major depressive episodes (in which case both bipolar II disorder and cyclothymic disorder may be diagnosed).
D. The symptoms in criterion A are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).
F. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

BIPOLAR II DISORDER (AND THE SOFT BIPOLAR SPECTRUM) Research conducted during the past 15 years has shown that between the extremes of classic manic-depressive illness defined by at least one acute manic episode (bipolar I disorder) and strictly defined major depressive disorder without any personal or family history of mania, there exists a large group of intermediary forms characterized by recurrent major depressive episodes and hypomanic episodes (variously termed as atypical, bipolar II, or unipolar II). Table 16.6-36 summarizes those nosological concepts. The most accepted of the subtypes is bipolar II disorder, elevated to the status of a nosological entity in DSM-IV (Table 16.6-37). Bipolar II disorder may actually be more common than bipolar I disorder. That certainly appears to be the case in the outpatient setting, where as many as 30 percent of persons with major depressive disorder might conform to the bipolar II pattern.

The self-description provided by a 34-year-old poet illustrates the pattern: "I have known melancholy periods, lasting months at a time, when I would be literally paralyzed: All mental activity comes to a screeching halt, and I cannot even utter one word. I become so dysfunctional that I was once hospitalized. Although the paralysis creeps into me insidiously—often lasting months—it typically reverses within hours. I am suddenly alive and vibrant, I cannot turn off my brain neither during the day nor at night; I usually go on celebrating like this for many weeks, needing no more than few hours of slumber each day."

The hypomania at the end of depressive episodes in most bipolar II disorders does not persist that long; it is usually measured in days. Another common form of bipolar II disorder is major depressive disorder superimposed on cyclothymic disorder, where hypomania precedes and follows major depres-

TABLE 16.6-36
Spectrum of Bipolar Disorders Compared with Unipolar Depression

	Bipolar I:	At leat one manic episode
Soft bipolar	Bipolar II:	Recurrent depressions with hypomania and cyclothymic disorder
Soft bipolar	Bipolar III: (pseudo-unipolar)	Recurrent depressions without spontaneous hypomania but often with hyperthymic temperament and bipolar family history
Unipolar depressions:		No evidence for hypomania, cyclothymic disorder, hyperthymic disorder, or bipolar family history

TABLE 16.6-37
Diagnostic Criteria for Bipolar II Disorder

A. Presence (or history) of one or more major depressive episodes.
B. Presence (or history) of at least one hypomanic episode.
C. There has never been a manic episode or a mixed episode.
D. The mood symptoms in criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify current or most recent episode:
Hypomanic: if currently (or most recently) in a hypomanic episode
Depressed: if currently (or most recently) in a major depressive episode

Specify (for current or most recent major depressive episode only if it is the most recent type of mood episode):
Severity/psychotic/remission specifiers **Note:** Fifth-digit codes cannot be used here because the code for bipolar II disorder already uses the fifth digit.
Chronic
With catatonic features
With melancholic features
With atypical features
With postpartum onset

Specify:
Longitudinal course specifiers (with and without interepisode recovery)
With seasonal pattern (applies only to the pattern of major depressive episodes)
With rapid cycling

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

sion, the entire interepisodic period being characterized by cyclothymic mood swings.

Hypomania in bipolar II disorder can be defined as minimanic episodes occurring spontaneously. Thus bipolar II disorder can be characterized as cyclical depression. In bipolar III disorder (which is not an official nosological term) evidence of bipolarity is softer, such as a single brief episode of antidepressant-mobilized switch. In a related subgroup of cryptic bipolar disorders, strong evidence for familial bipolarity raises the hypothesis that some phenotypically unipolar depressions might actually be genotypically bipolar. In such cases, also referred to as pseudo-unipolar, hypomania as such is not observed; instead the patient's habitual temperamental baseline is sunny, overenergetic, and overoptimistic (hyperthymic). Depending on the threshold of traits used in determining the presence of hyperthymia, those patients may constitute 10 to 20 percent of those with major depressive disorder. Recurrent hypomanic episodes without intermittent depressions (example 2 in the DSM-IV criteria for bipolar disorder NOS [Table 16.6-27]) are almost never observed clinically.

The depressive episodes of bipolar II or III patients often have mixed admixtures—for example, flight of ideas, increased drives and impulsivity. These are depressive mixed states completely ignored by DSM-IV. Their existence explains why antidepressants often fail in these patients.

Hypomania The common denominator of the soft spectrum of bipolar disorders is the occurrence of hypomania. Hypomania refers to a distinct period of at least few days of mild elevation of mood, sharpened and positive thinking, and increased energy and activity levels, typically without the impairment characteristic of manic episodes. It is not merely a milder form of mania. Hypomania occurring as part of bipolar II disorder rarely progresses to manic psychosis. Thus distractibility is uncommon in hypomania, and there is relative preservation of insight. Hypomania is distinguished from mere happiness by the fact that it tends to recur (happiness does not!), and can sometimes be mobilized by antidepressants. In cyclothymic disorder it alternates with minidepressions, whereas in hyperthymic disorder it constitutes the person's habitual baseline. Those definitions then recognize three patterns of hypomania: brief episodes heralding the termination of a retarded depressive episode (bipolar II disorder), cyclic alternation with minidepressions (cyclothymic disorder), and an elevated baseline of high mood, activity, and cognition (hyperthymic disorder or chronic hypomania).

Because hypomania is experienced either as a rebound relief from depression or as pleasant, short-lived, ego-syntonic moods, persons with bipolar II disorder rarely report them spontaneously. Skillful questioning thus is required in making the diagnosis of soft bipolar conditions; as in mania, collateral information from family members is crucial. In interviewing the patient the following probes have been found useful to elicit hypomania: "Have you had a distinct sustained high period (1) when your thinking and perceptions were unusually vivid or rapid, (2) your mood was so intense that you felt nervous, and (3) you were endowed with such energy that others could not keep up with you?" The clinician must ascertain that, when endorsed by the patient, those experiences were not due to stimulant abuse.

When in doubt, direct clinical observation of hypomania—sometimes elicited by antidepressant pharmacotherapy—will provide definitive evidence for the bipolar nature of the disorder. However, in some cases depressive and hypomanic periods are not easily discerned because chronic caffeinism or stimulant abuse complicates the depression. In such instances, diagnosis should be based on clinical observation at least one month beyond detoxification.

Seasonal patterns Another characteristic observed in many cyclic depressions is seasonality, which often becomes manifest with autumn or winter anergic depression and energetic or frankly hypomanic periods in the spring. Thus seasonal depressions conform, in large measure, to the bipolar II or III pattern. Preliminary evidence suggests that when treated with classic antidepressants, such persons exhibit a disruption of their baseline seasonality, with the depressive phase appearing in the spring and summer. The changes induced by antidepressants in seasonal depressions probably represent a special variant of the phenomenon of rapid cycling.

Temperament and polarity of episodes New research from collaboration between the University of Tennessee and the University of Pisa has shown that bipolar II disorder (characterized predominantly by depressive attacks) appears to arise more often from a hyperthymic or cyclothymic baseline, whereas bipolar I disorder (defined by manic attacks) not

Alkermes, Ex. 1060

uncommonly arises from the substrate of a depressive temperament. Bipolarity is conventionally defined by the alternation of manic (or hypomanic) and depressive episodes. Those data on temperaments suggest that a more fundamental characteristic of bipolarity is the reversal of temperament into its opposite episode (that is, from the depressive temperament to mania and from the hyperthymic temperament to depression).

Those considerations have implications for preventing recurrence. For instance, in a prospective study of the onset of bipolar disorder in the offspring or sibs of adults with the disorder, it was found that children with onsets of depression (treated with antidepressants) had significantly higher rates of recurrence than did those with manic or mixed onsets (treated with lithium) during a three-year prospective observation. Such data suggest the hypothesis that temperamental instability in the depressive group might have predisposed them to the cycling effect of antidepressants.

Alcohol, substance abuse, and suicide New evidence supports the high prevalence of alcohol and substance abuse in mood disorder subtypes, especially those with cyclothymic and hyperthymic temperaments. The relation appears particularly strong in the teenage and early adult years, at which time the use of such substances often represents self-medication. It is not to be viewed just as self-treatment for selected symptoms associated with the down or up phases (for example, alcohol to alleviate the insomnia and nervousness characteristic of both phases), but also as augmenting certain desired ends (for example, stimulants to enhance high-energy performance and sexual behavior associated with hypomania). The exact proportion of those with alcohol and substance abuse secondary to an underlying bipolar diathesis is a question for future research, and is of public health significance in view of findings suggesting a link between adolescent polysubstance abuse and suicide in those with bipolar familial backgrounds. Although alcohol and substance use often continues into adult years in a considerable number of bipolar patients, such use does not appear related to familial alcoholism and, in many instances, tends to dwindle during long-term follow-up. Those data provide support for the self-medication hypothesis. To complicate matters, in a substantial minority of cases, bipolar mood swings appear for the first time following abrupt cessation of long-term alcohol use.

Rapid-cycling bipolar disorder Rapid cycling is defined as the occurrence of at least four episodes—both retarded depression and hypomania (or mania)—a year. That means that rapid cyclers are rarely free of affective symptoms, resulting in serious vocational and interpersonal incapacitation. Lithium is often only modestly helpful to those patients, as are antipsychotics; tricyclic antidepressants readily induce excited episodes and thereby aggravate the rapid cycling pattern. A balance among lithium, antipsychotics, and antidepressants may be difficult to achieve. The patients require frequent hospitalization because they develop explosive excitement and precipitously descend into severe psychomotor inhibition. The disorder is a roller-coaster nightmare for the patient, significant others, and the treating physician.

As expected, rapid cycling commonly arises from a cyclothymic substrate, which means that most rapid cyclers have bipolar II disorder. Factors favoring its occurrence include (1) female gender; (2) hypothyroidism; (3) menopause; (4) temporal lobe dysrhythmias; (5) alcohol, minor tranquilizer, stimulant, or caffeine abuse; and (6) long-term use of antidepressant medications. The DSM-IV criteria for rapid-cycling specifier are presented in Table 16.6-38.

Rapid-cycling uncommonly arises from a bipolar I baseline. These patients might resemble examples 1 and 3 listed under bipolar disorder NOS (Table 16.6-27).

Leadership and creativity Persons with hyperthymic temperament, and soft bipolar conditions in general, possess assets that permit them to assume leadership roles in business, the professions, civic life, and politics. Increased energy, sharp thinking, and self-confidence represent the virtues of an otherwise stormy life.

Creative achievement is relatively uncommon among those with the manic forms of the disorder, which is too severe and disorganizing to permit the necessary concentration and dedication. It is among those with the soft bipolar disorders, especially cyclothymic disorders, that notable artistic achievements are found. Psychosis, including severe bipolar swings, is generally incompatible with creativity. That conclusion, based on recent systematic studies, tends to refute the romantic tendency to idolize insanity as being central to the creative process. As talent is the necessary ingredient of creativity, how might soft bipolarity contribute? The simplest hypothesis is that depression could provide insights into the human condition, which, however, requires the activation associated with hypomania to produce the artistic work. A more profound interpretation would suggest that the repeated self-doubt that comes with recurrent depression might be an important ingredient of creativity, because original artistic or scientific expression is often initially rejected, and the self-confidence that accompanies repeated bouts of hypomania can help in rehearsing such ideas or expressions until they are perfected. Finally, the tempestuous object relations associated with bipolarity often create the unique life situations that might be immortalized in an artistic medium.

MOOD DISORDER NOT OTHERWISE SPECIFIED After all diagnostic information has been obtained, some depressed and bipolar or otherwise affective patients do not meet the criteria for the mood disorders described thus far. The author prefers to consider them as undiagnosed mood disorders rather than using the DSM-IV rubrics of depression disorder NOS, bipolar disorder NOS, or mood disorder NOS. The DSM-IV criteria for mood disorder NOS appear in Table 16.6-39.

TABLE 16.6-38
Criteria for Rapid-Cycling Specifier

Specify if:
With rapid cycling (can be applied to bipolar I disorder or bipolar II disorder)
At least four episodes of a mood disturbance in the previous 12 months that meet criteria for a major depressive, manic, mixed, or hypomanic episode.
Note: Episodes are demarcated either by partial or full remission for at least two months or a switch to an episode of opposite polarity (e.g., major depressive episode to manic episode).

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 16.6-39
Diagnostic Criteria for Mood Disorder Not Otherwise Specified

This category includes disorders with mood symptoms that do not meet the criteria for any specific mood disorder and in which it is difficult to choose between depressive disorder not otherwise specified and bipolar disorder not otherwise specified (e.g., acute agitation).

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

Alkermes, Ex. 1060

What follows are descriptions of conditions that are commonly used in the epidemiological, clinical, or pharmacological literature, but do not easily fit into the classic nosology of mood disorders. They probably subsume many, but not all, of the situations implied in the DSM-IV NOS concepts.

Recurrent brief depressive disorder The disorder (now in a DSM-IV appendix) derives largely from epidemiological studies conducted in young adult cohorts in Zurich. The description is that of short-lived depressions that recur on a monthly basis but are not menstrually related. They could coexist with major depressive disorder and dysthymic disorder. It is believed that such patients are more prevalent in primary care than in psychiatric settings. The minority seen in psychiatric settings present with repeated suicide attempts, and are likely to be given Axis II diagnoses, such as borderline personality disorder. The research criteria for recurrent brief depressive disorder appear in Table 16.6-23.

The current nosological status of those patients is uncertain, but they testify to Kraepelin's observation that many transitional forms link the depressive temperament to affective episodes:

> A permanent gloomy stress in all the experiences of life . . . usually perceptible already in youth, and may persist without essential change throughout the whole of life . . . (or) there is actually an uninterrupted series of transitions to periodic melancholia . . . in which the course is quite indefinite with irregular fluctuations and remissions.

Given the high rate of brief depressive recurrences among the patients observed in the Zurich cohort, it is likely that brief hypomanic episodes have been missed during evaluations performed by nonclinicians. Some, if not most patients meeting the Zurich description might actually belong to the soft bipolar spectrum.

Reactive depression Classically such a depression is defined as resulting from a specific life event. In an ideal case the depression would not have occurred without the event (for example, love loss) to which it is a reaction, it would continue for as long as the event were present, and it would terminate with the reversal of the event (for example, the return of the lover). Depressions exhibiting all of those features are almost never seen in clinical practice. With interpersonal support most people are able to face life's reverses, which explains why reactive depression tends to be self-limiting. Hence, adjustment disorder would be the more appropriate diagnosis in most cases of reactive depression.

Conceptually, however, it is possible to envision chronically unsatisfactory life situations that might lead to chronic demoralization. However, such a condition, which could warrant the designation of chronic reactive depression, is a contradiction in terms. The question often raised is why a person would continue to stay in the situation. Sometimes the concept of masochism is invoked by psychodynamic authors to explain why certain persons are unable to rid themselves of painful life situations, the implication being that they somehow contribute to their maintenance. Current thinking is that many of those presumed self-defeating traits, believed to be indicative of masochism, are more situation specific than previously believed, and might resolve with the elimination of the situation. So-called self-defeating features then are best conceptualized as psychodynamic mechanisms, rather than as being indicative of a specific personality. At the present stage of knowledge, they do not deserve to be raised to the level of a nosological entity. Chronic adjustment disorder, seemingly a contradiction in terms, might describe the chronic demoralization observed among some individuals stuck in chronically unsatisfactory life situations. Others might fullfill the criteria for dysthymia.

Mixed anxiety-depressive disorder The inclusion of anxious depressive states in a DSM-IV appendix acknowledges the simultaneous occurrence of anxious (for example, the threat loss represents) and depressive (for example, the despair of loss) cognition when confronted with a major aversive life situation. The admixture implies that the progress of psychopathology is from anxiety to depression, that the patient's mental state is still in flux, and that the ongoing dynamics in part explains the subacute or chronic nature of the disorder. Anxious depression serves to point to the common presence of anxiety in depressive states, and especially its greater visibility when the depression is less prominent. Patients with the latter presentation are reportedly most prevalent in general medical settings. According to DSM-IV, persons whose presentation meets those research criteria would be diagnosed as having anxiety disorder not otherwise specified (see Section 17.5).

Some authorities argue that neurotic depressions arise in that fashion (that is, as maladaptive response to anxiety) and, on that etiological ground, suggest retaining the neurotic depressive rubric. Recent preliminary genetic data tend indirectly to support the contention that certain (unipolar) depressive and (generalized) anxiety states are related. However, more research needs to be conducted in the area before such an entity can be unequivocally accepted as an official nosological category. The difficulty lies in the fact that, as currently defined, anxious depressions are heterogeneous.

Neurasthenia Neurasthenia, a century-old term developed by the American neuropsychiatrist George Beard, refers to a more chronic stage of anxious-depressive symptomatology. The anxiety generated by overstimulation is so excessive that it is replaced by a chronic disposition to irritability, fatigue (especially mental fatigue), lethargy, and exhaustion. It is as if the sufferer's mind refuses to take on new stresses. The clinical picture described by Beard suggests that anxious manifestations were preeminent in his time. They included headache, scalp tenderness, backache, heavy limbs, vague neuralgias, yawning, dyspepsia, palpitations, sweating hands and feet, chills, flushing, sensitivity to weather changes, insomnia, nightmares, pantaphobia, asthenopia, and tinnitus.

Although the diagnosis of neurasthenia itself is now used more in China than it is in the United States, the recent worldwide upsurge in the popularity of the concept of chronic fatigue states attests to the clinical acumen of classic physicians. Despite much energy invested in a viral or immunological etiology, current descriptions tend to suggest an anxiety or mood disorder basis for many, if not most, of those with the syndrome. However, under what circumstances anxiety or depression would become manifest primarily in fatigue is as elusive as it was 100 years ago.

Like other patients presenting to primary care settings with somatic complaints, those with chronic fatigue tend to denounce psychiatric diagnoses as inadequate explanations for their ills. Empathic listening, perhaps in a group therapy format, might be a reasonable approach to that difficult group of patients, who can be quite disabled.

Atypical depression Although a delimited version of the construct has been incorporated into DSM-IV as atypical features (Table 16.6-7) to qualify the cross-sectional picture of depressive disorders, the construct is much broader in the clinical research literature and warrants further discussion. The

rubric, originally developed in England and currently under investigation at Columbia University in New York, refers to fatigue superimposed on a history of somatic anxiety and phobias, together with reverse vegetative signs (mood worse in the evening, insomnia, tendency to oversleep and overeat). Given that nighttime sleep is disturbed in the first half of the night in many persons with atypical depressive disorder, irritability, hypersomnolence, and daytime fatigue would seem to represent expected daytime stigmata of sleep deprivation due to intermittent initial insomnia. The temperaments of those patients are characterized by inhibited-sensitive traits. There seems to be some specificity of the MAOIs (and possibly serotonergic antidepressants) for such patients, which is the main reason that atypical depression is taken seriously.

Other research suggests that reverse vegetative signs can be classified as either (1) the anxious type just described, or (2) a subtle bipolar subtype with protracted hyperphagic-hypersomnic-retarded dysthymic disorder with occasional brief extroverted hypomanic-type behavior, often elicited by antidepressants. There is some affinity between atypical depression and bipolar II and III disorders. Many patients with dysthymic disorder at various times exhibit atypical features.

Hysteroid dysphoria The category combines reverse vegetative signs with the following characteristics: (1) giddy responses to romantic opportunities, and an avalanche of dysphoria (angry-depressive, even suicidal responses) upon romantic disappointment; (2) impaired anticipatory pleasure, yet the capability to respond with pleasure when such is provided by others (that is, preservation of consummatory reward); (3) craving for chocolate and sweets, which contain phenylethylamine compounds and sugars believed to facilitate cellular and neuronal intake of the amino-acid L-tryptophan, hypothetically leading to the brain's synthesis of endogenous antidepressants. The use of the epithet "hysteroid" was meant to convey that what appeared to be a character pathology was secondary to a biological disturbance in the substrates governing affect, drives, and reward. The hysteroid dysphorics' intense, giddy, and unstable life suggests links to cyclothymic disorder or bipolar II disorder. That suggestion is further supported by the Columbia group's tendency to subsume those patients under atypical depressions (some of which, as indicated, have bipolar affinities). Finally, like bipolar depressives, they show preferential response to MAOIs.

Postpsychotic depressive disorder of schizophrenia In DSM-IV the description of postpsychotic depressive disorder of schizophrenia appears as follows:

> The essential feature is a Major Depressive Episode that is superimposed on, and occurs only during, the residual phase of Schizophrenia. The residual phase of Schizophrenia follows the active phase (i.e., symptoms meeting Criterion A) of Schizophrenia. It is characterized by the persistence of negative symptoms or of active-phase symptoms that are in an attenuated form (e.g., odd beliefs, unusual perceptual experiences). The superimposed Major Depressive Episode must include depressed mood (i.e., loss of interest or pleasure cannot serve as an alternate for sad or depressed mood). Most typically, the Major Depressive Episode follows immediately after remission of the active-phase symptoms of the psychotic episode. Sometimes it may follow after a short or extended interval during which there are no psychotic symptoms. Mood symptoms due to the direct physiological effects of a drug of abuse, a medication, or a general medical condition are not counted toward postpsychotic depressive disorder of Schizophrenia.

TABLE 16.6-40
Research Criteria for Postpsychotic Depressive Disorder of Schizophrenia

A. Criteria are met for a major depressive episode.
   Note: The major depressive episode must include criterion A1: depressed mood. Do not include symptoms that are better accounted for as medication side effects or negative symptoms of schizophrenia.
B. The major depressive episode is superimposed on and occurs only during the residual phase of schizophrenia.
C. The major depressive episode is not due to the direct physiological effects of a substance or a general medical condition.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

According to DSM-IV, persons whose presentation meets those research criteria (Table 16.6-40) would be diagnosed as having depressive disorder NOS. In the author's opinion, mood or depressive disorder NOS represent such a hodgepodge of clinical situation that the designation of NOS is at best meaningless and at worst confusing.

DIFFERENTIAL DIAGNOSIS

Missing a mood disorder diagnosis, with the result that the disorder does not receive specific treatment, can have serious consequences. Many persons drop out of school or college, lose their jobs, are divorced, or commit suicide. Those with unexplained somatic symptoms are frequent utilizers of the general health system. Still others are unwell despite interminable psychotherapy. Some develop tardive dyskinesia unnecessarily. As with other medical disorders for which specific treatments are available, accurate diagnosis and early treatment are within the purview of all physicians. All psychiatrists, clinical psychologists, and psychiatric social workers should be competent in the detection of mood disorders. Despite massive educational efforts, underdiagnosis of mood disorders and their undertreatment are still serious problems worldwide.

Although much enthusiasm was generated a decade earlier about the potential utility of certain biological markers (such as REM latency, dexamethasone suppression test, and the thyrotropin-releasing-hormone test) as corroborating evidence in the differentiation of mood disorder from adjacent disorders, no definitive progress has been made along those lines that would justify their routine use in clinical practice. Faced with unusual or confusing presentations, a systematic clinical approach is still the only method in differential diagnosis (1) to characterize in great detail all the clinical features of the current episode, (2) to elicit a history of more typical major mood episodes in the past, (3) to assess whether the presenting complaints recur in a periodic or cyclical fashion, (4) to substantiate the adequacy of social functioning between periods of illness, (5) to obtain a positive family history for classic mood disorder and to construct a family pedigree, and (6) to document a history of unequivocal therapeutic response to thymoleptic medication or ECT in either the patient or in the family.

Using the foregoing validating approach, it is possible to examine the affective links of many DSM-IV disorders currently listed under conditions other than mood disorders. They include (1) conduct disorders; (2) borderline personality disorder; (3) impulse-control disorder; (4) polysubstance abuse; (5) psychotic disorder not otherwise specified; (6) pain disorder; (7) hypochondriasis; (8) hypoactive sexual desire disorder; (9) circadian rhythm sleep disorder, delayed sleep phase type; (10) bulimia nervosa; and (11) adjustment disorder (with work inhibition). It is apparent that those conditions place special emphasis on selected affective features, such as disinhibited behavior, temperamentality, lability, vegetative disturbances, and psychomotor retardation. What follows is a systematic examination of

the differential diagnosis of mood disorders with their more classic boundaries.

ALCOHOL AND SUBSTANCE USE DISORDERS The high comorbidity of those disorders with mood disorders cannot be explained merely as the chance occurrence of two prevalent disorders. Self-medication for mood symptoms is insufficiently appreciated by both psychiatrists and addictionologists. Given the clinical dangers of missing an otherwise treatable disorder, mood disorder should be given serious consideration as the primary diagnosis if marked affective manifestations continue beyond the period of detoxification (for example, two months). That consideration also pertains to cyclothymic disorder and dysthymic disorder, which are common substrates for self-medication. The clinical validating strategies listed can further buttress a mood disorder diagnosis.

The DSM-IV category of substance-induced mood disorder (Table 16.6-20) is difficult to validate clinically because, in the absence of an affective diathesis, detoxification will usually clear affective disturbances occurring in persons who abuse substances. In the author's view, a dual diagnosis of both a mood disorder and a substance use disorder is a better alternative than is the DSM-IV construct.

PERSONALITY DISORDERS The state dependency of most personality measures is well documented. Accordingly, as exhorted by DSM-IV, clinicians should refrain from using personality disorder labels in describing patients with active affective illness, but should focus instead on treating the disorder. As discussed earlier, even in those with chronic or intermittent subsyndromal mood disorders, personality maladjustment is postaffective, arising from the distortions and conflicts that mood disturbances produce in the life of the sufferer. The most problematic of the personality labels used in those with mood disorders is borderline personality disorder, usually applied to teenage and young adult patients. The DSM-IV diagnostic criteria for the disorder indicate a liberal assemblage of low-grade affective symptoms. As shown in Table 16.6-41, the overlap between borderline personality disorder and mood disorders is extensive, so that giving a borderline personality disorder diagnosis to a person with mood disorder is redundant. When personality disorder diagnoses are used, they lead to neglect of the mood disorder. Although much more research needs to be done on the complex interface of personality disorders and mood disorders, clinically they may be inseparable. As with alcohol and substance use disorders, it appears preferable to diagnose mood disorders at the expense of personality disorders, which should not be difficult to justify in most cases where the validating strategies outlined are satisfied. Although not all personality disturbances recede with the competent treatment of mood disorders, so many experienced clinicians have seen such disturbances disappear with the successful resolution of the mood disorder that erring in favor of mood disorders is justified.

TABLE 16.6-41
Overlap of Borderline Personality Disorder and Mood Disorders

Familial: High rates of mood disorder	
Phenomenology:	Dysthymic disorder
	Cyclothymic disorder
	Bipolar II disorder
	Mixed state
Pharmacological response:	Worsening on tricyclic antidepressants
	Stabilization on anticonvulsants
Prospective course:	Major mood episodes
	Suicide

Summarized from H Akiskal, S Chen, G Davis, V Puzantian, M Kashgarian, M Bolinger: Borderline: An adjective in search for a noun. J Clin Psychiatry *46:* 41, 1985.

TABLE 16.6-42
Misdiagnosis in the Affectively Ill Juvenile Kin of Adults with Bipolar Disorder

Total (N = 44)	Percent
Adjustment disorder	35
Conduct disorder	15
Attention-deficit/hyperactivity disorder	9
Mental retardation	6
Separation anxiety disorder	9
Overanxious disorder	11
Schizophrenia	15

Table adapted from H S, Akiskal, J Downs, S Watson, D Daugherty, D B Pruitt: Affective disorders in referred children and younger siblings of manic-depressives. Arch Gen Psychiatry *43:* 996, 1985.

The interface of mood disorders and behavioral disorders in children is even more problematic than in adult psychiatry. Some progress has occurred in recognizing certain behavioral manifestations as possible signs of depression in juvenile patients, including (1) decline in school performance; (2) restlessness and pulling or rubbing hair, skin, or clothing; (3) outbursts of complaining, shouting, or crying; and (4) aggressive or antisocial acts. Examined carefully, many of the children will meet the specific criteria for the diagnosis of major depressive disorder or dysthymic disorder. It is important, however, to note that many children do not complain of subjective dysphoria; instead, the clinician can observe the depressed affect in the child's facial expressions or overall demeanor. In brief, after much resistance, many child clinicians have come to accept the existence of childhood depression. Bipolar disorder in children, even among adolescents, is still grossly underdiagnosed at the expense of so-called externalizing disorders. Table 16.6-42 lists those and related conditions often confused with bipolar disorders in juvenile patients. In many of the children bipolar disorder is expressed in explosive outbursts of irritable mood and behavior (that is, as a mixed or dysphoric manic state). Another common pattern is intermittent hypomania and cyclothymia. The correct diagnosis depends on the index of suspicion by a clinician who is convinced that bipolarity exists in childhood.

NORMAL BEREAVEMENT As bereaved persons exhibit many depressive symptoms during the first one or two years after their loss, how can the 5 percent of bereaved persons who have progressed to a depressive disorder be identified? Here are some points on which they differ:

1. Whereas grieving persons, and their relatives, perceive bereavement as a normal reaction, those with depressive disorder often view themselves as sick, and may actually believe they are losing their minds.
2. Unlike the melancholic person, the grieving person is reactive to the environment, and tends to show a range of positive affects.
3. Marked psychomotor retardation is not observed in normal grief.
4. Although bereaved persons sometimes feel guilty about not having done certain things that might have saved the life of the deceased loved one, they typically do not experience guilt of commission.
5. Delusions of worthlessness or sin, and psychotic experiences in general, point toward mood disorder.
6. Active suicidal ideation is rare in grief but common in major depressive disorder.

Alkermes, Ex. 1060

7. Mummification, which refers to keeping the belongings of the deceased person exactly as they were before his or her death, is indicative of psychopathology.
8. Severe anniversary reactions should alert observers to the possibility of psychopathology.

In another form of bereavement depression, the sufferer simply pines away, unable to live without the departed person, usually a spouse. Although not necessarily pathological by the foregoing criteria, such persons do have a serious medical condition. Their immune function is often depressed and their cardiovascular status is precarious. Death within a few months of that of a spouse can ensue, especially among elderly men. Such considerations suggest that it would be clinically unwise to withhold antidepressants from certain persons experiencing an intensely mournful form of grief.

ANXIETY DISORDERS Anxiety symptoms—including panic attacks, morbid fears, and obsessions—are common during depressive disorders, and depression is a common complication of anxiety states. Systematic British studies have shown that early-morning awakening, psychomotor retardation, self-reproach, hopelessness, and suicidal ideation are the strongest clinical markers of depression in that differential diagnosis. On follow-up of depressed patients, the manifestations tend to remit, whereas those with anxiety states continue to exhibit marked tension, phobias, panic attacks, vasomotor instability, feelings of unreality, and perceptual distortions, as well as hypochondriacal ideas. A predominance of such anxiety features antedating the present disorder suggests the diagnosis of an anxiety disorder. Given that anxiety disorders rarely make their first appearance after the age of 40, such late appearance of marked anxiety features strongly favors the diagnosis of melancholia. The clinical picture is often one of morbid groundless anxiety with somatization, hypochondriasis, and agitation. The patient's depressive nature is further supported by the superior response to ECT.

Periodic monosymptomatic phobic and obsessional states also exist that can be regarded as affective equivalents, based on a family history of mood disorders and the response to thymoleptic agents, including lithium. There are also social phobias that usher in an adolescent depression, even a bipolar disorder.

The psychopathological differentiation of anxiety and depressive states has not been entirely resolved. Cognitive factors may best differentiate them (Table 16.6-43). Although recurrent (especially retarded) major depressive disorder is a distinct disorder from anxiety states, at least some forms of depression may share a common diathesis with anxiety disorders. Before assigning patients to such a putative mixed anxiety-depressive group (not yet an official nosological entity), the clinician must note that anxiety that arises primarily during depressive episodes is best considered as exiphenomenal to depressive disorder. The same is generally true for anxiety symptoms that occur in a person with depressive disorder who is using alcohol or sedative-hypnotic or stimulant drugs. Finally, anxiety symptoms could be prominent features of mixed bipolar states as well as of complex partial seizures.

TABLE 16.6-43
Unique Cross-Sectional Profiles of Clinical Anxiety and Depression

Anxiety	Depression
Hypervigilance	Psychomotor retardation
Severe tension and panic	Severe sadness
Perceived danger	Perceived loss
Phobic avoidance	Loss of interest—anhedonia
Doubt and uncertainty	Hopelessness—suicidal
Insecurity	Self-deprecation
Performance anxiety	Loss of libido
	Early-morning awakening
	Weight loss

Table from H S Akiskal: Toward a clinical understanding of the relationship of anxiety and depressive disorders. In *Comorbidity of Mood and Anxiety Disorders*, J P Maser, C R Cloninger, editors, p 597. American Psychiatric Press, Washington, 1990. Used with permission.

PHYSICAL DISEASE Somatic complaints are common in depressive disorders. Some, such as vegetative disturbances, represent the hypothalamic pathology that presumably underlies a depressive disorder. Autonomic arousal, commonly associated with depression, could explain such symptoms as palpitations, sweating, and headache. In some instances the physical symptoms might reflect delusional experiences.

Depression in the setting of physical disease The clinician must be alert, however, to the fact that somatic complaints in depression could also reflect an underlying physical illness. Table 16.6-44 lists the most common medical conditions that have been associated with depression. When depressive symptoms occur in the setting of physical illness, it is not always easy to determine whether they constitute a genuine depressive disorder. Before diagnosing depression, psychiatrists must make sure that they are not dealing with pseudodepression: (1) functional loss due to physical illness; (2) vegetative signs, such as anorexia nervosa, as manifestations of such an illness; (3) stress and demoralization secondary to the hospitalization; (4) pain and discomfort associated with the illness; and (5) medi-

TABLE 16.6-44
Pharmacological Factors and Physical Diseases Associated with Onset of Depression

Pharmacological	Steroidal contraceptives
	Reserpine; α-methyldopa
	Anticholine-esterase insecticides
	Amphetamine or cocaine withdrawal
	Alcohol or sedative-hypnotic withdrawal
	Cimetidine; indomethacin
	Phenothiazine antipsychotics
	Thallium; mercury
	Cycloserine
	Vincristine; vinblastine
Endocrine	Hypothyroidism and hyperthyroidism
	Hyperparathyroidism
	Hypopituitarism
	Addison's disease
	Cushing's disease
	Diabetes mellitus
Infectious	General paresis (tertiary syphilis)
	Toxoplasmosis
	Influenza; viral pneumonia
	Viral hepatitis
	Infectious mononucleosis
	AIDS
Collagen	Rheumatoid arthritis
	Lupus erythematosus
Nutritional	Pellagra
	Pernicious anemia
Neurological	Multiple sclerosis
	Parkinson's disease
	Head trauma
	Complex partial seizures
	Sleep apnea
	Cerebral tumors
	Cerebrovascular disorder
Neoplastic	Abdominal malignancies
	Disseminated carcinomatosis

Alkermes, Ex. 1060

cation side effects. The presence of the following might be useful in supporting a mood disorder diagnosis in the presence of physical illness: (1) persistent anhedonia; (2) social withdrawal; (3) observed depressed mood with frequent crying; (4) observed psychomotor retardation or agitation; (5) indecisiveness; (6) convictions of failure, worthlessness, or guilt; (7) suicidal ideation; (8) nonparticipation in the process of medical care.

One of the most difficult problems making the interface of mood disorder and physical disease is the rare development of malignancy in patients with an established mood disorder. The patient who had responded well to a given antidepressant during previous episodes will now evince an unsatisfactory response to the same medication. Even a small dose (for example, imipramine [Tofranil], 25 mg) may cause such alarming symptoms as agitation, dizziness, depersonalization, and illusions, which might be indicative of an occult malignancy, perhaps in the abdomen or the brain. Thus the psychiatrist should always be vigilant about the appearance of life-threatening physical diseases in patients with preestablished depressive disorder.

Stupor Although less common today, stupor still raises a diagnostic problem in differentiating between a mood disorder and somatic disease, as well as other psychiatric disorders. It is relatively easy to distinguish depressive stupor from so-called hysterical mutism or nonresponsiveness; in the latter, behavior is meaningfully directed to significant others in the patient's environment. The rubric of catatonic stupor is best reserved for a phase of schizophrenia; in such patients the schizophrenic origin of the catatonia might be apparent from the patient's history. Otherwise, most acute-onset stupors are probably affective in origin. The main differential diagnosis here is from organic stupor (due to drugs or acute intracranial events); the physical and neurological examination is not always decisive in such cases, and diagnosis depends on a high index of suspicion concerning possible somatic factors.

Depressive pseudodementia The geriatric equivalent of semistupor in younger persons with depressive disorder, it is distinguished from primary degenerative dementia by (1) its acute onset; (2) a history of past affective episodes; (3) self-reproach; (4) diurnality of the cognitive dysfunction (worse in the morning); (5) the circumscribed nature of those deficits, which, with proper coaching, can be reversed; and (6) a tendency to improve with sleep deprivation.

Chronic fatigue syndrome The syndrome represents a complex differential diagnostic problem in view of the subtle nature of the immunological disturbances presumably associated with it. The following self-report by such a patient illustrates many of the uncertainties marking the present knowledge of the interface between the syndrome and mood disorders.

I am a 39-year-old, never-married woman, trained as a social worker, but currently on disability. I have experienced extreme lethargy and fatigue for many years. I have always felt foggy headed and had trouble thinking and concentrating. My complaint is of fatigue, not of depression. My body feels like lead and aches all over. My brain feels achy and sore. I feel much worse in the morning and I can't get out of bed; I feel better at night. I feel bad every day. I ache all over, as though someone had beaten me up. Exercise has been prescribed to me, but it makes me worse. Also, I am very sensitive to hot and cold. My sexual drive is low. I have a general feeling of anhedonia. As far back as I remember—in junior high school—I was always exhausted. I always complained about fatigue, *not* depression, because that has been the overwhelming problem. I feel the depression is secondary to the fatigue. In high school I was a compulsive overeater and I was bulimic for a few years, but it was never severe and I was only about 10 pounds overweight. In those days I would sleep 10 or 12 hours a night on the weekend and still feel exhausted; I could not get up for school on Monday. As an adolescent, I felt inferior. I couldn't make decisions, I didn't want to go to camp or leave home for long periods of time—I felt so insecure. Recently I had a sleep study done, which showed a short latency to stage REM sleep (49 minutes). I was diagnosed as having dysthymic disorder, and began taking antidepressants. When I took tranylcypromine (Parnate), it was the first time in my life that I felt like a normal person. I could play sports, I had a sex drive, I had energy, and I was able to think clearly. But the benefits lasted for barely two months. My response was equally short-lived to phenelzine (Nardil), imipramine (Tofranil), seligeline (Eldepryl), and bupropion (Wellbutrin). I have not responded to serotonin-specific reuptake inhibitors (SSRI) at all. I also wish to point out that I had never experienced high periods before I took antidepressants. My main problem has always been one of exhaustion. When I responded to medications, they worked very quickly (within a few days) and I felt great, but they all stopped working after a short time. The dose would be raised, and again I would feel better. Eventually, when I got to high doses, I either could not tolerate the high dose or the drug would no longer help. I have taken different combinations of drugs for 10 years and I haven't been able to feel well for more than six weeks at a time. Recently, I went to an immunologist. He said I have an abnormality in regulating antibody production and recommended gammaglobulin shots. They did not help. When I first started working, I always felt tired and foggy headed, so it was difficult to be sharp while at work. At times I would close the door to my office and put my head down. Working has become increasingly difficult for me. I had two great jobs, which I blew. As of last year I had to go on disability. I am desperate for relief, as my condition has drastically affected my life. Disability has been hard for me. I am single and have no other financial resources. I am very despondent, as I feel that my life is passing by without the hope of my ever really improving.

Many mood disorder experts will consider that the foregoing clinical picture is compatible with pseudounipolar (bipolar III) disorder with an endogenous dysthymic disorder base. Some virologists and immunologists, and some psychiatrists, believe that abnormal humors circulate in the bloodstream that bathes the brains of such patients. Pending the positive identification of those humors, a mixture of phlegm and black bile is as adequate an explanation as any other! While awaiting more definitive research on the etiology of chronic fatigue, the psychiatrist can cautiously consider certain patients for thymoleptic trials. That decision can be bolstered by the following considerations: (1) fatigue is not alleviated by sleep or rest; and (2) the patient wakes up with it; (3) fatigue is part of a more generalized psychomotor inertia or lack of initiative; (4) fatigue is associated with anhedonia, including sexual anhedonia; and (5) fatigue coexists with anxious and pessimistic ruminations. Although none of the foregoing alone is pathognomonic for depression, in aggregate they point in that direction. The occurrence of hypomaniclike periods (as in the above vignette) further supports the link between chronic fatigue and mood disorder. Lithium and valproate, though not yet formally tested in such patients, represent rational choices.

SCHIZOPHRENIA Cross-sectionally, young bipolar patients might seem psychotic and disorganized and thus appear schizophrenic. Their thought processes are so rapid that they may seem loose, but, unlike in schizophrenia, it will be in the setting of expansive and elated affect. By contrast, the severely retarded bipolar depressive person, whose affect may superficially seem flat will almost never exhibit major fragmentation of thought. The clinician, therefore, should place greater emphasis on the pattern of symptoms, rather than on individual symptoms, in the differential diagnosis of mood and schizophrenic psychoses. There actually are no pathognomonic differentiating signs and symptoms. Differential diagnosis should be based on the overall clinical picture, phenomenology, family history, course, and associated features. Because the two groups of disorders entail radically different pharmacological treatments on a long-term basis, the differential diagnosis is of major clinical importance. Table 16.6-45, summarizing the author's research in the area, lists the most common pitfalls in the task of diagnosis.

Alkermes, Ex. 1060

TABLE 16.6-45
Misdiagnosis of Mood Disorder as Schizophrenia

Common pitfalls:
- Reliance on cross-sectional rather than longitudinal picture
- Incomplete interepisodic recovery equated with schizophrenic defect
- Equation of bizarreness with schizophrenic thought disorder
- Ascribing of irritable and cantankerous mood to paranoid delusions
- Mistaking of depressive anhedonia and depersonalization for schizophrenic emotional blunting
- Flight of ideas perceived as loose associations
- Lack of familiarity with the phenomenological approach in assessing affective delusions and hallucinations
- Heavy weight given to incidental Schneiderian symptoms

In the past many bipolar patients, especially those with prominent manic features at onset, were labeled as having acute schizophrenia or schizoaffective schizophrenia. Such misdiagnosis, which typically led to long-term treatment with antipsychotics, has proved very costly in view of the likelihood of tardive dyskinesia, vocational and social decline, and even suicide. Thus some patients with postpsychotic depressive disorder of schizophrenia in the DSM-IV scheme (Table 16.6-40) represent postmanic depressions that have been treated with antipsychotics.

Modern treatments, which tend to keep many persons with schizophrenia out of the hospital, do not seem to prevent an overall downhill course; by contrast, the intermorbid periods in bipolar illness are relatively normal or even supernormal, yet over time some social impairment may result from the accumulation of divorces, financial catastrophes, and ruined careers. (Although rapid-cycling disorders, which seem to be on the rise during the past decade, cause considerable social impairment, mood symptoms are of such prominence that differentiation from schizophrenia is generally not difficult; also, in such cases there is usually a more classic bipolar phase before the rapid cycling).

The postpsychotic depressions among persons with established schizophrenia are sometimes due to inadequate control of schizophrenic symptomological or pharmacological features. In other patients, especially more intelligent young schizophrenic patients, they reflect the experience of losing one's ego and sanity. It would be more meaningful to diagnose such patients with both schizophrenia and a depressive disorder. The concept of postpsychotic depression is too vague.

SCHIZOAFFECTIVE DISORDER The diagnosis should not be made for depressions in the setting of well-established schizophrenia as discussed above, but the concept of schizoaffective (or cycloid) psychosis should be restricted to recurrent psychoses with full affective and schizophrenic symptoms occurring nearly simultaneously during each episode. Such a diagnosis should not be considered in a mood psychosis where mood-incongruent psychotic features (for example, Schneiderian and Bleulerian symptoms) can be explained on the basis of one of the following: (1) affective psychosis superimposed on mental retardation, giving rise to extremely hyperactive and bizarre manic behavior; (2) affective psychosis complicated by concurrent brain disease, substance abuse, or substance withdrawal, known to give rise to numerous Schneiderian symptoms; (3) mixed episodes of bipolar disorder, which are notorious for signs and symptoms of psychotic disorganization.

In official diagnostic systems such as that of DSM-IV, the category of schizoaffective disorder is used broadly. Thus patients with clear-cut manic episodes will receive a schizoaffective diagnosis if delusions or hallucinations occur in the interepisodic period, in the absence of prominent affective symptoms. As discussed earlier, many psychotic symptoms in mood disorders often are of an explanatory nature, albeit delusional, whereby the patient tries to make sense of the core experiences of the illness. In patients with recurrent episodes, delusional thinking can be carried over into the interepisodic period. Such patients would thus be delusional in the absence of prominent mood symptoms and, technically (that is, by research diagnostic or DSM-IV criteria), might be considered schizoaffective. The author does not concur with that convention. Affective illness is typically a lifelong process, and it is artificial to limit its features to discrete episodes. Although antipsychotics might be prescribed on an as needed basis to reduce the strong affective charge of those interepisodic delusions, they are not effective in eliminating the affect-laden experiences. Continued thymoleptic treatment (resorting to ECT, if necessary) in the context of an empathic psychotherapeutic approach is more rewarding in the long run.

A 29-year-old female college graduate, mother of two children and married to a bank president, had experienced several manic and retarded depressive episodes that had responded to lithium carbonate. She was referred to the present writer, because she had developed the delusion that she had been involved in an international plot. Careful probing revealed that the delusion represented further elaboration, in a rather fantastic form, of a grandiose delusion she had experienced during her last postpartum manic episode; she believed she had played an important role in uncovering the plot, thereby becoming a national hero. Nobody knew about it, she contended, as the affair was top secret. She further believed that she had saved her country from the international scheme, and suspected that she was singled out for persecution by the perpetrators of the plot. At one point she had even entertained the idea that the plotters sent special radio communications to intercept and interrupt her thoughts. As is typical in such cases, she was on a heavy dosage of a lithium-antipsychotic combination. The consultation was requested because the primary mood symptoms were under control, and yet she had not given up her grandiose delusion. She flippantly remarked that one should be "crazy" to believe in her involvement in an international plot, but she could not help but believe in it. Over a period of several months, seen typically in 60 minute to 90-minute sessions weekly, the patient had developed sufficient trust that the author could gently challenge her beliefs.

She was, in effect, told that her self-professed role in the international scheme was highly implausible, and that someone with her superior education and high social standing could not entertain a belief, to use her own words, "as crazy as that." She eventually broke into tears, saying that everyone in her family was so accomplished and famous that, to keep up with them, she had to be involved in something grand; in effect, the international scheme, she said, was her only claim to fame: "Nobody ever gives me credit for raising two kids, and throwing parties for my husband's business colleagues. My mother is a dean, my older brother holds high political office, my sister is a medical researcher with five discoveries to her credit [all true], and who am I? Nothing. Now, do you understand why I need to be a national hero?" As she alternated, over subsequent months, between such momentary flashes of insight and delusional denial, antipsychotic medication was gradually discontinued. Maintained on lithium, she now only makes passing reference to the grand scheme. She was encouraged to pursue her career goal toward a master's degree in library science.

The vignette illustrates how phenomenological understanding, rational pharmacotherapy, and practical sociotherapeutic or vocational guidance can be fruitfully combined in the approach to patients with psychotic mood disorders. At a more fundamental level it suggests that clinical diagnoses in psychiatry cannot be entirely based on operational criteria, as what one thinks of patient's illnesses not infrequently changes based on how they respond to treatment. In the author's opinion, DSM-IV represents something good (operationalization of diagnostic criteria) carried to a ridiculous extreme (arbitrary precision often divorced from clinical reality).

SUGGESTED CROSS-REFERENCES

Diagnosis and psychiatry are discussed in Chapter 9, the clinical manifestations of psychiatric disorders are covered in Chapter

Alkermes, Ex. 1060

10, and the classification of mental disorders is presented in Chapter 11. Schizophrenia is the subject of Chapter 14. The somatic treatment of mood disorders is discussed in Section 16.7 and their psychosocial treatment in Section 16.8. Mood disorders and suicide in children are the topic of Chapter 44, anxiety disorders are presented in Chapter 17, and mood disorders in geriatric psychiatry are discussed in Section 49.6b.

REFERENCES

Akiskal H S: Dysthymic and cyclothymic depressions; therapeutic considerations. J Clin Psychiatry *55:* 46, 1994.

Akiskal H S, Akiskal K: Re-assessing the prevalence of bipolar disorders: Clinical significance and artistic creativity. Psychiatr Psychobiol *3:* 29s, 1988.

*Akiskal H S, Maser J D, Zeller P, Endicott J, Coryell W, Keller M, Warshaw M, Clayton P, Goodwin F K: Switching from "unipolar" to bipolar II: An 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry *52:* 114, 1995.

Andreasen N C, Akiskal H S: The specificity of Bleulerian and Schneiderian symptoms: A critical reevaluation. Psychiatr Clin North Am *6:* 41, 1983.

Beard G M: *A Practical Treatise on Nervous Exhaustion (Neurasthenia): Its Nature, Sequences, and Treatment*. Wood, New York, 1881.

Cassano G B, Akiskal H S, Savino M, Musetti L, Perugi G, Soriani A: Proposed subtypes of bipolar II disorder: With hypomanic episodes and/or with hyperthymic temperament. J Affect Disord *26:* 127, 1992.

Clayton P J: The sequelae and nonsequelae of conjugal bereavement. Am J Psychiatry *136:* 1530, 1979.

Coryell W, Winokur G, Shea T, Maser J, Endicott J, Akiskal H S: The long-term stability of depressive subtypes. Am J Psychiatry *151:* 701, 1994.

Davidson J R, Miller R D, Tumbull C D, Sullivan J L: Atypical depression. Arch Gen Psychiatry *39:* 527, 1982.

Himmelhoch J M, Mulla D, Neil J F, Detre T P, Kupfer D J: Incidence and significance of mixed affective states in a bipolar population. Arch Gen Psychiatry *33:* 1062, 1976.

James W: *The Varieties of Religious Experience*. Random House, New York, 1902.

Jouvent R, Hardy P, Bouvard M, Braconnier A, Roumengous V, Grasset F, Widlocher D: Heterogeneity of the depressive mood. Construction of a polydimensional scale. Encephale *13:* 233, 1987.

Judd L L, Rapaport M H, Paulus M P and Brown J L: Subsyndromal Symptomatic Depression: A New Mood Disorder? J Clin Psychiatry *55:* 18, 1994.

Kendler K S, Neale M C, Kessler R C, Heath A C, Eaves L J: A population-based twin study of major depression in women. The impact of varying definitions of illness. Arch Gen Psychiatry *49:* 257, 1992.

Klein D F: Endogenomorphic depression. A conceptual and terminological revision. Arch Gen Psychiatry *31:* 447, 1974.

*Kraepelin E (translated by R M Barclay): *Manic-Depressive Insanity and Paranoia*, G M Robertson, editor. Livingstone, Edinburgh, 1921.

*Kretschmer E (translated by E Miller): *Physique and Character*. Kegan, Paul, Trench, Trubner, London, 1936.

Nelson J C and Charney D S: The symptoms of major depressive illness. Am J Psychiatry *138:* 1, 1981.

*Nesse R M: What good is feeling bad? Sciences Nov/Dec: 30, 1991.

Rosenthal N E: *Winter Blues*, New York, Guilford Press, 1993.

Taylor M A and Abrams R: The phenomenology of mania: a new look at some old patients. Arch Gen Psychiatry *29:* 520, 1973.

*Widlocher D J: Psychomotor retardation: Clinical, theoretical, and psychometric aspects. Psychiatr Clin North Am *6:* 27, 1993.

Zisook S, Shuchter S R, Sledge P A, Paulus M and Judd L L: The spectrum of depressive phenomena after spousal bereavement. J Clin Psychiatry *55:* 29, 1994.

16.7 MOOD DISORDERS: SOMATIC TREATMENT

ROBERT M. POST, M.D.

INTRODUCTION

Treatment of the mood disorders has entered into a new era of therapeutics based on a variety of factors. There is increasing recognition that mood disorders have a prominent genetic component with well-documented neurobiological alterations that have been elucidated on biochemical, neuroendocrinological, and functional brain imaging measures. The descriptive and diagnostic aspects of the illness have been explicated, and it is recognized that in most cases the mood disorders are recurrent and have the potential for severe morbidity and even mortality. Thus, treatment requires the utmost in clinical management skills.

As knowledge of the classification, course, and mechanisms underlying acute episodes and their recurrences has increased, so also has the array of effective psychopharmacotherapeutic modalities and related somatic treatments. Although single drugs in one or two classes were available for the treatment of depression several decades ago, multiple therapeutic modalities now exist, often with many agents within each class. Thus, the treating physician should be aware of the nuances in the management of patients with acute and recurrent mood disorders so that treatment can be optimized from the outset and the impact of the illness on patients, their lives, and their families can be minimized.

There is also increasing consensus on several new treatment principles. Early recognition and intervention in an acute episode not only may save the patient months of pain and suffering but also may be lifesaving. More careful assessment of the efficacy of an agent at early and regular intervals, with early revision of the treatment modality if it is not optimal, is an important new guideline that applies not only to somatic treatments, but also to psychotherapeutic approaches and combination psychotherapy-pharmacotherapy when treatment is not proceeding optimally.

A large body of evidence supports the efficacy of long-term prophylactic management of recurrent mood disorders. Early institution of long-term prophylaxis is now recognized as a critical approach for the patient with recurrent mood disorders. Such an approach holds promise for reducing the morbidity of the illness and for altering favorably its subsequent course and treatment responsiveness. There is increasing consensus that a patient with a first episode of bipolar disorder is a candidate not only for continuation therapy following the resolution of that episode, but also for long-term prophylaxis, particularly if the patient has a family history of bipolar illness. Correspondingly, in major depressive disorder there is a new appreciation for the recommendation of prophylaxis after the third episode or two closely occurring episodes.

Thus, a variety of factors and guidelines shape the physician's approach to the patient with an acute episode of mood disorder. The illness should be treated with the same respect as is given to the early diagnosis and treatment of a malignancy, with the same skills brought to bear in choosing targeted and, at times, multimodal therapeutics. In a parallel fashion, early and effective intervention may be lifesaving, whereas delayed or inadequate treatment may be associated with considerable

Alkermes, Ex. 1060

acute and long-term morbidity from both the illness and its secondary consequences. The recurrent mood disorders should be conceptualized not as trivial, mental, or illusory phenomena that can easily be modified by patients' acts of will, but as serious and potentially life-threatening medical illnesses that have clearly defined mood, cognitive, motor, somatic, and neurobiological concomitants.

Major depressive disorder is a common illness, occurring in 7 to 12 percent of male patients and 20 to 25 percent of female patients during their lifetimes. Although bipolar disorder occurs in approximately 1 percent of the population, that percentage translates into 2.5 million people in the United States alone. The bipolar disorders are disabling in the short and long term. For example, it is estimated that the average woman with onset of a bipolar disorder at age 25 will lose 14 years of effective lifetime functioning as a result of the illness. In addition, up to 15 to 20 percent of patients with inadequately treated mood disorders commit suicide. Thus, diagnosis and treatment should be approached with the knowledge that the patient is experiencing a potentially recurrent, disabling medical illness.

HISTORY

Until the middle of the 20th century the available treatments for mood disorders were largely supportive and palliative. Electroconvulsive therapy (ECT) then emerged as efficacious treatment for major depressive disorder. In the following decades, the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants were introduced. Today, second- and third-generation treatment modalities are available. The latter preparations include drugs with novel structures, different mechanisms of action, and more benign side-effect profiles than the original agents. Those agents include the serotonin-specific reuptake inhibitors (SSRIs) (fluoxetine [Prozac], sertraline [Zoloft], paroxetine [Paxil], fluvoxamine [Luvox]), the mixed serotonergic-noradrenergic drug venlafaxine (Effexor), and the dopaminergic-noradrenergic agent bupropion (Wellbutrin). The emergence of a new range of acute antidepressant psychopharmacological agents raises important treatment issues for the clinician, particularly when those agents must be chosen on the basis of an inadequate literature on potential clinical and biological markers of responsiveness to a given drug in a given person. There is general consensus in the field that, with the possible exception of ECT, no antidepressant modality is more effective or more rapid in onset than another. Thus, agents may be chosen based on their side-effect profile, acceptability in long-term prophylaxis, and clinical lore regarding possible syndromal selectivity of response.

A similar revolution has occurred in the treatment of bipolar disorder. In the first half of the 20th century no adequate treatment for bipolar disorder was available, whereas in the second half lithium (Eskalith) emerged as a wonder drug for the acute and prophylactic management of the disorder. It is noteworthy, however, that there were marked oscillations in the assessment of the efficacy and utility of lithium, and it was initially abandoned as unsafe (until adequate monitoring of blood levels was devised so as to eliminate cardiovascular and central nervous system [CNS] toxic effects). After many decades of use, the limitations of lithium are better recognized. As many as 50 percent of patients do not show adequate response to lithium even when conservative criteria for clinical response, such as one episode of illness during a two-year follow-up, are employed. Fortunately, as the limitations of lithium were increasingly recognized, a variety of other treatment modalities became available, particularly the anticonvulsants carbamazepine (Tegretol) and valproate (Depakene, Depakote). However, as is the case of matching treatment to patient in the depressive disorders, there is even less evidence in the bipolar disorders for clinical and biological predictors of acute and long-term responsiveness to the mood-stabilizing agents.

In treating patients with bipolar disorders the clinician often has to resort to educated guesses and to systematic, sequential clinical trials to delineate optimal responsivity. Even with the availability of new treatment modalities, episodes of illness can emerge through otherwise partially successful pharmacoprophylaxis, necessitating adjunctive measures. The role of combination therapies is well recognized in many branches of medicine; for example, it is central to the treatment of congestive heart failure, tuberculosis, and most malignancies. By comparison, research on combination therapies in the mood disorders has lagged behind clinical practice, and clinicians are often left to their own devices without the aid of controlled studies as a guide for determining the optimal algorithm in cases refractory to standard treatments.

This section reviews the knowledge base gleaned from both systematic controlled clinical trials and anecdotal observations, and delineates novel treatment interventions that may be employed when patients fail to respond to first-, second-, and third-line treatment options. Although many of the specific recommendations may change in the years to come as the results of new, more systematic research are reported, the principles enunciated here should provide useful guidelines for physicians formulating optimal treatment options for acute and long-term prophylaxis for patients with mood disorders.

INITIAL DIAGNOSTIC AND THERAPEUTIC APPROACHES

IMPEDIMENTS TO ACUTE AND LONG-TERM TREATMENT Although the mood disorders are treatable, several illness-related variables complicate access to treatment and the ability of the patient to follow through. It is estimated that as many as 25 percent of patients with major depressive disorder do not receive treatment. Depressed patients often do not recognize their constellation of symptoms as a medical illness, and the symptoms of depression, such as motor retardation, apathy, inertia, and hopelessness, may preclude the patient's becoming involved in treatment. Thus, the patient's family, acquaintances, and medical physician may have to play active roles in encouraging the patient to initiate treatment.

Treatment must be conducted against the backdrop of the patient's distorted depressive cognitions, sense of hopelessness, and view of the untreatability of the illness. Patients should be informed that such beliefs and feelings are symptoms of the illness and that a positive response to treatment is likely, based on the literature and the physician's own experience with the illness. However, the physician's empirically based hope for recovery should be conveyed to the patient without the promise of immediate results. The physician should also explain that lags in onset of treatment efficacy are expected so that the patient does not misinterpret such delays as confirmation that the illness is untreatable. Finally, the risk for suicide during each phase of a depressive illness must be continually reassessed.

Similar impediments to the effective treatment of manic patients exist. For example, in the early stages of hypomania the sense of well-being and increased productivity may lead the patient to ignore more severe consequences of the illness, including irritability, intrusiveness, insomnia, poor judgment,

Alkermes, Ex. 1060

engagement in high-risk behaviors without appropriate appreciation of the consequences, and other activities and behaviors that may be detrimental to the patient's social structure, marriage, and employment. Early recognition of those symptoms as part of the illness may be crucial to instituting appropriate treatment and to preventing full-blown manic episodes in patients with bipolar I disorder.

There are important roles for the family in both the diagnostic evaluation and the ongoing treatment of a patient with a bipolar disorder. Family participation may be needed to assist the patient in confronting the denial of illness and the thought disorder that are associated with hypomania and mania and that can be just as great impediments to adequate treatment as are the apathy and hopelessness of depression. Therefore, therapeutic activism, engagement of the family, and early and aggressive treatment of mood disorders are important. The patient and family should receive immediate and regular information about the medical aspects of the illness, its course, and its response to treatment. The long-term goals of education are to increase compliance and destigmatize the illness. Compliance and destigmatization may become focal issues later in therapy when the physician considers recommendations for long-term prophylaxis; at that time society's negative attitudes toward taking psychotropic medications may have to be addressed. The conceptualization of mood disorders as medical illnesses that deserve the same attention and respect as other medical disorders may be important to the patient and family in choosing and committing to a long-term treatment option.

Thus, a variety of societal, attitudinal, and illness-related variables may interfere with appropriate help-seeking and maintenance behavior in the various phases of treatment of mood disorders. During each of the successive phases—acute care, continuation treatment, and long-term prophylaxis—the patient and family should be assisted in their evaluation of the medical data and the potential impact of the disorder on the patient. The variables affecting treatment should be addressed sequentially as they arise in each phase of the illness rather than in aggregate at the start of treatment. For example, the importance of continuation therapy, which should have a duration of four to nine months following the resolution of acute symptoms, should be discussed once the patient has begun to respond to treatment, rather than being raised with the acutely depressed patient, who may feel hopeless about ever achieving a therapeutic outcome.

Similarly, education on the importance of long-term treatment, with appropriate provision of data to the patient and family, may be critical for achieving an optimal outcome. Patients taking medications long term for any reason may decide to test the need for therapy by discontinuing the medication. As an example, even with an illness such as juvenile diabetes, in which it is unequivocally demonstrated that the patient cannot survive without adequate insulin treatment, many adolescents nevertheless feel compelled to test the long-term need for insulin and consequently experience periods of marked hyperglycemia that often lead to hospitalization. In parallel fashion, it should be anticipated that patients with bipolar mood disorders are likely to be tempted to discontinue their recommended treatment, all the more so because data on the potential lethality of the regimen or its morbid consequences may be less well delineated. Consequently, the treating clinician has the educational responsibility of providing patients and families with information on the high likelihood of a recurrence in a relatively short time in patients with several prior episodes and with information on the ability of a variety of antidepressant agents and bimodal mood-stabilizing agents to prevent recurrences of major depressive disorder and bipolar disorder, respectively.

After several prior episodes of major depressive disorder, the likelihood of a new episode after successful, acute antidepressant treatment and placebo substitution is approximately 50 percent in the first year and increases with time. Maintenance treatment can reduce that rate by more than half. Although often a helpful adjunct, long-term psychotherapy cannot substitute for pharmacotherapy in the prophylaxis of either major depressive disorder or bipolar disorder.

In bipolar disorder the high likelihood of relapse (80 to 90 percent) following lithium discontinuation is widely recognized. In addition, although it had previously been assumed that if a well-treated patient experienced a relapse following drug discontinuation, the patient would readily respond again once treatment was reinstituted, several reports of lithium discontinuation-induced refractoriness have been noted. After long periods of successful lithium treatment, the patients discontinued the drug, experienced a relapse, and did not re-respond once treatment was restarted at similar or higher doses. Other patients may not respond as rapidly as they did to the first treatment sequence. Several studies suggest that lithium may be less effective in patients who experienced more than three or four episodes prior to lithium initiation than in those in whom lithium is initiated earlier in the illness sequence. Thus, in recommending long-term preventive therapy, the physician should consider not only the potential morbidity and mortality of an episode recurrence, but also the possibility that new episodes could affect the subsequent course of the illness and its pharmacological responsivity.

PSYCHIATRIC HISTORY A thorough history and medical examination is paramount. Because several medical conditions may mimic both manic and depressive syndromes, the diagnosis should be approached from the perspective that a medical cause may exist for the illness until proved otherwise. Throughout the history taking and physical examination, attention should be paid to obvious and subtle hallmarks of associated pathology. The physician should be alert to the signs and symptoms indicative of CNS neuropathology, underlying endocrinopathy, and associated medical illness. Although aggressive in exploring those themes with the patient and family, the physician should directly state that the patient's somatic and vegetative symptoms are most likely indicative of a typical depressive process.

Thus, even the earliest parts of the history taking can be used not only for diagnostic purposes but also to begin educating the patient about the types of symptoms that are characteristic of mood disorders, the likely course of remission of episodes, and the likely response to somatic and pharmacological interventions. Simultaneously, the physician should be isolating the target symptoms for future assessment of the efficacy of psychological and pharmacological interventions and constructing a framework for longitudinal monitoring of the patient. The same symptoms are likely to appear in future recurrences and thus may provide an early warning system to aid in early detection and the aggressive institution of treatment. The medical history and examination should also look for evidence of glaucoma (a relative contraindication to anticholinergic antidepressants) and cardiac, renal, and thyroid abnormalities that may preclude certain treatments.

A detailed family history of medical and psychiatric illness is crucial to the initial diagnostic assessment of the patient. It is recommended that a formal family tree be graphically constructed and information recorded on the potential diagnosis, course of illness, and response to therapy of each first-degree relative, as that information may provide a guide to current treatment of the patient. Patients with a positive family history

of bipolar disorder should be more strongly considered for prophylaxis after the first manic episode than those without such a family history. Similarly, patients with a family history of major depressive disorder should be strongly considered for prophylaxis after two depressive episodes. Some data suggest that clinical response to a given agent may generalize across family members or generations; in the absence of other clinical predictors, that may provide a reasonable initial treatment guideline.

Graphing the course of illness The author suggests developing a graphical representation of the patient's prior depressive and manic episodes (Figures 16.7-1 through 16.7-4). A formal graphical representation of the patient's longitudinal course of illness is useful for several reasons: (1) It provides a clear-cut picture of the earlier course of illness (which appears to be the best predictor of the future pattern of episodes). (2) It clarifies medication responsiveness (by indicating the efficacy of previous treatments, if any) and helps in the medicalization of the history taking and management process (with regard to current and future prescriptions). (3) It encourages the patient to collaborate and thus may enhance the doctor-patient relationship by bringing the patient into the process as an active rather than passive participant. (4) If a number of past recurrences are uncovered in the history, that information may help in determining the subsequent long-term approach to the illness and in identifying the patient's willingness to comply with prescribed regimens. (5) Graphing the course of illness often uncovers important psychosocial events and possible precipitants of the illness; unique characteristics of the illness, such as seasonal variation and relation to anniversaries; and other patterns that cannot be discovered easily without systematic and graphical representation of the prior course. Elucidation of periods of increased vulnerability to illness provides a template for future intensification of observation and augmentation of therapeutic modalities as appropriate.

With a little practice the course of an illness can be graphed easily. It is suggested that graphing be done as part of the initial intake session and be the primary mode of history taking, rather than a verbal account that is later converted to graphical form. A graphical rather than verbal representation immediately and systematically focuses the patient and physician on the longitudinal course of the illness and its variation over time. The graphical approach and its associated temporal landmarks can also facilitate recall of important events, dates, and episodes that would otherwise be obscured or forgotten.

Levels of severity Physicians can devise their own ways of plotting the longitudinal course of illness or can adopt a system like the one the author and his colleagues have used successfully over the past decade. That consists of graphing three levels—mild, moderate, and severe—of mania or depression, based on the degrees of associated functional incapacity, and can easily be assessed retrospectively (Figures 16.7-1 and 16.7-2).

MILD LEVEL The mild level is one in which the patient or family notes a distinct change from the patient's usual behavior without a notable impairment in the patient's functional status. This state is readily discerned by depressed patients and may represent the baseline of double depression from which more severe episodes erupt. Hypomanic patients, however, may deny a mild state, and the physician may have to obtain additional information from family members and relatives. (That observation underscores the utility of an initial nonanalytic approach

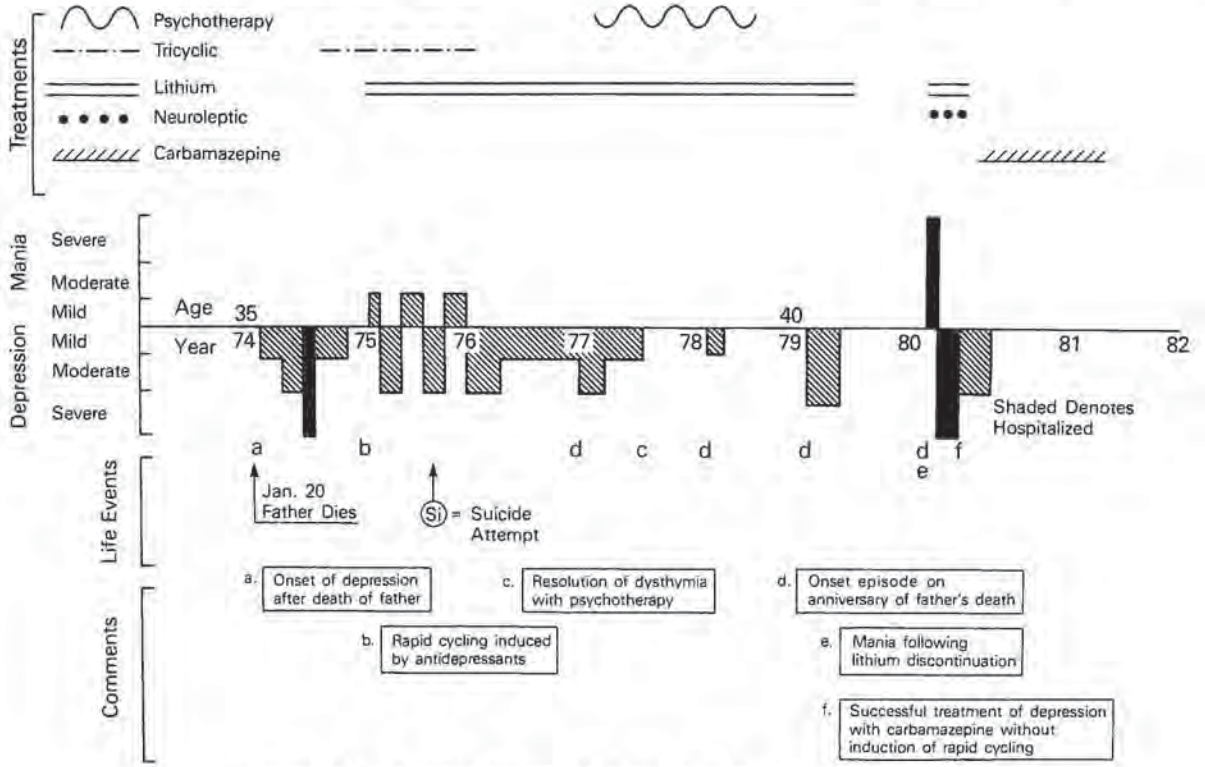

FIGURE 16.7-1 *Graphing the course of affective illness: Prototype of a life chart.*

Alkermes, Ex. 1060

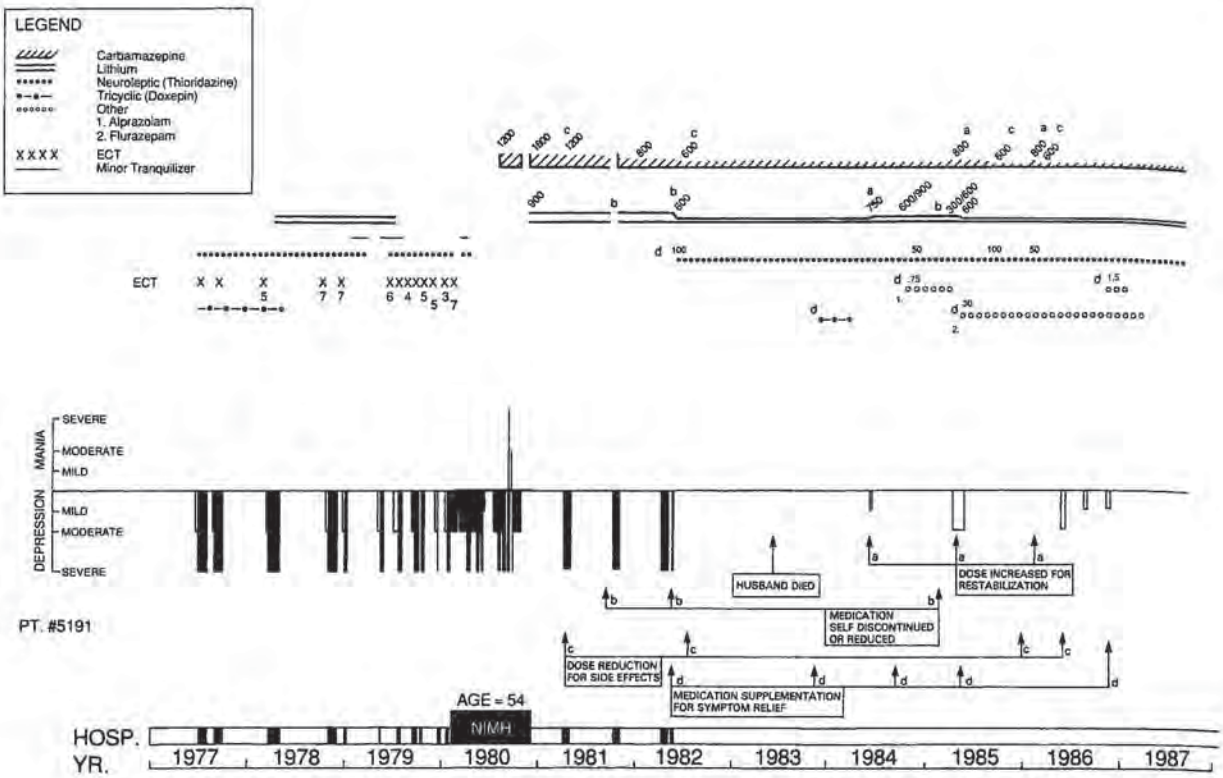

FIGURE 16.7-2 *Carbamazepine prophylaxis maintained with optimal management of dose titration against side effects.*

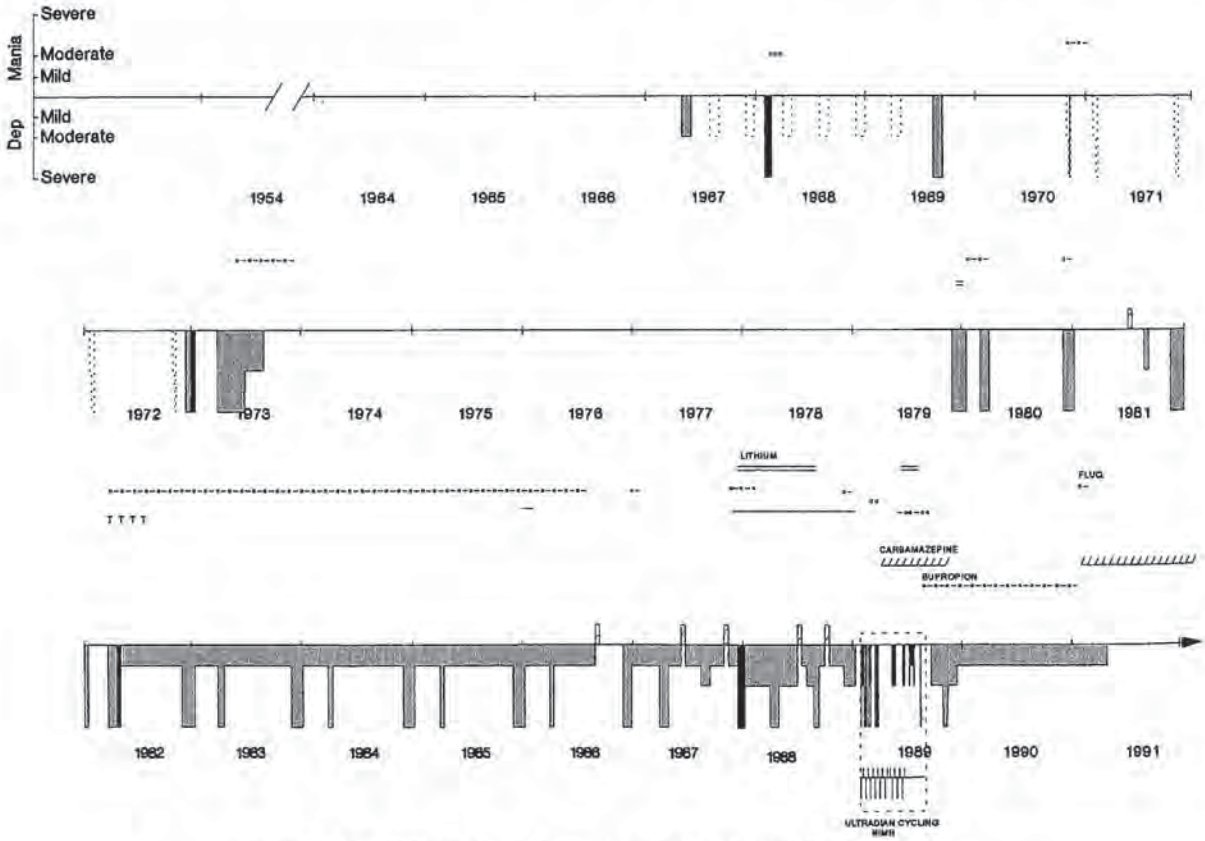

FIGURE 16.7-3 *Evolution of cycle frequency in a male patient with bipolar II disorder.*

Alkermes, Ex. 1060

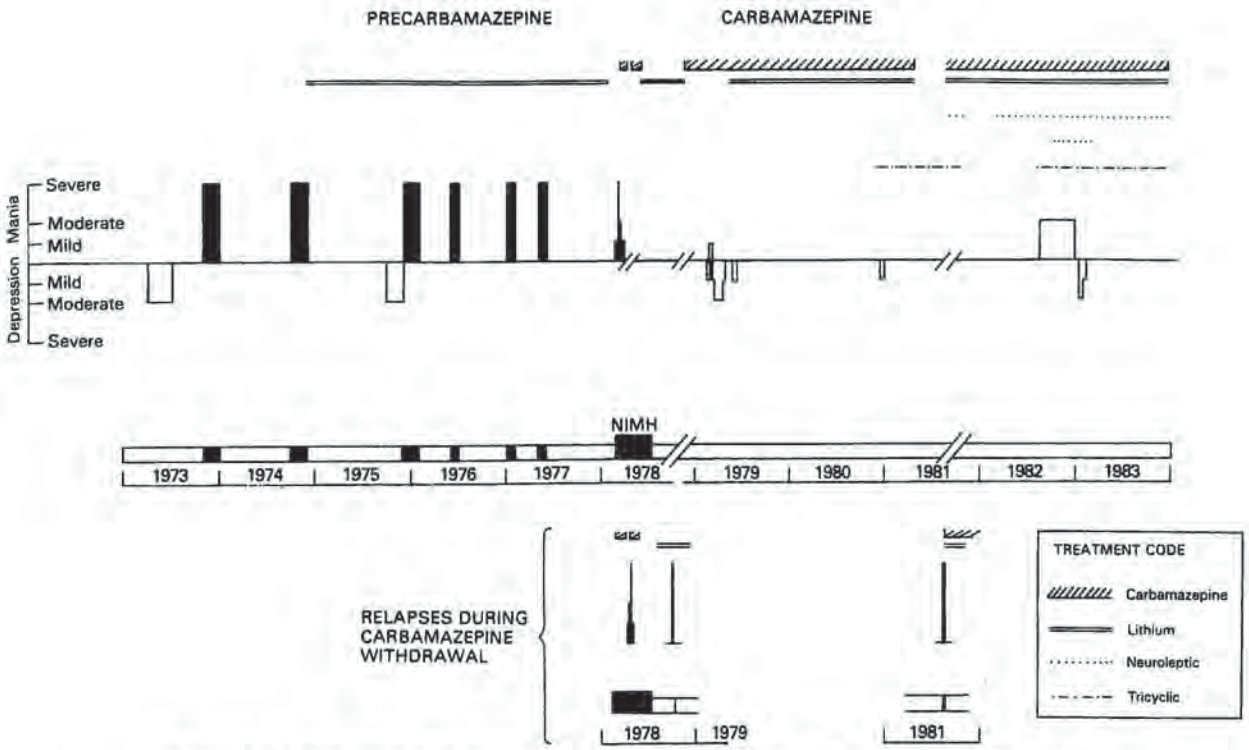

FIGURE 16.7-4 *Response to acute and prophylactic treatment with carbamazepine in a lithium nonresponder.*

to the patient's illness and its diagnosis and the value of family participation and support from the outset.) Information from the family may be of value in both gaining historical information and in managing the potential suicidality of depression and the denial of the adverse consequences of hypomania and mania. Hypomanic signs and symptoms such as distinct periods of increased energy, productivity, creativity, and decreased need for sleep should be asked about in a nonpejorative fashion. Those milder periods may also be easier to explore once the more severe phases of a patient's illness have been detected and the characteristic components of the early presentation agreed on.

MODERATE LEVEL Moderate levels of depression and mania can be graphed at the next level to represent illness with distinct functional impairment. Patients have difficulties continuing their social or employment responsibilities, showing absences from work or performance deficits on routine social tasks.

SEVERE LEVEL The third or severe level of impairment is graphed when patients are functionally incapacitated and are unable to perform consistently in their usual roles (that is, they are no longer able to go to work or to perform socially). Hospitalization can be indicated by shading in the severe manic or depressive episode. When an episode has occurred in the past but its precise timing is not available, it can be indicated on the life chart with dotted lines.

Earlier psychopharmacological interventions Superimposed on this template of mood fluctuations can be the history of prior psychopharmacological interventions, which is plotted above the mood disorder episodes, as illustrated in Figure 16.7-1 (life chart schema) and in Figures 16.7-2 and 16.7-3 (case examples). When plotted in this fashion, the efficacy of earlier treatments is often reclassified. A treatment previously deemed ineffective may, on careful reexamination, be shown to be partially effective (that is, a decreased frequency or severity of prior episodes compared with the pretreatment baseline may emerge). If that is the case, the reassessment may suggest supplementing this partially effective treatment rather than abandoning it. Previous psychotherapeutic interventions should also be included so that their impact on the illness and patient satisfaction can be assessed. Important psychosocial events (for example, anniversaries, suicide attempts) and other notes about drug side effects, dosages, reasons for discontinuation of medications, and the like can be noted below the mood graph (Figure 16.7-1).

Descriptive symptoms The anamnestic account of symptomatology provides a basis for following clinical improvement during an acute episode and possible subsequent episodes. The clinician should develop a sense for the major symptoms that are the best descriptors of a patient's episodes. In some patients impaired sleep with early morning awakening may be the major symptom; in others it may be inability to concentrate, decreased energy or increased agitation, isolation, anxiety, a change in appetite, or weight gain. The sequential ebbing of symptoms during a treated episode may be a clue to the duration of maintenance treatment required and to the earliest symptoms that may recur during a subsequent episode. Should the more difficult or residual symptoms emerge during prophylaxis, or should they recur or become more profound as medication is tapered, they can be used as indicators for renewed, more aggressive management of a potential episode.

Similarly, clinicians should decide on and make a contract with their patients in advance about specific symptoms that may

be forerunners to a manic episode and require monitoring and intervention. Early signs of the emergence of a patient's typical symptoms, such as increased energy, religiosity, and decreased sleep, which may be welcomed by the patient, may nonetheless be precursors to more adverse symptoms. Attention to early symptoms while the patient's insight is preserved and denial is manageable may spare patients more severe and prolonged episodes. A specific contract, such as "Call if you have two successive nights with less than five hours of sleep," is often more helpful than a general admonition or the ambiguous instruction to "call if you are feeling really good."

Prospective charting For patients with recurrent major depressive disorder, and definitely for patients with multiple episodes of bipolar disorder, the author suggests that some elements of the life chart process be continued prospectively. That can be done quite easily in a number of ways. As an example, the patient can be asked to keep a nightly calendar and record a number from 0 to 100, with 0 representing most depressed ever, 50 representing normal or usual self, and 100 representing most activated or manic ever. The patient's record can later be converted to life chart episodes based on functional incapacity following discussion with the clinician.

By nightly recording on a simple scale, patients can systematically track their mood fluctuations in a manner that is unobtrusive and takes only seconds to complete. In an analogy to the urine glucose self-assessments of diabetic patients, systematic mood ratings by mood-disordered patients may provide an important measure of how well the illness is responding to a given treatment modality or of dose-side effect titration. It is worth reemphasizing that the morbidity and mortality of the mood disorders can be no less severe than those of many medical illnesses in which a great deal more attention is paid to the longitudinal and systematic monitoring of fluctuations in symptoms, biochemistry, and underlying pathology. Patients should be encouraged to help in the life chart process, if they are amenable to it, and should receive copies of the ongoing or completed chart, as it may be helpful in any future transfer of medical care, orientation of hospital staff, or consultation should they move or experience future episodes requiring review of treatment.

Subjective and objective differences Asking patients to make a calendar and rate their moods with a specific number from 0 to 100 has an additional, secondary benefit: It addresses the possibility of becoming attuned to the major subjective or objective differences in the assessment of a patient's illness. Many patients with major depressive disorder can detect mood changes and side effects before the therapist observes them. Conversely, many patients with bipolar disorder show remarkable objective improvement in major symptom areas, including sleep, appetite, energy, spontaneity, and sociability, without any subjective sense of clinical improvement attending those changes. If patients do not recognize that their depression is improving, it may lead to further therapeutic pessimism and may increase the possibility of suicide as the patient may have more energy to carry out such a plan while still convinced that improvement is not imminent. Moreover, return to previous levels of social and occupational functioning may lag even further behind the patient's objective and subjective appreciation of symptomatic improvement, and the patient should be adequately supported and encouraged during that time.

Time frame of education Although a hopeful perspective on the treatability of a patient's episode should be maintained, the patient should also be told that more than one drug may have to be tried before the best treatment regimen is found. The evaluation of a treatment response often requires three to six weeks, and a given agent's lack of efficacy should be regarded as additional information about the patient's illness rather than as an indication that the illness is not responsive. At the start of treatment the availability of different effective treatments, with many drugs in each class, should be brought to the patient's attention. That puts possible treatment sequences in their proper perspective and emphasizes to the patient that a lack of response to or intolerance of a drug does not portend a negative therapeutic outcome.

Those points should be reemphasized throughout the entire therapeutic process, particularly in light of the different temporal perspectives of the therapist and the patient. The therapist is aware not only of the many treatment alternatives but also of the extended treatment course that may be necessary to achieve optimal efficacy. From the patient's perspective the current mood-disordered state may be overwhelming in its immediacy and desperation. Particularly for the depressed patient, pain and hopelessness can override the realities of the situation and increase the risk of suicide before a positive treatment outcome is established.

Reassurance without promising an immediate therapeutic effect is therefore an important part of treating a depressed patient. A similar but inverse process may be required for the manic patient, who also may see only the immediate time frame and not the longer-term perspective. The therapist should encourage and help supply the ego for the longer-term view in both cases. Thus, supportive, interpersonal, cognitive, and behavioral approaches to the psychopharmacotherapy of the mood disorder may be essential. The patient should be counseled not to make important long-term decisions on the basis of a distorted view of himself or herself during an acute manic or depressive episode.

Stressing the time frame of possible improvement and the need to evaluate a given treatment over a matter of weeks to months may not only aid in maintaining patients' and families' morale but may also be helpful in obtaining adequate informed consent and avoiding malpractice litigation. In regard to the latter, it is important to indicate the possible side effects of each drug treatment so that they are seen as expected and not worrisome or, conversely, can be recognized as out of the ordinary and something that merits a call to the physician.

Hospitalization The decision to hospitalize severely depressed or manic patients depends on a variety of clinical and pharmacological issues. Hospitalization is often indicated for the acutely suicidal patient, but it may also be considered for a patient with associated medical problems or one who needs close management and monitoring of complicated or novel psychopharmacological regimens. For the knowledgeable patient with a supportive family, it may be possible to institute psychopharmacological approaches on an outpatient basis, particularly if there is close coordination between patient and physician regarding dosage, titration, side effects, and the like. Despite societal criticisms of ECT, that modality should be given higher than usual priority when the physician is faced with an extremely suicidal patient, one with associated medical illnesses, one whose profile of side effects from routine psychopharmacological agents precludes use of those agents, or one in whom other medical and psychological situations pose a therapeutic emergency necessitating the most rapid treatment response available.

For the patient with recurrent, severe episodes of mania, who

may refuse voluntary hospitalization at the height of an episode, obtaining informed consent in advance during a well interval for a future hospitalization may avoid many practical and medicolegal difficulties should another manic episode occur that requires hospitalization.

PSYCHOTHERAPY AND PHARMACOTHERAPY

Depression is a serious, potentially life-threatening medical illness, and patients and their families deserve much support. The author emphasizes the importance of combining psychosocial and pharmacological approaches in a majority of patients, not only because of evidence of the efficacy of both treatment modalities, but also because of the potential for mutual interaction and support of the patients and their social system in the context of ongoing pharmacotherapy.

Although psychotherapy may not be considered an appropriate primary treatment modality for severe depression, it may behoove the clinician to use combined treatment, for several reasons. Not only does initial evidence suggest that the two types of therapy may target different symptoms, but the therapeutic process may provide support for the patient before the psychopharmacological interventions are effective, especially if several agents must be tried before a successful one is found. Psychosocial issues and stresses not only may play important etiological roles in the onset and amelioration of some types of depression, they may also indicate the need for more aggressive pharmacological management during a period of high vulnerability.

Frequent meetings with the patient may also help in assessing the progress of pharmacotherapy, titrating the dose against blood levels and side effects, and facilitating compliance in the face of pessimism. Finally, if a depressed patient experiences severe pain and suffering, frequent meetings may encourage the physician to apply maximum clinical and therapeutic leverage and to revise regimens as appropriate within the shortest time frame (generally two to four weeks) if improvement is not forthcoming in optimal fashion. Combined treatment may also be helpful in instances of only partial response to extensive pharmacotherapy, if an episode is very protracted, or if there is poor interepisode recovery of function, associated personality disorder, or the presence of acute psychosocial stressors.

THEORETICAL ASSUMPTIONS AND RATIONALE: NEUROTRANSMITTER THEORIES Because most of the effective treatments for mood disorders were discovered by serendipity or empiricism, the effectiveness of somatic treatments has propelled theoretical formulations rather than vice versa. Neurotransmitter theories of the basis of depression and the transmitters involved have included serotonergic (5-hydroxytryptamine [5-HT]), noradrenergic (NE), cholinergic (ACh), dopaminergic (DA), and γ-aminobutyric acid (GABA)-ergic theories, each based on presumed mechanisms of effective pharmacotherapeutic interventions. For example, the findings that several drugs (which acutely potentiated catecholamines and indoleamines) were antidepressants and that reserpine (Serpasil) (which depleted these neurotransmitters) could exacerbate depression and treat mania led to the amine hypotheses of deficiencies in depression and excesses in mania.

Insofar as relatively selective manipulations of each of several different neurotransmitter systems (5-HT, NE, DA) appear to be associated with antidepressant effects (Table 16.7-1), a critical psychopharmacological question is raised as to whether a patient may respond to one type of treatment targeting one neurotransmitter system but not to another that targets an alternative system. Because definitive studies that would answer that question are lacking, the sequential use of drugs that act differently within or among classes of agents may be appropriate (for example, changing from a relatively more serotonergic drug to a relatively more noradrenergic tricyclic reuptake blocker or from a tricyclic to an MAOI to lithium). Because relatively few validated clinical or biological markers of responsivity to given treatment agents exist, the clinician must move through various treatments or adjuncts for a patient with a refractory condition until an effective one is found, with the process largely being trial and error. In mania, a similar strategy of using agents with different mechanisms of action may also be warranted.

TREATMENT OF DEPRESSIVE DISORDERS

ACUTE AND CONTINUATION THERAPY FOR MAJOR DEPRESSIVE DISORDER The drugs of choice may vary for an agitated, retarded, or psychotic depression. Because clinical trials of many weeks' duration are needed to evaluate the clinical efficacy of any individual drug, before switching treatment modalities the physician might attempt to potentiate a specific drug treatment once adequate blood levels have been reached. Thus, thyroid or lithium potentiation warrants earlier emphasis in the treatment sequence than do multiple trials with single alternative agents (Figure 16.7-5).

Once a detailed history from the patient and, perhaps, a friend or relative has revealed no prior personal or family history of mania, the acute and prophylactic treatment of a patient with major depressive disorder proceeds very differently from that for a patient with bipolar disorder. The acute approaches form a backdrop to continuation treatment and longer-term prophylaxis of either recurrent major depressive disorder or bipolar disorder. When an antidepressant treatment modality is found to help alleviate an acute episode of major depressive disorder, treatment should be continued for six to nine months—a period during which vulnerability to relapse is high. The presence of residual symptoms (such as minor sleep disturbance, anergy, lack of concentration, or minor early morning awakening) suggests continued and more aggressive treatment with higher doses or potentiation. Minor increases in depression after a gradual reduction in dosage may also suggest the need for continuing the therapy. (Tapering of cyclic and MAOI antidepressants may also help in avoiding minor drug withdrawal symptoms, which include sleeplessness, nausea, vomiting, and irritability, as well as rapid eye movement [REM] rebound with the MAOIs.)

Although more research is needed on biological predictors of treatment response, initial data suggest that the failure to normalize on the dexamethasone suppression test may be associated with a higher risk of relapse. Thus, a positive test may point to continuing antidepressant treatment even though the patient is clinically asymptomatic. Some evidence indicates that the sleep electroencephalogram (EEG) may remain abnormal for a long time after remission, although that test does not appear to be a practical marker for continuation therapy. The course of an episode may best be predicted from scrutiny of past episodes. Therefore, if the history reveals earlier, protracted episodes with some evidence of relapse before medication was stopped, the treatment of the current episode should be extended.

Serotonin-specific reuptake inhibitors Fluoxetine, sertraline, and paroxetine are available in the United States for the treatment of acute and recurrent depressions, and fluvoxamine is likely to be approved soon. Fluoxetine is one of the leading

Alkermes, Ex. 1060

TABLE 16.7-1
Side-Effect Profiles of Some Commonly Prescribed Antidepressants

Drug (Dose Range, mg/day)	Sedation/ Weight Gain	Hypo-tensive	Anticholinergic	Lethality from Overdose	Inhibits Reuptake of Ne/ 5-HT	Dosage	Elimination Half-life (hr)	Blood Levels, nmol/L (ng/mL)	Other
Serotonin-Specific Reuptake Inhibitors (SSRIs)									
Fluoxetine (Prozac) (5–80)	±/0	−	0	Low	0/+++	AM	24–96	660–2,300 (15–55)	Following discontinuation, wait 6 wk before starting MAOI; enzyme inhibition (increased drug interactions) Long-acting metabolite (elimination half-life = norfluoxetine 4–16 days)
Sertraline (Zoloft) (50–200)	±/0	−	0	Low	0/+++	AM or PM	24	(50–200)	Some enzyme induction rather than inhibition; no active metabolite
Paroxetine (Paxil) (20–50)	±/0	−		Low	0/+++	AM or PM	21	(1–150)	Most potent of SSRIs for binding at 5-HT uptake site (6× more potent than fluoxetine) moderate enzyme inhibition
Serotonin-Nonselective Reuptake Inhibitors									
Venlafaxine (Effexor) (75–375)	±/0	−	±	Low	++/+++	3× a day	5 Metabolite: 11 hr		Some anticholinergic side effects despite low binding potency at this receptor; moderate effects on dopamine; mild increases in blood pressure
Dopamine Active									
Bupropion (Wellbutrin) (225–480)	0/−−	++	++	Low	+/0	3×–4× a day	10–14	100–400 (25–75)	Divided dose required; increased risk of seizures at doses above 450 mg/day Consider for depressive episodes in bipolar disorder
Norepinephrine Active									
Desipramine (Norpramin) (75–300)	+/+	+++	+	High	+++/0	Bedtime	12–76	470–1,125 (125–300)	(?) Less weight gain than with other TCAs
Maprotiline (Ludiomil) (100–225)	++/++	++	++	High	+++/0	Bedtime	27–58	720–2,160 (50–350)	Increased risk of seizures
Secondary Amines									
Nortriptyline (Pamelor, Aventyl) (40–200)	++/+	+	++	High	+++/++	Bedtime	13–88	190–570 (50–150)	Inverted U shape of blood levels-response curve; increased levels in blacks; persons of Japanese ancestry require one-half the dose
Protriptyline (Vivactyl) (15–60)	±/?	++	+++	High	+++/+	AM	54–124	260–990	
Trimipramine (Surmontil) (75–300)	+++/++	++	+	High			7–30	(70–260)	Blocks D_2–D_4 receptors

Alkermes, Ex. 1060

Other									
Trazodone (Desyrel) (150–600)	++/+	+++	0	Low	0/++	3× a day,	4–9	2,150–4,300 (800–1,600)	Priapism; no prolongation of cardiac conduction, but possibly arrhythmogenic
Amoxapine (Asendin) (100–600)	++/±	+	++	Low	+++/++		8		Extrapyramidal side effects and tardive dyskinesia
Buspirone (BuSpar) (5–35) (?)	+/	0		?		3×–4× a day	2–3	(200–600)	5-HT_{1A} selective; generalized anxiety disorder
Alprazolam (Xanax) (2–6)	+++/0	0	0	Low		3×–4× a day	6–27	(20–55)	Generalized anxiety disorder; panic; (?) dependence and withdrawal
Lithium (Eskalith) (900–2,400)	±/+++	0	0	Low to high		Bedtime	10–40	0.5–1.5	Low therapeutic index; careful blood monitoring required; excellent adjunct to other antidepressants
Clonazepam (Klonopin) (1–4)	+++/0	+	+	None		3× a day	18–50		
ECT (6–10 Rxs)	NA/0	0	0	—		AM		NA	Rapid onset, especially for delusional depression; transient confusion and memory loss common
Tertiary Amines									
Clomipramine (Anafranil) (75–300)	+++/++	+++	+++	High	+/+++	Bedtime	17–28	650–2,300	Only approved agent for obsessive-compulsive disorder; relatively 5-HT selective
Amitriptyline (Elavil) (75–300)	+++/+++	+++	+++	High	+/+++	Bedtime	14–46	300–925 (75–250)	Typical TCA side effects common (dry mouth, drowsiness, dizziness, constipation, fatigue, and blurred vision)
Imipramine (Tofranil) (75–300)	++/++	+++	+++	High	++/+++	Bedtime	14–34	630–1,050 (150–300)	Same as above
Doxepin (Adapin, Sinequan) (75–300)	+++/++	++	++	High	++/+	Bedtime	8–36	550–920 (30–250)	Useful block of H_2 receptors; does not reverse guanethidine
MAOIs									
Tranylcypromine (Parnate) (20–60)	+/++	+++	0	?	NA	AM/3× a day	1–3		Dietary restrictions necessary, especially for refractory depressive and retarded bipolar depression Wait 6 wk after discontinuing fluoxetine before starting MAOI
Deprenyl (Eldepryl) (10)		++		High		AM/lunch	2–20		

Abbreviations: NE, norepinephrine; 5-HT, 5-hydroxytryptamine; MAOIs, monoamine oxidase inhibitors; —, unknown; NA, not applicable; TCA, tricyclic antidepressants.

Alkermes, Ex. 1060

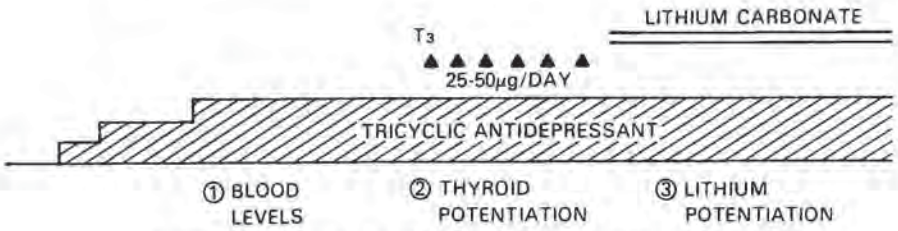

FIGURE 16.7-5 *Maximizing and potentiating antidepressant treatment.*

antidepressants sold in the United States, not so much because of its unique profile of therapeutic efficacy, but because of its relatively benign side-effect profile (Table 16.7-1). In contrast to many of the first-generation tricyclic antidepressants, which affect multiple receptor systems (α_1, α_2, ACh, histamine, and the like), fluoxetine use is not associated with weight gain, orthostatic hypotension, anticholinergic side effects, and high lethality when taken in an overdose. Its side effects are more likely to include increased agitation with insomnia, an internal sense of being driven, headache, tremor, gastrointestinal (GI) upset, and sexual dysfunction. To avoid a potentially lethal serotonergic syndrome, it is mandatory to wait six weeks after fluoxetine discontinuation before initiating MAOI treatment. The wait is necessary because of the long-acting metabolite of fluoxetine, norfluoxetine, which has an elimination half-life of five to seven days.

Sertraline has a shorter half-life than fluoxetine and does not have a long-lasting metabolite. Despite those differences, sertraline shares most of the side effects seen with fluoxetine, including GI distress and sexual dysfunction. In contrast to fluoxetine, sertraline exhibits first-order kinetics (that is, it does not inhibit its own metabolism). Further, some patients intolerant of fluoxetine may respond to and tolerate sertraline. It does not increase the blood levels of other drugs. The most prominent side effects are GI effects (nausea, diarrhea, dyspepsia) and sexual effects (anorgasmia).

Serotonin nonselective reuptake inhibitors Venlafaxine is a mixed serotonin, norepinephrine, and, to a lesser extent, dopamine reuptake inhibitor with a novel phenylethylamine structure. Unlike the specific SSRIs fluoxetine, sertraline, and paroxetine, venlafaxine provides substantial inhibition of norepinephrine reuptake. Like other antidepressants, venlafaxine decreases locus coeruleus firing. A single dose in rats produces down-regulation of β-adrenergic receptors, suggesting the possibility of more rapid onset of action than with existing agents, although clinical data are inconclusive. Unlike many older antidepressants, venlafaxine lacks significant binding to adrenergic, serotonergic, dopaminergic, histaminergic, and cholinergic receptors. That may explain why venlafaxine therapy is less likely to yield the orthostasis, sedation, weight gain, tachycardia, dry mouth, and constipation seen during therapy with older-generation antidepressants.

The mixed serotonergic, noradrenergic, and dopaminergic action of venlafaxine makes it a potentially useful agent in the treatment of patients with depression who are refractory to agents that affect only one of those monoamine systems. A 40 percent response rate to venlafaxine has been reported in patients who have failed adequate trials of other treatments, including MAOIs and ECT. MAOIs (which also affect all three monoamine systems) have been found effective in treating refractory depression, but side effects, dietary restrictions, and drug interactions have limited their utility.

Venlafaxine has a plasma elimination half-life of about five hours, requiring administration two or three times a day. Its principal metabolite, O-desmethylvenlafaxine, is active and has a half-life of about 11 hours. Venlafaxine is metabolized by and is a weak inhibitor of the cytochrome P-450 2D6 isoenzyme, so that pharmacokinetic interactions with other drugs (including some antidepressants) metabolized by that system may occur. Knowledge of the pharmacokinetic interactions of venlafaxine with other psychotropic agents is preliminary.

Venlafaxine is generally well tolerated, with a side-effect profile similar to that of the SSRIs. The most frequent side effects include nausea, weight loss, sweating, sedation, dry mouth, and sexual dysfunction. Except for nausea, side effects appear to be dose-related, and most attenuate over time or with a decrease in dosage. Infrequently, they require discontinuation of the medication. Increases in supine diastolic blood pressure have been reported with venlafaxine. Such increases are generally mild, but are more common with higher doses (mean increase of about 7 mm Hg at 375 mg a day). About 3 percent of patients develop a rash that requires discontinuation of the drug. Approximately 0.25 percent of patients develop seizures, an incidence similar to that seen with other antidepressants. In addition, about 1 in 200 patients experience hypomania or mania while taking venlafaxine.

The recommended dosage titration in the clinical treatment of depression includes starting with 25 mg three times a day (75 mg a day) and increasing by 75 mg a day at four-day intervals until the dosage reaches 125 mg three times a day (375 mg a day), if necessary.

Heterocyclics The antidepressant properties of bupropion do not involve potent effects on brain 5-HT. Bupropion does increase levels of dopamine in the nucleus accumbens and striatum. Preliminary reports in patients with bipolar disorders suggest that it may have prophylactic effects without increasing the risk of mania in those patients. A positive effect on motor retardation has been reported. Bupropion has few anticholinergic side effects, and its administration is not associated with weight gain. The risk of seizures is increased at doses above 450 mg; the dose should be divided and generally should not exceed 150 mg at a given time.

Despite sporadic claims to the contrary, there is little convincing evidence that one particular antidepressant works more rapidly than another. That statement remains true for the newer second- and third-generation heterocyclic (tetracyclic and bicyclic) antidepressants. Although further research may uncover some exceptions to the rule, clinicians should be familiar with several different antidepressants in the heterocyclic class and their dose-response and dose-side effects characteristics. The clinical response profiles and side effects of heterocyclic and other antidepressants are summarized in Table 16.7-1. Given the relatively uniform incidence and time of onset of efficacy, the side-effect profile may be the deciding factor in the choice

Alkermes, Ex. 1060

of antidepressants for both acute treatment and long-term prophylaxis. A benign side-effect profile not only may help the patient achieve adequate therapeutic levels in the relative absence of side effects, it may also facilitate optimal compliance during the more difficult phases of continuation therapy and long-term prophylactic therapy.

Thus, for the first antidepressant, a second- or third-generation antidepressant compound with a relatively benign side-effect profile or a secondary amine tricyclic antidepressant might be selected over the better studied but less well-tolerated primary amine compounds. One possible exception to that general recommendation is the use of clomipramine (Anafranil) in the patient with comorbid obsessive-compulsive disorder, as clomipromine, unlike desipramine (Norpramin), is highly effective in the treatment of obsessive-compulsive disorder.

Monoamine oxidase inhibitors MAOIs may be started shortly after the termination of tricyclic antidepressant therapy, but the converse is not recommended, as MAO inhibition can persist for two weeks or more after cessation of treatment. Treatment with an MAOI should not be started until five weeks after termination of fluoxetine therapy because of the possibility of a lethal serotonergic syndrome. The lag in onset of relief with the MAOIs is similar to that of the heterocyclics. Consequently, three to six weeks may be required to assess the treatment's effectiveness. Doses in the higher range (phenelzine [Nardil], 60 to 90 mg; tranylcypromine [Parnate], 30 to 60 mg) should be given to achieve adequate MAO inhibition in the absence of clinical response and side effects at lower doses. Antidepressant effects may be more closely associated with inhibition of MAO type A (MAO_A) (clorgylinelike), primarily affecting NE (and 5-HT). Thus, high doses of MAO type B (MAO_B)-selective agents such as L-deprenyl (30 to 60 mg), may be required to achieve antidepressant effects. Phenelzine and tranylcypromine are A,B nonselective. The potentiation of antidepressant efficacy during MAOI therapy has also been reported for both L-triiodothyronine (T_3, liothyronine) (Cytomel) and lithium carbonate.

Side effects Conventional wisdom suggests using initial minor selection criteria to choose one agent over the next. For example, among the tricyclics the clinician might consider protriptyline (Vivactil) or desipramine for a patient with retarded depression and a more sedating drug, such as amitriptyline (Elavil) or doxepin (Adapin, Sinequan), for a patient with agitated depression. In general, the tertiary amine antidepressants, such as amitriptyline, imipramine, trimipramine (Surmontil), and doxepin, tend to be more sedating than the secondary amines desipramine, nortriptyline (Pamelor), and protriptyline (Vivactil).

The SSRIs fluoxetine, sertraline, and paroxetine, and bupropion, venlafaxine, desipramine, and possibly trazodone (Desyrel) may be considered for the overweight depressed patient or one with a history of weight gain during previous tricyclic administration, as preliminary evidence suggests that those drugs may be less likely to induce weight gain than most tricyclics. Bupropion and the SSRIs may even be associated with weight loss rather than gain. Isocarboxazid (Marplan), which is no longer generally available, was thought to be less likely to cause weight gain than tranylcypromine and phenelzine.

Anticholinergic effects (dry mouth, blurred vision, sweating, constipation, urinary hesitancy and retention, delayed ejaculation) tend to be more prominent with the tertiary amine tricyclics and less so with trazodone, desipramine, amoxapine (Asendin), maprotiline (Ludiomil), and the MAOIs, SSRIs, and lithium.

Orthostatic hypotension, particularly in the elderly, may be associated with the administration of imipramine, amitriptyline, desipramine, trazodone, and the MAOIs but less frequently with the SSRIs, bupropion, nortriptyline, amoxapine, maprotiline, and doxepin (or lithium and carbamazepine). The heterocyclics amoxapine, maprotiline, and trazodone, touted for their less sedating and possibly less anticholinergic and less cardiotoxic profile, are not consistent in that regard.

Orthostatic hypotension may become more prominent in the second and third weeks of MAOI treatment. Salt loading, the use of pressure stockings, and fludrocortisone (Florinef) administration may prove effective in the treatment of MAOI-induced hypotension. MAOIs can be given in a single morning dose or in divided doses. If marked insomnia occurs, nighttime doses of trazodone have been recommended by some authorities. Bouts of daytime drowsiness and sedation may also become problematic. The clinician might attempt to titrate the dose against side effects, as variations in dosage or timing of administration may be helpful.

The necessity of restricting substances that release tyramine or catecholamines and can produce hypertensive crises during MAOI treatment should be emphasized to the patient. Hypertensive crises may be clinically manifested as explosive headaches, flushing, palpitations, perspiration, and nausea. Immediate treatment with a slow infusion of phentolamine (Regitine), 5 mg given intravenously in an emergency room, is the recommended treatment (Tables 16.7-2 through 16.7-4).

TABLE 16.7-2
Instructions for Patients Taking Monoamine Oxidase Inhibitors (MAOIs)

Background Information

Foods rich in tyramine and some related amines have been known to cause serious side effects and hypertensive responses in patients taking MAOIs. Tyramine is an amino acid found in many protein substances and is produced by fermentation, aging, spoiling, or pickling. The enzyme MAO found in the liver normally inactivates tyramine. In the presence of an MAOI, tyramine is not deactivated by MAO and is allowed to circulate and indirectly cause the release of norepinephrine from nerve endings. This may lead to detrimental side effects, especially hypertensive responses.

Summary of Guidelines to Follow While Taking an MAOI

1. The foods in the "high tyramine" category should be completely avoided. If you consume small quantities of foods in this category without symptoms, do not assume that you can repeat this. These foods vary greatly in tyramine content and their ability to cause a severe reaction. You may have a reaction the second time.
2. You are allowed foods with moderate to low tyramine content (categories 2 and 3). These foods should be eaten in moderation. Try to avoid eating combinations of foods in these categories because of the possible additive effects of tyramine.
3. Avoid aged, spoiled, improperly refrigerated, or frozen foods. Do not eat tuna fish that has been in the refrigerator for 2 or 3 days. Eat only fresh food or freshly prepared frozen or canned foods. Beware of many foods that derive their flavor from aging, smoking, or pickling. Also note that cooking of degraded protein does not alter the tyramine content of these foods.
4. Avoid any foods that have previously caused adverse side effects.
5. Cheeses have been responsible for the greatest number of reported hypertensive responses. Observe that many foods contain cheese as an ingredient, such as cheese crackers, pizza, and cheese bread.
6. There are certain prescription and nonprescription medicines that should be avoided. See list of MAOI Drug Incompatibilities [Table 16.7-4]. Be certain to tell your physician, dentist, or pharmacist that you are taking an MAOI.
7. Call your physician immediately or go to your nearest emergency medical facility if you should suffer from the following symptoms: a throbbing, explosive headache of sudden onset associated with flushing, visual disturbances, nausea or vomiting. Major muscle jerks, confusion, or excitement may also occur, and in the case of a reaction with another drug, sometimes without a severe headache.

Table from D L Murphy, T Sunderland, R M Cohen: Monoamine oxidase-inhibiting antidepressants: A clinical update. Psychiatr Clin North Am 7: 549, 1984. Used with permission.

Alkermes, Ex. 1060

TABLE 16.7-3
MAOI Dietary Restrictions

High Tyramine Content—Not Permitted	
Aged, matured cheeses (unpasteurized)	Cheddar, Camembert, Stilton, bleu, Swiss
Smoked or pickled meats, fish, or poultry	Herring, sausage, corned beef
Aged putrefying meats, fish, and poultry	Chicken or beef liver, paté, game
Yeast or meat extracts	Bovril, marmite, brewer's yeast (beware of drinks, soups, and stews made with those products)
Red wines	Chianti, burgundy, sherry, vermouth
Italian broad beans	Fava beans
Moderate Tyramine Content—Limited Amounts Allowed	
Meat extracts	Bouillion, consommé
Pasteurized light and pale beers	
Ripe avocado	
Low Tyramine Content—Permissible	
Distilled spirits (in moderation)	Vodka, gin, rye, scotch
Cheese	Cottage cheese, cream cheese
Chocolate- and caffeine-containing beverages	
Fruits	Figs, raisins, grapes, pineapple, oranges
Soy sauce	
Yogurt, sour cream (made by reputable manufacturers)	

Table from D L Murphy, T Sunderland, R M Cohen: Monoamine oxidase-inhibiting antidepressants: A clinical update. Psychiatr Clin North Am 7: 549, 1984. Used with permission.

TABLE 16.7-4
MAOI Drug Incompatibilities

Generally Contraindicated Hazardous Potentiations*	
Stimulants	Weight-reducing or antiappetite drugs; amphetamines, cocaine
Decongestants	Sinus, hay fever, and cold tablets; nasal sprays or drops; asthma tablets or inhalants, cough preparations (or any products containing ephedrine, phenylephedrine, or phenylpropanolamine)
Antihypertensives	Methyldopa, guanethidine, reserpine
TCAs	Imipramine, desipramine, clomipramine
MAOIs	Tranylcypromine, after other MAOIs
Sympathomimetics	Dopamine, Metaraminol
Amine precursors	L-dopa, L-tryptophan
Narcotics	Meperidine (Demerol)
Some Potentiation Possible	
Narcotics	Morphine, codeine
Sedatives	Alcohol, barbiturates, benzodiazepines
Local anesthetics containing vasoconstrictors	
Sympathomimetics	Ephedrine, norepinephrine, isoproterenol
General anesthetics	

*Under certain circumstances, some of these drugs may be used together with MAOIs in specialized treatment approaches and with additional precautions. For example, TCAs and L-tryptophan have been used with MAOIs in antidepressant regimens. Also of note, other agents from these drug classes are safely used (for example, the antihypertensive agent chlorothiazide) as only mild potentiation occurs.

Table from D L Murphy, T Sunderland, R M Cohen: Monoamine oxidase-inhibiting antidepressants: A clinical update. Psychiatr Clin North Am 7: 549, 1984. Used with permission.

Blood levels Blood levels of tricyclics above 450 μg/mL may be cardiotoxic, and doses of tricyclics equivalent to 2,500 mg or more of imipramine may be fatal. Electrocardiographic (ECG) monitoring should be considered in patients on high-dose tricyclic therapy (above 300 mg a day). The risk of seizures increases with increasing dosages of many cyclic antidepressants, especially maprotiline (above 225 mg a day). Maprotiline should therefore be avoided in patients with an abnormal EEG or a family history of epilepsy. Many of those guidelines are based on anecdotal evidence and may not stand the test of time and careful clinical research evaluation.

As a general rule, blood levels among patients treated with the same dose of a tricyclic or heterocyclic agent vary widely. Thus, giving all patients doses within the conventional range will leave some with subtherapeutic blood levels and others with very high levels. That may be important for nortriptyline, for which there is evidence of an inverted U-shaped curve (that is, there is a therapeutic window for clinical improvement below and above which patients do not do well). Thus, with the exception of nortriptyline, it appears clinically useful to increase doses slowly, titrating against side effects with blood level monitoring at (maintenance) doses in patients who do not show an adequate therapeutic effect. During nortriptyline treatment with a moderate to a high, but ineffective, dose, one might decrease the dose to bring blood levels back into the therapeutic range, which is highly variable across studies.

It may be useful to assess the blood level of a heterocyclic agent in a patient who fails to show adequate therapeutic response to conventional doses of the drug. Evaluation may be done once steady-state blood levels have been reached and a clinical response can be expected, generally two to three weeks after initiation of the drug. Blood levels may also be helpful in assessing the patient with substantial side effects at the lower dosage ranges. Finally, a single blood level determination in the well-maintained patient may be prudent, as a score of medicolegal cases are pending in which massive blood levels of tricyclic antidepressants were associated with sudden death. Although general blood level guidelines for some agents are given in Table 16.7-1, the clinician should remember that blood level-response relations are obscure for most drugs and that laboratories may differ widely in the accuracy of the determination and in the agreed-upon therapeutic range. Nonetheless, blood levels may be helpful in the general assessment of the nonresponsive patient and may provide an opportunity for discussing issues such as fast metabolism and noncompliance when unexpectedly low levels are ascertained. In contrast, blood level monitoring may be less important for the SSRIs.

Time frame With the traditional tricyclics and other antidepressants, initial improvement in sleep in the first weeks of treatment is not necessarily predictive of subsequent clinical outcome. Nevertheless, the patient may be comforted by the fact that sleep is improving. Antidepressants often require two to four weeks to produce substantial effects and four to eight weeks to produce maximal effect; however, gradual improvement often begins in the first and second weeks of treatment. Thus, there may not be an absolute lag in time to onset of clinical efficacy, only in time to onset of substantial or maximal change.

Potentiation Because antidepressants have to be administered for several days to weeks before the response can be evaluated, the clinician should consider antidepressant potentiation in either the first or second antidepressant trial before switching antidepressants, even if the category of agents seems to lack efficacy in the patient under treatment. Thus, if a patient is

TABLE 16.7-5
Approaches to Refractory Depression

Level of Refractoriness	Therapeutic Strategies
I Failure to respond	Optimize dosage; assess blood levels
II Failure to respond to adequate trial of first agent	Consider potentiation or switch to new antidepressant with different mechanism of action, or to one in a new class
III Failure to respond to second agent	Potentiate with T_3. If no response, discontinue and potentiate with lithium Switch to a third agent Strongly consider an MAOI Add or revise psychotherapy
IV Failure to respond to third agent	Definitely consider an MAOI, with or without potentiation with T_3 and lithium Consider ECT, depending on severity and suicidality Add or revise psychotherapy Consider consultation and reexamination of compliance and diagnosis, especially previously unrecognized physical, psychiatric, or substance abuse comorbidity If comorbidity is present, treatment should be better targeted to that comorbid condition (i.e., medical therapy, revised pharmacotherapy, and adjunctive group work such as Alcoholics Anonymous, a related "12-step" program, or a self-help group)
V Failure to respond to numerous clinical trials of agents with different mechanisms of action, MAOIs and ECT	Consider novel therapies, including • extreme doses of MAOIs (80–120 mg tranylcypromine) • carbamazepine or valproate with or without an adjunct antidepressant such as bupropion (especially if recurrent or rapid cycling) • alprazolam (especially if increased anxiety) • bromocriptine (dopamine-acting, especially for retarded depression) • TCA plus MAOI (in this but not reverse order) • MAOI plus stimulant (pemoline, amphetamine, methylphenidate). *Use stimulant or MAOI only with great care and after appropriate informed consent has been obtained* • adjunctive folate

receiving the maximal tolerated dose or has adequate blood levels of the drug and is not responding adequately, the clinician might consider adding thyroid hormone or lithium carbonate (Table 16.7-5 and Figure 16.7-5).

There is a sizable literature on the efficacy of thyroid potentiation in converting antidepressant nonresponders to responders, but only in some 20 to 30 percent of patients. This appears to be independent of an initial clinical thyroid status or any evidence of hypothyroidism. A response to the addition of T_3 (25 to 50 μg a day in the morning) may occur within days and usually occurs within the first week or two of treatment. If no response to antidepressant potentiation occurs during that time frame, the clinical trial of T_3 can be exchanged for other options. Side effects are unusual but may include tachycardia, hypertension, anxiety, and flushing.

A second option is potentiation with lithium carbonate. An extensive literature, including several controlled clinical trials, reveals that the addition of lithium carbonate to a variety of antidepressant modalities, including tricyclic, heterocyclic, and MAOI antidepressants and carbamazepine, is often accompanied by a rapid clinical improvement in 50 to 60 percent of patients. Improvement may begin within 24 to 48 hours but may be slower in onset and stretch over the first week to 10 days. Doses of lithium that are slightly lower than those conventionally used for monotherapy are generally effective (that is, 600 to 900 mg in a single dose taken at bedtime may be sufficient). When lithium is used in that fashion, its side-effect profile appears to be quite benign. Lithium potentiation may be effective in all subtypes of depression. The initial reports of estrogen potentiation of antidepressant response do not appear as promising as those of either thyroid or lithium potentiation.

Drug sequence The clinician might consider exchanging one type of antidepressant for another should unacceptable side effects appear before adequate blood levels or clinical response have been achieved. If an adequate dose and adequate blood levels have been achieved but the clinical response is inadequate, the clinician may switch to a drug with a different biochemical profile within the same class or to a different class altogether, such as an MAOI.

APPROACHES TO DEPRESSIVE SYMPTOMS AND SUBTYPES

Comorbid anxiety disorder and panic disorder DSM-IV notes the existence of a mixed anxiety-depressive disorder among the anxiety disorders. It is not known whether patients with significant symptoms of both anxiety and depression are affected by two different disease processes or by one disease process that produces both kinds of symptoms.

If panic disorder coexists with a depressive disorder, an SSRI, tricyclic antidepressant, or MAOI should be tried initially, as those drugs are among the best for treating primary panic disorder. If symptoms of panic or anxiety remain prominent despite apparently adequate antidepressant treatment, the physician might consider the acute adjunctive use of a benzodiazepine-active agent such as alprazolam (Xanax) or the less well-studied clonazepam (Klonopin), which has also been reported to be useful in treating primary panic disorder. Those benzodiazepine agents may also have a role in the first weeks of tricyclic treatment, when anxiety symptoms occasionally increase. Alprazolam should be used with caution in patients with borderline personality disorder as it may be associated with an increased incidence of dyscontrol acts. Patients with panic or marked anxiety symptoms have often been reported to respond to MAOIs, with or without lithium potentiation. Trazodone and bupropion should be avoided as first-line treatments as they are ineffective in patients whose primary diagnosis is panic disorder or anxiety disorder. Trazodone should be avoided in male patients because of the risk of irreversible priapism that requires surgical intervention.

The new antianxiety drug buspirone (BuSpar) has recently been reported to produce moderate to marked antidepressant effects in 50 percent of patients with depressive disorders without melancholic features, although it had no effect on those with melancholic features, and responses were not associated with

baseline anxiety scores. Buspirone has been used to potentiate and to maintain response to fluoxetine, and vice versa.

The early literature suggested a response to MAOIs in atypical depressed patients with rejection sensitivity, leaden paralysis, hypersomnia, and hyperphagia, although a recent study reported characteristics of typical depression as predictive of a positive response to tranylcypromine. Those characteristics included greater initial severity of depressed mood, psychomotor retardation, weight loss, but less middle and late insomnia (early morning awakening). Thus, the MAOIs should be considered for patients in whom multiple agents have failed, regardless of the subtype of clinical presentation. Five to six weeks must elapse following the discontinuation of fluoxetine before an MAOI is initiated.

Psychosis A growing literature suggests that if a patient's depression has reached psychotic proportions and delusions are present, the adjunctive use of low to moderate doses of antipsychotics may help produce an antidepressant response and alleviate delusional symptoms. Preliminary evidence also suggests that lithium carbonate may be useful and that a triple drug regimen consisting of a heterocyclic agent, an antipsychotic, and lithium may be needed in some patients. When using antipsychotic potentiation in delusional depression, the physician should taper and discontinue the antipsychotics as early as possible in the continuation phase in order to lessen the risk of tardive dyskinesia. Amoxapine may also be considered for agitated, delusionally depressed patients as it has some inherent antipsychotic (dopamine receptor-blocking) properties that may be advantageous, although it, too, has been associated with the development of tardive dyskinesia.

ECT is more likely to be successful in treating delusionally depressed patients and has a more rapid onset than most psychopharmacological regimens. Thus, ECT may be considered earlier for depressed patients with delusions rather than as a treatment of last resort after psychopharmacological trials have failed. An absolute contraindication to ECT is the presence of a cerebral aneurysm or increased intracranial pressure, but a recent myocardial infarction is only a relative contraindication. Additional indications for implementing ECT may include severe medical or suicidal risk, cardiac problems (which make tricyclics dangerous), and, possibly, severe mood episodes associated with pregnancy.

Insomnia Persistent insomnia may accompany an inadequate antidepressant response but should begin to resolve as the treatment begins to take effect. Giving more sedating antidepressants in a once-a-day evening dose is usually an effective strategy for the insomniac depressed patient because of the long half-life of most cyclic antidepressants. That regimen makes positive use of the sedation at bedtime and increases the likelihood of compliance with a single nighttime dose. Acute adjunctive treatment with a benzodiazepine may be warranted in rare instances of severe sleep loss, although the physician should be cautious about prescribing benzodiazepines and related sedatives on a long-term basis because of the possibility of habituation and addiction. Benzodiazepines should not be used as the primary antidepressant modality, as is still common in many general practice settings. The physician may also consider adjunctive nighttime medication with such agents as nortriptyline or buspirone in the patient experiencing insomnia while taking SSRIs.

Paradoxically, sleep deprivation may be an adjunctive procedure, whether or not there is severe sleep loss. An acute but transient antidepressant response to one night of sleep deprivation has been consistently reported in studies from different laboratories. Although many patients relapse after one night's recovery of sleep, sleep deprivation may be used in combination with more traditional tricyclic antidepressant or lithium carbonate treatment. Lithium may help sustain the sleep deprivation response. Moreover, preliminary evidence suggests that deprivation of sleep in the last half of the night (from 3 to 7 AM) may be just as effective as total sleep deprivation and thus may be more convenient for clinical use in outpatient treatment. The rapid onset of effects achieved in approximately one half of severely depressed patients is different from the slower but sustained effects following selective deprivation of REM sleep, which is not amenable to easy clinical induction.

Lethargy and retardation Extreme morning lethargy and retardation may be an indication for the use of SSRIs, bupropion, venlafaxine, or secondary amine tricyclic antidepressants. In the face of unsuccessful drug trials, including T_3 and lithium potentiation, the short-term supplementation of cyclic antidepressants (not MAOIs) with psychomotor stimulants has been recommended by some until there is an adequate antidepressant response to the other agents. Small doses of methylphenidate (Ritalin, 5 to 10 mg) or an amphetamine in the morning may help the otherwise incapacitated, severely retarded depressed patient face the day with more energy. Stimulants as a primary antidepressant modality in elderly depressed patients have been recommended by some authorities but remain relatively understudied.

For depressed patients with decreased appetite and associated decreased nutritional intake, the physician may consider potentiating with folic acid supplements, as a folic acid deficiency has been reported to cause refractory depression in patients receiving anticonvulsants and, presumably, could also occur because of decreased dietary intake. Moreover, intracellular deficits can occur in the setting of apparently normal plasma levels.

Obsessive-compulsive symptoms The associated occurrence of marked obsessive-compulsive symptoms may lead to the consideration of clomipramine, which has been reported to be highly effective in adults and children with primary obsessive-compulsive symptoms when more traditional antidepressants are ineffective. Fluoxetine and the other SSRIs may share that positive effect on obsessive-compulsive symptoms.

Double depression It is important to assess the possible occurrence of a double depression, defined by DSM-IV as the condition in which major depressive disorder is superimposed on dysthymic disorder. As the patient's superimposed depressive symptoms are alleviated, a core of chronic, minor depression may be left. In such a case the physician may erroneously conclude that the superimposed episode has not been successfully treated. Psychopharmacological approaches to the baseline level of the double depression have not been adequately delineated, but the physician might consider drugs used for the cyclic mood disorders (for example, lithium) in addition to the more traditional antidepressant agents and the SSRIs. Psychotherapy may also be indicated for some patients.

Atypical depressive features The occurrence of atypical features or reverse or vegetative symptoms, such as hypersomnia, carbohydrate craving, and weight gain, suggests a careful reevaluation for the possible bipolar II disorder and seasonal affective disorder (SAD) (called mood disorder with seasonal pattern in DSM-IV). The atypical features may be effectively targeted with the SSRIs, bupropion, venlafaxine, and the MAOIs.

A clear-cut diagnosis of SAD with increased depression that is selectively associated with decreased daylight hours in the winter months suggests the use of light treatment. The syndrome responds well over a period of several days to high-intensity light given in the morning or evening. Light treatment can be used prophylactically throughout the winter months in a patient with marked SAD. Ordinary light is not effective; rather, light in the intensity of 2,500 lux or greater is required to achieve a therapeutic response. It is unclear whether light treatment could be an effective adjunct for nonseasonal depressions.

APPROACHES TO REFRACTORY DEPRESSION A sequence of treatment reevaluations and options for different levels of refractoriness is outlined in Table 16.7-5. During each sequence the physician should consider optimizing a given regimen by appropriately maximizing the dose and titrating blood levels against the emergence of side effects, and using appropriate augmentation strategies. Switching among different classes of antidepressants or, within the heterocyclic class of agents, among drugs with different mechanisms of action appears most appropriate, although occasionally response to one but not another of the SSRIs may be observed. A trial of an MAOI should definitely be considered in a patient in whom multiple previous trials have failed. Venlafaxine also has a relatively positive response profile in patients who have not responded to multiple previous clinical trials. With increasing levels of refractoriness the physician should reevaluate the diagnosis (with careful assessment of possible physical, psychological, and substance use comorbidity) and should consider consultation, psychotherapy revision, ECT, and combination modalities.

Clinical trials have suggested some antidepressant efficacy of the direct dopamine agonist bromocriptine (Parlodel), which is used to treat parkinsonian patients. One double-blind study indicated that bromocriptine was equally as effective as imipramine. A related dopamine agonist, piribedil (Trivastal), has also been effective for the occasional patient with treatment-refractory depression. Dopamine-active drugs had been reported to be more effective in patients with low cerebrospinal fluid (CSF) levels of the dopamine metabolite homovanillic acid (HVA). Whether that relation holds for bupropion, with its ability to increase dopamine levels in the nucleus accumbens and striatum, remains to be explored. A similar relation between low levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and a better response to the serotonin-active compounds clomipramine and sertraline has been reported. The results are inconsistent as to whether urinary levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) can predict the response to noradrenergically active antidepressants, such as desipramine, maprotiline, and venlafaxine. Consistent endocrine or other biochemical markers of antidepressant response have not yet been found.

Although the acute antidepressive effects of lithium have been repeatedly reported, especially in patients with bipolar disorders, they remain controversial; nonetheless, consideration of lithium for patients with unresponsive major depressive disorder, particularly in augmentation trials, appears reasonable. The lag in onset to full antidepressant response is often two to four weeks or longer when lithium is used as monotherapy. Combination treatment with a tricyclic antidepressant and an MAOI has been advocated by some for patients with treatment-resistant major depressive disorder, although the superiority of that combination regimen to single-agent treatment remains controversial and virtually unstudied in a systematic fashion. If used (under extreme circumstances), both drugs can be started together (at low doses), or the MAOI can be added later. The reverse order should be avoided. The tricyclic nortriptyline may have a better safety record than imipramine or protriptyline.

Carbamazepine has been reported to be effective when used acutely and prophylactically in some patients with major depressive disorder in whom multiple trials with traditional antidepressants have failed, especially those with a history of head trauma or EEG abnormalities. For patients with treatment-refractory bipolar disorder the anticonvulsants carbamazepine and valproate may be used in combination with bupropion. Those and other combination treatments for the patient with refractory depression warrant further systematic research to provide adequate statistical and sequence-ordering guidance for the clinician.

OTHER ANTIDEPRESSANT MODALITIES A host of studied but unproven antidepressant modalities have been reported; many are unavailable in the United States and are not generally accepted treatments. Among them are *S*-adenosylmethionine (SAM), β-noradrenergic agonists, GABA agonists (such as progabide [Gabrene]), the opiate agonist buprenorphine (Temgesic), the α_2 antagonist idazoxan, very high parenteral doses of reserpine, anticholinergics, thyrotropin-releasing hormone (TRH), melanocyte inhibitory factor (MIF-1), vasopressin, and circadian-phase interventions.

Because of the rapid onset of effects of SAM in a high percentage of patients and the relative absence of side effects in a large number of controlled studies, that agent warrants further clinical and theoretical investigation. In double-blind studies SAM in doses of 400 mg a day produced rapid effects.

Compounds active in the dopamine biosynthetic pathway—phenylalanine, tyrosine, and levodopa (Larodopa, Dopar)—have each been reported effective in small groups of depressed patients. Levodopa may be more activating in retarded depressed patients with low CSF HVA levels, but its effectiveness is limited by increases in agitation, psychosis, and the switch into mania in patients with bipolar disorders. The precursors of 5-HT, tryptophan and 5-hydroxytryptophan (5-HTP), also have been reported to have antidepressant effects. Surprisingly favorable results in 12 of 14 studies have been reported with 5-HTP in 53 percent of a total of 547 depressed patients. The status of those agents remains in considerable doubt, however, especially in light of a reported association with malignant eosinophilia.

PHARMACOPROPHYLAXIS Although ongoing interpersonal psychotherapy may delay the onset of subsequent episodes in patients with recurrent major depressive disorder, only maintenance, standard-dose pharmacotherapy appears highly effective in preventing subsequent relapses and the emergence of new episodes. There is a high rate of relapse in depressed patients who have been entered into controlled studies after having had two or more previous episodes (Table 16.7-6). When effective treatment with an antidepressant agent has been followed by placebo substitution, the rate of recurrence of depressive episodes has averaged 55 percent by one year, 74 percent by two years, and 85 percent by three years. Double-blind maintenance of the original effective treatment reduced the rate of relapse by more than half at each of those time points. Statistically significant results have been obtained using a variety of treatment agents, among them the tricyclics imipramine and amitriptyline, the SSRIs fluoxetine, sertraline, and paroxetine; noradrenergic selective agents, such as maprotiline (whose effects were shown to be dose-dependent); and other agents,

Alkermes, Ex. 1060

TABLE 16.7-6
Impact of Prophylaxis on Relapse Rates in Major Depressive Disorder

	% Relapsed	
	Placebo	Active
1-yr trials (12 studies)	55	21
2-yr trials (6 studies)	74	32
3-yr trials (3 studies)	85	35
All trials (21 studies)	**65**	**26**

including lithium and buspirone. Based on a meta-analysis of 18 studies, John Davis and colleagues calculated that the likelihood that those results are due to chance is the astronomically low value 1×10^{-32}.

Given those data, the physician should strongly recommend pharmacoprophylaxis to patients with recurrent major depressive disorder who have had three or more prior episodes or several closely occurring episodes in the past two years. Prophylaxis should be strongly considered for the patient with two prior depressive episodes in the past five years. The strength of the recommendation should be highly integrated with a variety of other factors, including prior episode severity, refractoriness, degree of incapacitation, and the likelihood of suicidal risk if another depressive episode should occur. The recommendation should be strengthened if there is a family history of mood disorder.

Investigators in the field have observed the phenomenon of lithium-induced discontinuation refractoriness when effective prophylactic treatment was stopped in patients with bipolar disorder (Figure 16.7-6). Though the question of whether a similar phenomenon could occur in the treatment of major depressive disorder has not been systematically examined, it is at least possible that repeated depressive episodes after discontinuation of effective treatment with an antidepressant might lead not only to the reemergence of new episodes (Table 16.7-6) but also, in some percentage of patients, to refractoriness. Repeated episodes, in addition to carrying their own morbidity and potential for mortality (through suicide), may affect the subsequent course of illness. Thus, recurrent episodes could render the patient more vulnerable not only to subsequent relapses, but also to the possibility of decreased responsiveness to medications.

Patients should be specifically educated about the known risks for recurrence on a percentage basis (Table 16.7-6), and their negative attitudes concerning prophylaxis should be addressed and discussed. Negative attitudes include viewing the need for long-term prophylaxis as reflecting weakness, lack of effort, a character defect or flaw, and the like. Those attitudes need to be explored and countered. Societal stigma against open recognition of psychiatric illness and its short- and long-term treatment should also be addressed.

The risks of recurrence should be weighed against the relative lack of evidence of long-term side effects when the agents are used for prophylaxis, acknowledgment of the few potential side effects that can occur (such as the effects of lithium on the kidney and thyroid), and evidence for the lack of habituation

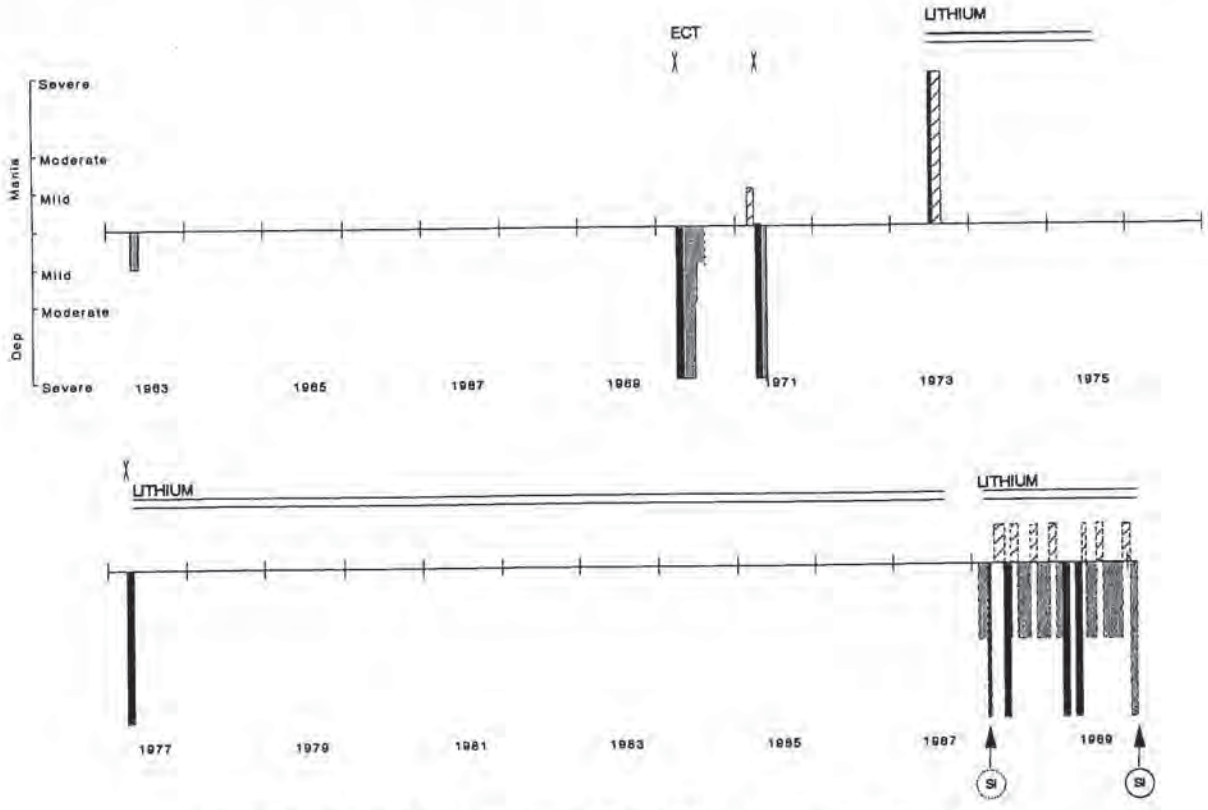

FIGURE 16.7-6 *Loss of drug responsiveness following lithium discontinuation—a fatal outcome.*

Alkermes, Ex. 1060

or addiction to those medical regimens. Analogies to long-term prophylaxis for other medical diseases may help dissipate negative stereotypes regarding the long-term medical management of psychiatric disorders. For example, most patients do not consider it useful to attempt a clinical trial of digitalis discontinuation in order to give their hearts a renewed experience of congestive failure and the associated potential for the occurrence of severe, even irreversible changes in the size and function of the heart muscle. In parallel fashion, it may be equally unreasonable for a patient to practice having depressive episodes, because of the chance that the neurochemical changes underlying the episodes may similarly be progressively facilitated.

If the patient chooses to discontinue prophylaxis, it is recommended that the drug treatment be very slowly tapered. Slow tapering avoids withdrawal insomnia and may serve other functions as well. If minor episodic symptoms begin to reemerge, treatment can be reinstituted early, before a full-blown episode has occurred and gained a momentum of its own. Thus, a specific contract should be made with the patient to contact a physician should symptoms reemerge. Reminding the patient of the long time frame to clinical response in prior episodes and his or her associated despair and incapacitation may also help the patient arrive at the decision for prophylaxis. In analogy to a fully loaded tanker, it is much easier to deal with a depression before it gains a full head of steam than to try stopping it once it has gained full speed and a momentum of its own.

Regular psychiatric visits during the prophylactic phase are recommended at intervals ranging from one to four months, depending on a variety of ancillary circumstances, including completeness of response, lack of psychosocial crises, excellent history of compliance, lack of ambivalence about the process, absence of side effects, and the financial constraints and wishes of the patient. In addition to periodic assessment of all of those issues, regular treatment visits are recommended to assess separately the potential risks of suicide, independent of the occurrence of discrete episodes. Periodic assessment of suicidal risk is particularly important if there is a family history of suicide or if other risk factors are present, among them male sex, older age, comorbid alcohol abuse, and prior suicide attempts (particularly if they were severe). One study of maprotiline, for example, indicated that although patients showed a substantial and highly significant ($P < 0.0001$) decreased likelihood of recurrence of depressive episodes during treatment with that agent compared to placebo, there was a small but statistically significant increased likelihood of suicide attempts in the patient group that remained on active treatment. Thus, suicidal impulses and acts may not always vary directly with either severity of depression or reemergence of a full-blown episode that requires hospitalization, and the assessment of such risks should be part of the ongoing clinical assessment of each patient in all phases of the illness and treatment. A specific contract for communicating with the clinician on reemergence of suicidal thoughts should be considered for patients with some of the risk factors described above.

TREATMENT OF BIPOLAR DISORDER

ACUTE MANIA

Lithium carbonate Lithium remains the paradigmatic treatment for acute mania. In comparative studies with antipsychotics, it demonstrates better overall improvement in all aspects of manic symptomatology, including psychomotor activity, grandiosity, manic thought disorder, insomnia, and irritability.

The typical clinical profile of the manic patient most responsive to lithium carbonate consists of (1) a classic presentation and euphoric mania rather than severe or dysphoric mania, (2) a pattern of mania followed by depression and then a well interval (MDI) rather than DMI (depression-mania-well interval) or continuous cycling, (3) a history of few prior episodes and no rapid cycling illness (defined as four episodes a year), and (4) a positive family history of primary mood disorder in first-degree relatives. Lithium doses should be administered to achieve blood levels between 0.8 and 1.2 mEq/L. Although a high-dose strategy (to 1.5 mEq/L) is advocated by some investigators, the author has not seen many patients who, after failing to respond at more typical blood levels of lithium, responded well when the dosage was pushed to higher, potentially toxic levels. Dose-limiting side effects may include GI disturbances, particularly diarrhea, and neuropsychiatric syndromes, including tremor, confusion, and myoclonic twitches. For the inadequate responder the author recommends potentiation with other agents rather than increasing lithium to toxic levels. Blood levels of lithium achieved at a given dose may also increase further if the patient switches from mania to depression, thus leading to greater side effects.

Lithium's antimanic action may take several weeks to manifest, even with aggressive dosing, and so, for acutely deteriorating, aggressive, or psychotic manic patients, lithium may need to be supplemented in the early phases of treatment. In a recent collaborative study that used the liberal criterion of 50 percent improvement in manic severity, only 50 percent of patients treated with lithium (or valproate) had improved at the end of the three-week monotherapy trial in an intent-to-treat analysis. That figure speaks to the frequent need for combination strategies, particularly as short stays and rapid discharges from inpatient units are increasingly mandated by managed care. Augmentation has traditionally been accomplished with antipsychotics, including the phenothiazines and butyrophenones, such as haloperidol (Haldol). Because of growing evidence of the acute antimanic efficacy of carbamazepine and valproate, it is suggested that those agents or the high-potency benzodiazepines be used for initial supplementation (rather than an antipsychotic), for reasons discussed below.

Double-blind controlled evaluations reported from different laboratories have indicated that the onset of antimanic efficacy is often as rapid with carbamazepine as it is with traditional antipsychotics, including chlorpromazine (Thorazine), thioridazine (Mellaril), pimozide (Orap), and haloperidol. As of 1994, 19 double-blind studies of carbamazepine in acute mania had indicated clinical efficacy. Fewer controlled studies have been performed with valproate, but those available, including a recent large collaborative study, also indicate acute antimanic efficacy. Because initial acute antimanic response may be a guide to subsequent prophylaxis (the major focus of therapeutics in bipolar disorders), the author encourages the investigation of an individual patient's response to those alternative anticonvulsant agents. Antipsychotics can be employed later in the sequence if there is a lack of clinical response to the mood stabilizers.

Antipsychotics Long-term maintenance treatment with traditional antipsychotics should be avoided, if possible, in patients with bipolar disorder, as they are reported to have an increased risk for tardive dyskinesia. The strategy of rapid tranquilization with suprathreshold doses of antipsychotics should clearly be avoided. Many double-blind evaluations of that high-dose strategy in acutely psychotic and manic patients have shown it to be no more efficacious than traditional dose regimens, and it may be associated with toxic effects. Particularly

for extremely manic patients, the use of heroic doses to decrease psychomotor activation may not be justifiable because of the added risk of ordinary toxic effects, the risk for neuroleptic malignant syndrome, and the risk for sporadic syndromes of reversible and irreversible organic impairment when used in conjunction with lithium.

Carbamazepine Several preliminary studies have suggested that some of the variables associated with a poor response to lithium may be associated with a good antimanic response to carbamazepine. Thus, the drug should be considered for lithium-nonresponsive manic patients.

Typical doses of carbamazepine to treat mania have ranged between 600 and 1,600 mg a day and are associated with blood levels ranging from 6 to 12 μg/mL. However, within that dose and blood level range, there does not appear to be a clear relation to the degree of clinical response across patients. For an individual patient, however, clinical response and side effects are typically dose-related. Thus, it is important to individualize dose administration, as there is wide variability in the dose and blood level at which side effects occur. Increasing the dose to achieve a clinical effect while titrating the increases against the emergence of side effects is an appropriate strategy for a drug with such wide dose-response variability.

Valproate Typical dose levels are 750 to 2,000 mg a day, to achieve blood levels between 50 and 120 μg/mL. Oral loading with 20 mg per kg a day from the outset is likely to be well tolerated and rapidly effective. In several case series patients with more typical manic syndromes and fewer schizoaffective symptoms appeared to show a high frequency of response. Dysphoric manic patients and rapid cyclers may also be responsive. Carbamazepine and valproate have been used in combination to treat epilepsy, and preliminary evidence for the efficacy of that combination in the acute and prophylactic management of the patient with refractory bipolar disorder is available. Valproate may act by enhancing GABAergic tone, although it also has actions shared by carbamazepine and lithium. Typical side effects are listed in Table 16.7-7.

Clonazepam and lorazepam Benzodiazepine anticonvulsants that have been studied in acute mania include clonazepam and lorazepam (Ativan). The sedating side effects of clonazepam may be problematic in some outpatients but may be useful in the management of inpatients or for bedtime medication for severely insomnic manic patients. The two anticonvulsants work at the central-type benzodiazepine receptor; in contrast, carbamazepine is not active at that receptor and appears to act at the peripheral-type benzodiazepine receptor. Classic central-type benzodiazepine receptors are associated with GABA receptors and surround the chloride ionophore through which chloride influx mediates neuronal inhibition. In contrast, the peripheral-type benzodiazepine receptor appears to be more closely associated with calcium fluxes and neurosteroid biosynthesis. Those findings may have ramifications for a possible differential clinical response between the two classes of anticonvulsants.

Calcium channel antagonists A series of preliminary reports suggest that the calcium channel antagonist verapamil (Calan), and possibly also nifedipine (Procardia) and nimodipine (Nimotop), have acute antimanic efficacy. The clinical utility of the calcium channel antagonists appears promising but needs to be more systematically documented.

TABLE 16.7-7
Comparative and Differential Clinical and Side-Effect Profile of Lithium Carbonate, Carbamazepine, and Valproate

	Lithium Carbonate	Carbamazepine	Valproate
Clinical Profile			
Mania (M)	+ +	+ +	+ +
Dysphoric	±	(+ +)	+ +
Rapid cycling	+	+ +	+ +
Family history negative	±	+	±
Depression (D)	(+)	(+)	(+)
M D prophylaxis	+ +	+ +	+ +
Epilepsy	0	+ +	+ +
Pain syndromes	0	+ +	0 (+ +)
Side Effects			
White blood cell count	↑*	↓	–
Diabetes insipidus	↑*	↓	–
Thyroid hormones (T_3, T_4)	↓	↓	↓
TSH	↑*	–	?
Serum calcium	↑	↓	?
Weight gain	↑	(–)	↑
Tremor	↑	–	↑
Memory disturbances	(↑)	(↑)	(↑)
Diarrhea, GI symptoms	(↑)	(↑)	(↑)
Teratogenic	(?)	(↑)	(↑)
Psoriasis	(↑)	–	–
Pruritic rash	–	↑	–
Alopecia	–	–	(↑)
Agranulocytosis	–	(↑)	–
Aplastic anemia	–	(↑)	–
Thrombocytopenia	–	(↑)	(↑)
Hepatitis	–	(↑)	↑
Hyponatremia, water intoxication	–	↑	–
Dizziness, ataxia, diplopia	–	↑	(+)
Hypercortisolism, escape from dexamethasone suppression	–	↑	–

Key: Clinical efficacy:
0 = None
± = Equivocal
+ = Effective
+ + = Very effective
( ) = Ambiguous or insubstantial data base
* = Effect of lithium predominates in combination with carbamazepine

Side effects:
↑ = Increase
↓ = Decrease
( ) = Inconsistent or rare
– = Absent

Other anticonvulsants The clinical utility of other anticonvulsants, such as the GABA agonist progabide or the traditional anticonvulsant phenytoin (Dilantin), also requires further evaluation. Acetazolamide (Diamox) has been reported to be effective in patients who were not responsive to lithium or carbamazepine, especially those with atypical psychoses associated with dreamy confusional states occurring premenstrually or in the puerperium. The efficacy of the newly approved anticonvulsants felbamate and gabapentin and those about to be approved, such as lamotrigine, remains to be studied.

Electroconvulsive therapy Older clinical observations and recent controlled clinical trials have demonstrated the efficacy of ECT in acute mania. Bilateral treatments are necessary; unilateral, nondominant treatments have been reported to be ineffective and to exacerbate manic symptoms in some studies. Because of the many effective pharmacological treatments that are available, assessing their usefulness for long-term preventive therapy, based on their acute antimanic efficacy, should be emphasized. ECT may then be reserved for the rare refractory patient or one with medical complications, extreme exhaustion, lethal catatonia, or malignant hyperthermia. Otherwise, after a

course of successful ECT the clinician still faces the task of deciding on the most likely effective pharmacological approach to prophylaxis.

Antiadrenergic drugs Several other nonanticonvulsant compounds with some neurotransmitter selectivity have been reported to be effective in the treatment of mania. Clonidine, an α_2-adrenergic receptor agonist, is used to treat hypertension. It acutely inhibits the firing of the noradrenergic locus ceruleus and has been reported to have acute antimanic efficacy in some, but not all, controlled trials. However, response in the first few days of treatment may not be associated with the ultimate outcome. Another agent that inhibits noradrenergic function is the β-adrenergic receptor antagonist propranolol (Inderal). Because very high doses of propranolol in either the *d*- or *l*-isomer form have been effective, it is not known whether the β-antagonist properties or some other membrane-stabilizing effects of the drug account for its acute antimanic efficacy.

Cholinomimetics Intravenous administration of the indirect-acting cholinergic agonist physostigmine (Antilirium, Eserine) has an almost immediate antimanic effect. Physostigmine inhibits acetylcholine esterase function, making more acetylcholine available at the synapse. Although intravenous administration can produce rapid decreases in manic symptoms, physostigmine also has a short half-life and can be associated with marked increases in dysphoria and other side effects such that its long-term utility is doubtful. The success of attempts to increase cholinergic function chronically through other methods, such as lecithin, deanol, or direct acetylcholine agonists, has not been adequately delineated.

Overview of antimanic agents The ability to achieve rapid antimanic effects with intravenous physostigmine suggests that, with appropriate pharmacological intervention and pharmacokinetics, there is no theoretical reason why an acute antimanic response cannot be achieved extremely rapidly, even though most of the other antimanic treatments have a moderate delay in onset. Manipulations of a variety of neurotransmitter systems (inhibition of noradrenergic and dopaminergic systems, but potentiation of cholinergic, benzodiazepinergic, GABAergic, and, perhaps, serotonergic systems) are all capable of inducing antimanic effects. The antipsychotics block dopamine receptors; clonidine and propranolol appear to decrease α- and β-noradrenergic function, respectively; lithium, ECT, and carbamazepine each alter DA, NE, and GABA function, among others. Reserpine, which depletes catecholamines and indoleamines, has also been reported to have antipsychotic and antimanic effects. The literature on tryptophan-induced altered serotonergic function in relation to antimanic efficacy is ambiguous. Awareness of the multiple neurotransmitter approaches to the treatment of mania not only may be clinically useful in changing treatments that target different systems in nonresponsive patients, but it also suggests the current weakness of any hypothetical single neurotransmitter defect in mania.

Alterations in endogenous neuropeptide function also have been postulated in mania. Although manipulations of opiates or cholecystokinin (CCK) have not produced consistent results in psychotic schizophrenic patients, calcitonin has been reported successful in treating excited psychotic states including mania. Preliminary evidence suggests that other calcium-active treatments may also be effective in treating acute mania. The clinical efficacy of calcitonin and other peptide interventions in mania remains to be confirmed but is mentioned because peptides could represent the next generation of antimanic treatments, particularly in light of increasing evidence that peptide neurotransmitters coexist in the same neurons with the more classic neurotransmitter substances that have been indirectly linked to the manic syndromes.

MAINTENANCE TREATMENT OF BIPOLAR DISORDER

Lithium prophylaxis Lithium carbonate originally appeared to be effective in some 70 to 80 percent of bipolar patients, but current estimates suggest that even with adjunctive use of antidepressants and antipsychotics, a figure of 40 to 50 percent efficacy in many lithium clinics is more accurate.

Although early studies indicated the need for blood levels between 0.8 and 1.2 mEq/L, some case studies have suggested that lower levels, in the range of 0.5 to 0.8 mEq/L might also be effective in maintenance treatment. However, a recent controlled study found that the lower levels of side effects are achieved at the cost of a three-times-higher relapse rate when a low lithium level range (0.4 to 0.6 mg/L) is used in comparison to higher levels (0.8 to 1.0 mg/L). Monitoring of trough levels (performed in the early morning, before the morning dose is given) at one- to two-month intervals, or more frequently if the patient's course is unstable, is recommended.

Because of the overwhelming data on long-term efficacy, it is important to consider preventive treatment after a single severe episode of mania particularly if there is a family history of mood disorder. The development of a life chart, outlined above, so that the frequency, severity, and interval between episodes can be accurately assessed, may also assist in arriving at the decision for prophylaxis. If previous episodes were severe—that is, socially incapacitating and requiring hospitalization, or associated with extremely adverse events for the patient and family—the physician should consider prophylaxis earlier rather than later, despite moderately long well intervals between episodes. Those factors should be discussed with the patient during a euthymic interval so that the appropriate risk-benefit ratios can be weighed intelligently and adequate informed consent can be obtained. New data from several studies indicate that a history of more than three or four prior episodes is associated with a poor response to lithium prophylaxis; therefore, a delay in instituting prophylaxis may have consequences not only for morbidity during recurrence but also for ultimate treatment response.

Lithium-induced side effects The profile of lithium-induced side effects has proved to be generally benign even in the long-term maintenance treatment of patients over several decades. Several of lithium's effects deserve comment, however.

THYROID FUNCTION Lithium can impair thyroid function by several different mechanisms, and it has even been used to treat hyperthyroidism. Lithium lowers T_3 and T_4 levels circulating in the plasma and, in some patients, increases the production of thyroid-stimulating hormone (TSH). TSH increases above normal can be indicative of the hypothalamic-pituitary-adrenal axis working overtime to maintain normal levels of thyroid hormones. Thus, thyroid replacement with T_4 might be considered when TSH levels are substantially elevated, even when thyroid hormone indices are still within the lower limits of normal. Thyroid function should be assessed at six-month intervals, and more frequently if there is a breakthrough of depressive symptoms during otherwise adequate lithium maintenance treatment. Treatment of underlying hypothyroidism can, in those

Alkermes, Ex. 1060

instances, help alleviate a depression that is linked to this hormonal deficit. Whereas T_4 is generally used for suppression of TSH and for replacement therapy, anecdotal evidence suggests that the addition of T_3 to T_4 replacement therapy may help some patients with refractory depression or cycling.

RENAL FUNCTION By the 1980s, the scare regarding the possible high incidence of long-term adverse consequences of lithium on the kidneys had largely dissipated. Original reports of severe nephrotoxicity and pathology induced by lithium were in part related to the absence of an age-matched control group of psychiatric patients not treated with lithium. Thus, although lithium impairs vasopressin function at the level of adenylate cyclase and often produces a syndrome of diabetes insipidus, it is less consistently associated with other evidence of renal toxicity. Preliminary data suggest that less renal toxicity may occur with single nighttime dosing, which produces higher peaks but lower nadirs than conventional dosing regimens. Single nighttime dosing may also facilitate compliance.

Current practice suggests that frequent monitoring of renal function is not indicated. It is important, however, to obtain baseline measures of renal function, including the creatinine clearance rate, before beginning lithium treatment, particularly in patients with a history of renal alterations. Because of the induction of diabetes insipidus syndrome related to the blockade of antidiuretic hormone actions, patients must have adequate fluid intake to maintain an appropriate fluid and electrolyte balance. Several cases have been reported in which high levels of lithium during intoxication were associated with irreversible cerebellar toxicity. Thus, lithium levels, fluid and electrolyte status, or both should be monitored closely during periods of febrile illness, decreased fluid intake, or greater than ordinary fluid loss (such as during extreme athletic stress or GI illnesses accompanied by vomiting or diarrhea). Amiloride (Midamor, 5 to 10 mg) has been useful in the treatment of lithium-induced diabetes insipidus. If diuretics (furosemide [Lasix] or thiazide [Diuril]) are used, lower doses of lithium may be indicated.

TREMOR Tremor can be problematic for a small but substantial percentage of patients treated with lithium. Tremor is frequently exacerbated by social stress. When the tremor persists at doses at the lower end of the therapeutic range or at the minimum doses necessary for therapeutic efficacy, attempts can be made to treat it symptomatically. Some investigators find that 10 to 40 mg of the β-blocker propranolol in divided daily doses may reduce lithium tremor. Relief may occur within 30 minutes and may last from four to six hours.

GASTROINTESTINAL EFFECTS GI side effects (diarrhea and indigestion) can be problematic for many patients but may be attenuated by reducing the dose or giving it at meal times (for indigestion). Antidiarrheal agents should be restricted to acute treatment.

MENTAL EFFECTS Patients may express concern about the effects of lithium on their memory, spontaneity, and creativity. Although impairment can be objectively delineated on some, but not all, types of detailed neuropsychological testing, most patients either do not experience that effect or do not find it unduly impairing. In fact, productivity and creativity may, overall, be enhanced during lithium treatment because it prevents unproductive manic and depressive episodes. Though no adequate approach to measuring the subjective cognitive effects of lithium has been reported, it is important to rule out associated causes for cognitive impairment, including possible hypothyroidism or an inadequately treated coexisting depression, and to consider a careful dose reduction. Many so-called drug-related side effects occur during placebo treatment and thus appear to be more closely associated with illness-related variables than with a particular psychopharmacological treatment. That perspective on lithium maintenance treatment needs to be explored with the patient to avoid premature discontinuation of treatment or noncompliance.

WEIGHT GAIN Lithium-induced weight gain is a problem in a small percentage of patients. If there is a reactive hypoglycemic component, carbohydrate restriction may help avoid the problem. Thyroid indices should be rechecked and the patient reminded not to use calorie-containing beverages to maintain the necessary increased fluid intake associated with diabetes insipidus. The role of bupropion for weight loss in the context of antidepressant augmentation remains to be studied systematically.

Dose reduction Dose reduction may be a first maneuver in treating a variety of lithium-induced problems (for example, tremor, weight gain, thirst, urinary frequency, diarrhea, and psychomotor slowing). If lower doses are not adequate for prophylaxis, combination or alternative treatment, especially with carbamazepine (which has a different side-effect profile) or valproate, may be indicated. Other lithium-related effects during combination treatment with carbamazepine are discussed below. Because the renal clearance of lithium appears to decrease with age, a lower dose may be adequate and necessary in the older patient on lithium maintenance therapy. The calcium channel blockers may be effective in lithium responsive patients, yet avoid most lithium-related side effects.

Treatment of depressive breakthrough episodes during lithium prophylaxis The treatment of a depressive episode in an untreated patient with bipolar disorder or of an episode emerging during lithium prophylaxis is very different from the treatment for major depressive disorder. Although SSRIs, cyclic antidepressants, and MAOIs are the mainstays of treatment of major depressive disorder, they should be used cautiously in patients with bipolar disorder. Some studies have reported an increased incidence of switches into hypomania or mania during tricyclic or MAOI therapy, above that expected for the patient's natural course of illness (Figures 16.7-3 and 16.7-7). Although it is unknown whether the increased incidence of switching is sufficient cause to reduce the use of unimodal antidepressants in patients with bipolar disorder, it is clear that treatment with those compounds can speed up the rate of cycling in rapid-cycling patients. Thus, a depressive episode may be shortened at the cost of more rapid onset of the subsequent manic episode. Withdrawal of antidepressants has also attenuated cycle frequency in some patients.

Some uncontrolled observations implicate tricyclics and related compounds in the development of continuous cycling phases (that is, successive episodes without a well-interval) (Figures 16.7-3, 16.7-7, and 16.7-8). Continuous cycling is difficult to treat and tends to be refractory to lithium. There is anecdotal evidence (requiring further investigation) that bupropion may not be associated with the same tendency toward cycle induction as are other antidepressant modalities (Figure 16.7-3). The SSRIs (or venlafaxine) may have the same effect on the switch phenomenon and on cycle induction as the tricyclics, but that conjecture requires further investigation.

Once a switch has been observed while the patient was taking

Alkermes, Ex. 1060

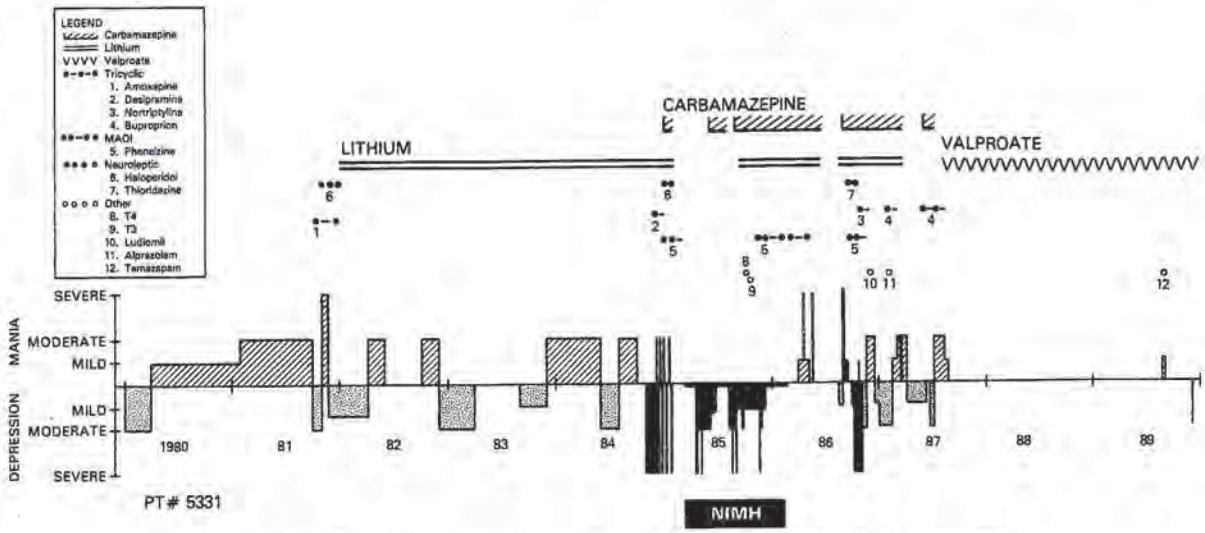

FIGURE 16.7-7 *Prophylactic response to valproate in a nonresponder to lithium and carbamazepine.*

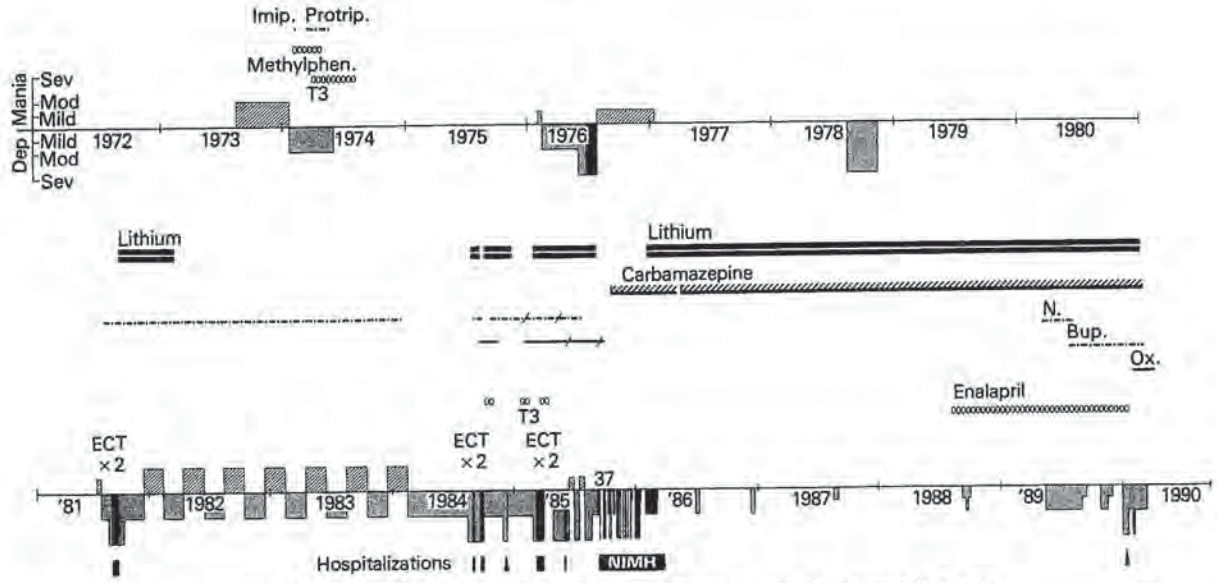

FIGURE 16.7-8 *Loss of prophylactic efficacy in a woman with rapid-cycling bipolar II disorder.*

an MAOI, reexposure, even to a different MAOI, has been reported to lead to earlier onset of a switch, perhaps reflecting the occurrence of sensitization. It is unclear whether a drug-induced switch occurs only in those predestined to have spontaneous switches or whether it predisposes to the development of further spontaneous manic episodes.

Therefore, the unimodal antidepressants should be used with caution in treating the depressive episodes of bipolar disorder, particularly if there is a history of drug-induced switches. In addition, other options should be considered, such as adding another mood stabilizer (for example, lithium, carbamazepine, or valproate). Women appear to be particularly predisposed to heterocyclic- and antidepressant-induced cycling. If unimodal antidepressants are used for a bipolar depressive episode, they should be tapered and discontinued as soon as possible to avoid the potential for drug-induced switches and cycle acceleration. Lithium and other mood stabilizers may not be able to prevent those phenomena entirely. Several case reports suggest that alprazolam may induce switches into hypomania and mania even in nonpredisposed patients.

The MAOIs in general may be less likely to induce switches than the tricyclics (Figure 16.7-7). They should be given relatively greater consideration, especially for anergic, hypersomnic, hyperphagic patients with bipolar disorders. A substantially higher rate of antidepressant response has been reported in one controlled series for tranylcypromine (81 percent) compared with imipramine (48 percent) in patients with bipolar disorder. Clorgyline, a selective MAO type A inhibitor that is not yet clinically available, has been reported to slow the cycling frequency. The efficacy of other type A-selective drugs,

such as meclobemide, remains to be studied more extensively in bipolar patients.

CARBAMAZEPINE One alternative to traditional unimodal antidepressants for depressive breakthroughs during lithium prophylaxis is the addition of carbamazepine (Figure 16.7-8). Although evidence of the overall clinical benefit of carbamazepine when used as sole treatment in primary depression is scanty, in conjunction with the emerging literature on the efficacy of carbamazepine prophylaxis for both manic and depressive episodes, it raises the priority of using carbamazepine as a supplement to lithium in depressive breakthroughs, particularly of the rapid-cycling variety. Although only one third of acutely depressed patients responded in one study, responders tended to be patients with greater initial severity of depression and histories of discrete episodes rather than chronic depression. An abnormal EEG and increased psychosensory symptoms did not predict an acute response to carbamazepine in that series. When antidepressant response to carbamazepine was observed, it tended to exhibit the typical lag observed with other agents, so that only minor improvement was noted in the first and second weeks of treatment, whereas considerable improvement was observed after the third and fourth weeks.

In a small series of patients who responded inadequately to carbamazepine alone, one half showed a rapid onset of antidepressant effect with lithium augmentation. Thus, the combination of carbamazepine and lithium appears to be helpful for a subgroup of patients with treatment-refractory conditions. Whether the combined efficacy of the two agents is sufficient to block tricyclic- and MAOI-induced switches into mania or hypomania is unknown.

VALPROATE In uncontrolled studies valproate, alone or in addition to lithium, has been reported to be successful in the long-term treatment of a subgroup of previously lithium-refractory patients. The antidepressant efficacy of valproate is less well delineated than its antimanic efficacy, and the utility of valproate in the treatment of an acute depressive episode remains to be further elucidated. Nonetheless, valproate, alone or in combination with lithium, offers another option in the long-term management of patients with bipolar disorder who do not respond to lithium alone. A response to one anticonvulsant may not predict response to another, and positive long-term effects of valproate plus lithium have been noted in patients not responsive to lithium or carbamazepine prophylaxis (Figures 16.7-7 and 16.7-9).

BUPROPION Bupropion in combination with a mood stabilizer has shown promise in the acute and prophylactic management of patients with bipolar disorder, including rapid cyclers. Although bupropion may be added to lithium or valproic acid prophylaxis without major pharmacokinetic interactions, when used with carbamazepine its blood levels are markedly decreased and those of its metabolites are increased.

THYROID HORMONE Although thyroid hormone potentiation similar to that observed in major depressive disorder can be attempted, treatment with greater than suppressive doses should be approached with caution. Medical toxic effects have been reported with high-dose thyroid treatment, and long-term prophylaxis was inadequate unless other agents were used concurrently. Thus, T_3, because of its short half-life, is recommended for acute augmentation strategies, whereas T_4 is recommended by some for long-term maintenance during prophylaxis. However, the addition of T_3 to T_4 in nonresponders has been reported to be helpful.

CALCIUM CHANNEL BLOCKERS Although the calcium channel blockers, especially verapamil, have been reported effective in the treatment of acute mania in most, but not all, controlled clinical trials, their effectiveness in depression has received little attention. Recently, the dihydropyridine L-type calcium

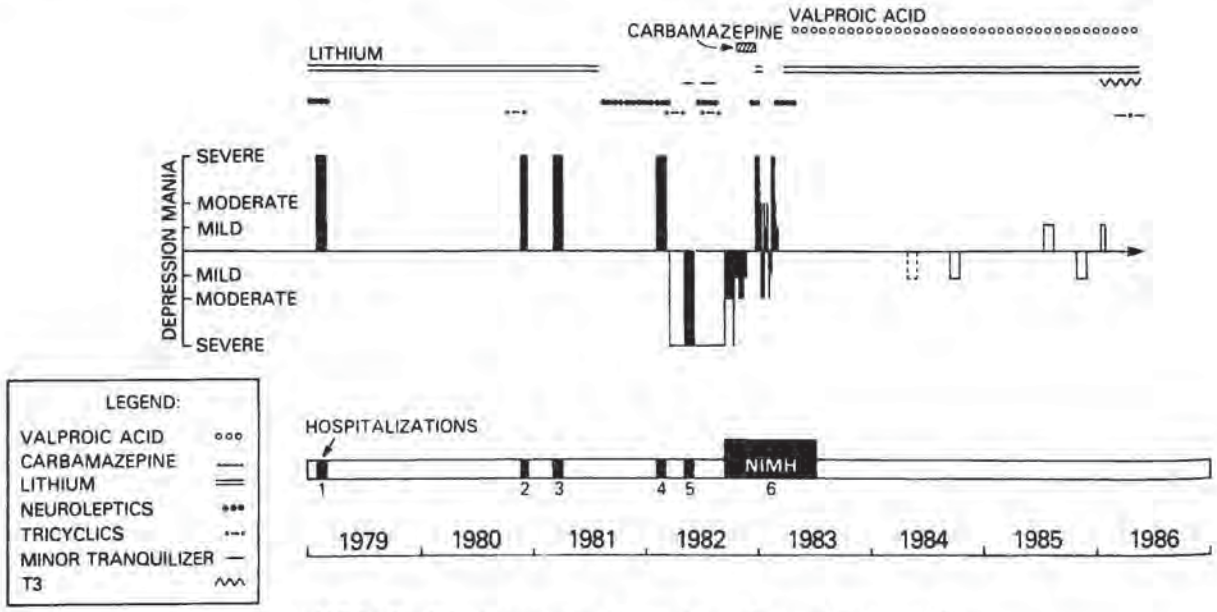

FIGURE 16.7-9 *Prophylactic response to valproate in a carbamazepine nonresponder.*

Alkermes, Ex. 1060

channel blocker nimodipine was studied in placebo-controlled designs and appeared to be effective in approximately one third of patients with treatment-refractory bipolar disorder.

Among those showing responses, confirmed with the use of blind off-on-off-on (placebo-drug-placebo-drug) designs, were those with bipolar refractory depression, rapid and ultradian cycling, and recurrent, brief episodes of major depressive disorder. All of the patients with bipolar disorder who responded to nimodipine failed to respond to verapamil, but did respond to the dihydropyridine isradipine. Studies on the use of nimodipine in combination with lithium or carbamazepine for inadequate responders to those agents alone are promising.

SPIRONOLACTONE Spironolactone (Aldactone) was reported to be effective in six lithium-intolerant patients. It has received no further systematic study.

FOLIC ACID A single investigation reported that folic acid supplementation in the dose range of 300 to 400 μg a day significantly reduced affective morbidity, compared with results in a placebo group maintained on lithium. The promising result and the benign nature of folic acid treatment suggest that it be considered while awaiting further clinical investigation.

ELECTROCONVULSIVE THERAPY ECT may be useful for bipolar depressed patients who do not respond to lithium and adjunctive agents. Whether ECT would help abbreviate recurrent depressive episodes in rapid-cycling patients and whether it would be useful in long-term prophylaxis are questions that await further investigation.

Treatment of manic breakthroughs during lithium prophylaxis A wide range of drugs is available for breakthrough manic episodes occurring during lithium treatment. They include the entire spectrum of drugs indicated for the treatment of acute mania, and particularly carbamazepine and valproate because of their longer-term prophylactic efficacy. Clonazepam or lorazepam may also be useful acute alternatives to antipsychotic supplementation even though the benzodiazepines (and antipsychotics) appear to have a lesser role in the long-term management of bipolar disorders than does carbamazepine or valproate.

Other approaches to the manic breakthrough include the judicious use of antipsychotics at minimal doses and for the shortest period of time. The use of clozapine for refractory bipolar and schizoaffective patients (that is, those unresponsive to lithium, carbamazepine, and valproate) appears promising in light of preliminary reports of its efficacy and its lack of induction of tardive dyskinesia.

Lithium augmentation with carbamazepine or valproate Supplementing the clinical effects of lithium with anticonvulsants such as carbamazepine and valproate is often more effective than using the anticonvulsant alone. Because lithium treatment is continued, evaluation of the anticonvulsant's efficacy is not confounded by a lithium withdrawal-induced episode, and time may be saved in the assessment of one clinical trial of the combination rather than two sequential trials (the anticonvulsant alone and then the combination). For patients who are unable to tolerate lithium carbonate, carbamazepine or valproate alone may be useful in preventing both manic and depressive episodes when given as long-term maintenance treatment. The literature on open clinical trials with carbamazepine is substantial, and several double-blind studies support the preliminary evidence of its long-term efficacy. Most of the data on valproate are based on clinical case series. The choice of carbamazepine or valproate may depend on the development of better clinical predictors or on the current assessment of their relative side-effect profiles.

Side Effects During Combination Therapy

HEMATOLOGICAL EFFECTS The side-effect profile of carbamazepine tends to be quite different from that of lithium or valproate (Table 16.7-7). As a rule of thumb, whenever lithium and carbamazepine act on a common target system, the effects of lithium tend to override those of carbamazepine. In almost every instance that is a clinical disadvantage except in terms of white blood cell (WBC) count suppression: The ability of lithium to increase the WBC count and override the count-suppressing effects of carbamazepine may be useful. Lithium is effective only against carbamazepine's benign suppression of the WBC count, and its effects are doubtful if there is evidence of more problematic interference by carbamazepine in hematological function in other cell lines, such as platelets or red cells, indicative of a pancytopenic or aplastic process. If levels of those other blood elements are normal, potentiation with lithium to reverse the benign WBC count suppression of carbamazepine may be attempted. Valproate has been associated with thrombocytopenia; the potential impact of lithium on that syndrome has not been reported.

VASOPRESSIN FUNCTION AND ELECTROLYTES Because carbamazepine appears to act as a vasopressin agonist, either directly or by potentiating vasopressin effects at the receptor, it is not sufficient to reverse lithium-induced diabetes insipidus, which occurs by an action of lithium below the receptor level at the adenylate cyclase second-messenger system. Lithium may counter the hyponatremic effects of carbamazepine, however. To the extent that the minor cognitive impairments of lithium are, in part, related to its ability to impair vasopressin function in the brain, those data suggest not only that carbamazepine would be less likely to cause that side effect but that during combination treatment the side effects of lithium would override those of carbamazepine. Carbamazepine tends to induce a benign hypocalcemia that is generally not associated with bone demineralization. In contrast, lithium often produces a transient increase in serum calcium levels.

THYROID FUNCTION Not only does carbamazepine tend to decrease T_4, free T_4, and T_3 levels, as does lithium, but, when the two drugs are given in combination, the decreases are potentiated. However, during carbamazepine treatment there is a negligible incidence of clinical hypothyroidism or above-normal increases in TSH. Consequently, thyroid supplementation of carbamazepine is rarely needed, but when the two drugs are used in combination, lithium's effect on TSH will override that of carbamazepine and the patient may require thyroid supplementation.

ALLERGIC RASH Carbamazepine induces an allergic rash in 5 to 15 percent of patients treated. In most instances the drug should be discontinued. However, if carbamazepine has shown efficacy and other available agents have not, prednisone (40 mg a day) has been reported to be effective in suppressing uncomplicated carbamazepine-induced rashes.

HEPATITIS There are extremely rare cases of carbamazepine-induced hepatitis. Routine monitoring for that side effect does not appear to be indicated.

Alkermes, Ex. 1060

Valproate has been associated with reports of severe hepatitis in the neurological literature; most of the fatalities have been in children, particularly those under the age of 2 years and on polytherapy. Few serious hepatic side effects have been reported in the adult psychiatric patients so far studied with valproate, but liver function should be monitored periodically when that agent is used, and the patient should be warned to report symptoms that might be referable to hepatitis, such as fever, right upper quadrant pain, malaise, nausea, anorexia, and jaundice. Benign elevation of values on liver function tests (to two or three times normal) can be followed without drug discontinuation, however. Selenium vitamin supplements may be helpful in avoiding valproate-induced hepatitis-pancreatitis.

NEUROTOXICITY There have been occasional reports of neurotoxicity when lithium and carbamazepine were used together. Because both agents can cause neurotoxic effects at or below clinically accepted dose ranges, they may occasionally occur from the combination treatment as well. In most studies the combination appears to be well tolerated, without producing side effects greater than those seen with either agent alone. Many of the side effects reported in the literature appear to have been caused by starting with relatively large doses of carbamazepine (rather than increasing the dosage slowly) in combination with other agents and assuming that the side effects were related to the combination treatment rather than to carbamazepine alone. Lithium and valproate are generally well tolerated in combination, but effects on tremor or GI distress may be additive.

PHARMACOKINETIC INTERACTIONS There do not appear to be major pharmacokinetic interactions between carbamazepine and lithium. However, that is not the case with carbamazepine and haloperidol, as haloperidol blood levels are markedly reduced by carbamazepine. Nevertheless, most studies report improvement with carbamazepine supplementation, which suggests that carbamazepine might potentiate antipsychotic effects because of its action on systems not involving dopamine receptor blockade.

Agents commonly employed in medical practice can markedly increase carbamazepine levels and produce attendant toxicity. The most frequent dose-related toxic manifestations are dizziness, drowsiness, ataxia, diplopia, and confusion. Those effects may occur in a patient who may tolerate carbamazepine well until another agent is added. Erythromycin, troleandomycin, isoniazid (but apparently not other MAOIs), and the calcium channel blockers verapamil and diltiazem (Cardizem) (but not nifedipine or nimodipine) increase blood levels of carbamazepine. Less marked increases occur during cotreatment with propoxyphene (Darvon), fluoxetine and fluvoxamine, and, transiently, cimetidine (Tagamet). Carbamazepine lowers the blood levels of various agents (especially oral contraceptives, so that higher-dose formulations or other contraceptive strategies are indicated) and interfere with some tests that are dependent on protein binding.

In contrast to the multiple pharmacokinetic interactions between carbamazepine and other drugs—in large part owing to carbamazepine's metabolism by and its ability to be an inducer of hepatic P-450 enzymes—valproate is largely without those effects. If carbamazepine and valproate are used together, the clinician should consider reducing the dose of carbamazepine (because valproate displaces carbamazepine from protein-binding sites, increases levels of free drug, and increases levels of the -10,11-epoxide metabolite) and increasing the dose of valproate (because carbamazepine lowers levels of valproate).

TERATOGENIC EFFECTS Cardiac and great vessel (Ebstein's) anomalies have been reported to occur with a higher frequency than expected in patients treated with lithium during pregnancy. However, recent retrospective and prospective studies have indicated that the risk may be only minimally greater than in control patients not exposed to lithium and in the normal population. In light of those data and the substantial risk of episode recurrence and its possible effects on the subsequent course of illness should lithium be stopped, routine discontinuation of lithium in all patients wishing to become pregnant should be reevaluated.

Lithium may be safer than valproate or carbamazepine for the patient with prior frequent, severe, psychotic, or suicidal episodes that might render discontinuation inadvisable. If lithium is to be discontinued for a planned pregnancy, discontinuation should be done so slowly, since a taper is less likely than rapid discontinuation to be associated with episode re-occurrence. Recently, an increased risk of inducing minor congenital malformations and developmental delay has been reported for carbamazepine. A substantial and increased risk of spina bifida has been reported for valproate. The risk is only slightly lower with carbamazepine, and use of those mood-stabilizing agents should be avoided in pregnancy if possible.

Using the lowest effective doses and supplementing with folic acid should be considered in patients who need those agents during pregnancy. Consultation with a specialist for fetal monitoring and assessment of possible defects with ultrasound and other techniques is also recommended. Persisting biochemical alterations have been found in some animal studies of fetal exposure to antipsychotics, but have not been assessed systematically in follow-up studies in humans. ECT may have the lowest risk to the fetus among the somatic treatments, but risks to the fetus from maternal seizures have not been adequately elucidated.

SENSITIZATION EFFECTS ON THE MOOD DISORDERS

Early clinical observations and more recent systematic controlled studies suggest that recurrent major depressive disorder and bipolar disorders may undergo a transition from initial episodes that are often precipitated by psychosocial stressors to later episodes that tend to occur more spontaneously. The transition often occurs in the context of an overall pattern of cycle acceleration with decreasing well intervals between successive episodes. It has been postulated that psychosocial stressors and recurrent episodes of mood disorder themselves not only may cause acute biological perturbations but also may leave behind residual biological memory traces, based on their ability to alter gene expression. It is thought that, following stress- and episode-induced changes in neurotransmission, a cascade of neurobiological effects takes place that includes not only short-term adaptations but also longer-lasting alterations initiated by a variety of transcription factors, including immediate early genes such as c-fos and c-jun. Those transcription factors are then capable of inducing changes in the long-term regulation of transmitters, receptors, nerve growth factors, neuropeptides, and possibly even in the microstructural synaptic organization of the brain, as demonstrated in many models of learning and memory.

If that conceptualization proves to be correct, it suggests the potential twofold importance of preventing episodes of mood disorder. Not only would the associated morbidity and potential mortality be prevented, but the longer-lasting neurobiological

Alkermes, Ex. 1060

vulnerabilities associated with the experience of repeated episodes of mood disorder (sensitization) might be attenuated as well. In light of increasing evidence that greater numbers of episodes of mood disorder are a poor prognostic sign and may be associated with relative resistance to effective treatment with lithium, the clinical and theoretical data speak to the importance of early institution and long-term maintenance of prophylaxis, particularly in patients already identified as being at high risk for episode recurrence. A specific focus on education and other practical ways of avoiding noncompliance is similarly important.

Treatment efficacy may vary as a function of the stage or severity of evolution of illness. For example, pharmacotherapies such as lithium may be more effective in initial and midphases of the illness, but with the emergence of rapid and ultrarapid cycling, alternative and adjunctive treatments with the anticonvulsants may be required. Similar treatment alterations may be necessary in patients with major depressive disorder, for whom psychotherapy may be effective in the early, milder forms of the illness, but, with major recurrent episodes (and particularly melancholic and psychotic syndromes), aggressive acute and maintenance pharmacotherapy may be mandatory. Adjunctive interpersonal, cognitive, and behavioral psychotherapeutic techniques may also play important roles in the late and severe stages of illness as problem-solving, remoralization, and suicide prevention techniques and in facilitating compliance with prescribed pharmacological regimens.

If two or more episodes of major depressive disorder have occurred, the clinician should strongly consider recommending long-term pharmacoprophylaxis, whether or not the patient is in ongoing psychotherapy, as recent data unequivocally support the long-term efficacy of a variety of antidepressant agents. In contrast, psychotherapy appears to be of only minor utility in delaying the onset of the next episode.

The mood disorders involve multiple areas of brain dysfunction and affect a variety of organ systems, producing alterations not only in mood but also in motor, cognitive, sleep, appetite, reward, and other somatic systems. Neurobiological alterations are evident at the level of endocrine dysfunction, as reflected not only in alterations in the regulation of glucocorticoids, corticotropin-releasing hormone, TRH, and somatostatin, but also in the size of the pituitary and the adrenals. Brain imaging has revealed alterations in blood flow and glucose utilization reflecting hypofrontality in primary and secondary depression in many studies in direct proportion to the severity of the depressive syndrome. Thus, patient and clinician should be reminded of the wealth of evidence indicating that the mood disorders are grave, potentially life-threatening, medical illnesses not different from those that afflict other major organ systems of the body and as such should be treated with equal respect.

SUGGESTED CROSS-REFERENCES

Biological therapies are discussed in Chapter 32. Obsessive-compulsive disorder is covered in Section 17.3. The range of psychotherapeutic modalities and techniques useful in treating depressed patients is discussed in Section 16.8. The rest of Chapter 16 can be consulted for other aspects of mood disorders.

REFERENCES

Aronson T A, Shukla S, Hirschowitz J: Clonazepam treatment of five lithium-refractory patients with bipolar disorder. Am J Psychiatry *146:* 77, 1989.

Baldessarini R J: Antidepressant agents. In *Chemotherapy in Psychiatry: Principles and Practices,* R J Baldessarini, editor, Harvard University Press, Cambridge, MA, 1985.

Basco M R, Rush A J: *Cognitive Behavioral Treatment of Manic Depressive Disorder.* Guilford, New York, 1994.

Blumenthal S J: Suicide: A guide to risk factors, assessment, and treatment of suicidal patients. Med Clin North Am *72:* 937, 1988.

Bowden C L, Brugger A M, Swann A C, Calabrese J R, Janicak P G, Petty F, Dilsaver S C, Davis J M, Rush A J, Small J G, Garza-Trevino E S, Risch S C, Goodnick P J, Morris D D: Efficacy of divalproex vs lithium and placebo in the treatment of mania. JAMA *271:* 918, 1994.

Calabrese J R, Markovitz P J, Kimmel S E, Wagner S C: Spectrum of efficacy of valproate in 78 rapid-cycling bipolar patients. J Clin Psychopharmacol *12:* 53S, 1992.

Cohen L S, Friedman J M, Jefferson J W, Johnson E M, Weiner M L: A reevaluation of risk of in utero exposure to lithium. JAMA *271:* 146, 1994.

Cooke R G, Joffe R T, Levitt A J: T_3 augmentation of antidepressant treatment in T_4-replaced thyroid patients. J Clin Psychiatry *53:* 16, 1992.

Davis J M, Wang Z, Janicak P G: A quantitative analysis of clinical drug trials for the treatment of affective disorders. Psychopharmacol Bull *29:* 175, 1993.

Dubovsky S L: Calcium antagonists in manic-depressive illness. Neuropsychobiol *27:* 184, 1993.

Faedda G L, Tondo L, Baldessarini R J, Suppes T, Tohen M: Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. Arch Gen Psychiatry *50:* 448, 1993.

Fawcett J, Kravitz H M, Zajecka J M, Schaff M R: CNS stimulant potentiation of monoamine oxidase inhibitors in treatment-refractory depression. J Clin Psychopharmacol *11:* 127, 1993.

*Frank E, Kupfer D J, Perel J M, Cornes C, Jarrett D B, Mallinger A G, Thase M E, McEachran A B, Grochocinski V J: Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry *47:* 1093, 1990.

Gelenberg A J, Kane J M, Keller M B, Lavori P, Rosenbaum J F, Cole K, Lavelle J: Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med *321:* 1489, 1989.

*Goodwin F K, Jamison K R: *Manic-Depressive Illness.* Oxford University Press, New York, 1990.

Gupta S, Ghaly N, Dewan M: Augmenting fluoxetine with dextroamphetamine to treat refractory depression. Hosp Community Psychiatry *43:* 281, 1992.

Hoschl C: Do calcium antagonists have a place in the treatment of mood disorders? Drugs *42:* 721, 1991.

Joffe R T, Schuller D R: An open study of buspirone augmentation of serotonin reuptake inhibitors in refractory depression. J Clin Psychiatry *54:* 269, 1993.

Joffe R T, Singer W, Levitt A J, MacDonald C: A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. Arch Gen Psychiatry *50:* 387, 1993.

Keller M B: Diagnostic and course-of-illness variables pertinent to refractory depression. In *Review of Psychiatry,* vol 9, A Tasman, S M Goldfinger, C A Kaufmann, editors, p 10. American Psychiatric Press, Washington, 1990.

Kramlinger K G, Post R M: The addition of lithium carbonate to carbamazepine: Antidepressant efficacy in treatment-resistant depression. Arch Gen Psychiatry *46:* 794, 1989.

*Kupfer D J, Frank E, Perel J M, Cornes C, Mallinger A G, Thase M E, McEachran A B, Grochocinski V J: Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry *49:* 769, 1992.

Maj M, Pirozzi R, Kemali D: Long-term outcome of lithium prophylaxis in patients initially classified as complete responders. Psychopharmacology (Berlin) *98:* 535, 1989.

McElroy S L, Keck P E, Pope H G, Hudson J I: Valproate in the treatment of bipolar disorder: Literature review and clinical guidelines. J Clin Psychopharmacol *12:* 42S, 1992.

Montgomery S A, Dufour H, Brion S, Gailledreau J, Laqueille X, Ferrey G, Moron P, Parant-Lucena N, Singer L, Danion J M, Beuzen J N, Pierredon M A: The prophylactic efficacy of fluoxetine in unipolar depression. Br J Psychiatry *153:* 69, 1988.

Montgomery S A, Roberts A, Patel A G: Placebo-controlled efficacy of antidepressants in continuation treatment. Int Clin Psychopharmacol *9:* 49, 1994.

Murphy D L, Sunderland T, Cohen R M. Monoamine oxidase-inhibiting antidepressants: A clinical update. Psychiatr Clin North Am *7:* 549, 1984.

Nolen W A, Van de Putte J J, Dijken W A, Kamp J S, Blansjaar B A, Kramer H J, Haffmans J: Treatment strategy in depression: I. Non-tricyclic and selective reuptake inhibitors in resistant depression. A double-blind partial crossover study on the effects

of oxaprotiline and fluvoxamine. Acta Psychiatr Scand *78:* 668, 1988.
O'Connell R A, Mayo J A, Flatow L, Cuthbertson B, O'Brien B E: Outcome in bipolar disorder of long-term treatment with lithium. Br J Psychiatry *159:* 123, 1991.
Okuma T: Effects of carbamazepine and lithium on affective disorders. Neuropsychobiology *27:* 138, 1993.
Okuma T, Yamashita I, Takahashi R, Itoh H, Kurihara M, Otsuki S, Watanabe S, Sarai K, Hazama H, Inanaga K: Clinical efficacy of carbamazepine in affective, schizoaffective, and schizophrenic disorders. Pharmacopsychiatry *22:* 47, 1989.
Peselow E D, Fieve R R, Difiglia C, Sanfilipo M P: Lithium prophylaxis of bipolar illness: The value of combination treatment. Br J Psychiatry *164:* 208, 1994.
*Post R M: Alternatives to lithium for bipolar affective illness. In *Review of Psychiatry,* vol 9, A Tasman, S M Goldfinger, C A Kaufmann, editors, p 170. American Psychiatric Press, Washington, 1990.
Post R M: Prophylaxis of bipolar affective disorders. Int Rev Psychiatry 2: 277, 1990.
Post R M: Sensitization and kindling perspectives for the course of affective illness: Toward a new treatment with the anticonvulsant carbamazepine. Pharmacopsychiatry *23:* 3, 1990.
Post R M: Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry *149:* 999, 1992.
Post R M, Leverich G S, Altshuler L, Mikalauskas K: Lithium discontinuation-induced refractoriness: Preliminary observations. Am J Psychiatry *149:* 1727, 1992.
Post R M, Weiss S R B: Endogenous biochemical abnormalities in affective illness: Therapeutic vs. pathogenic. Biol Psychiatry *32:* 469, 1992.
Preskorn S H: Pharmacokinetics of antidepressants: Why and how they are relevant to treatment. J Clin Psychiatry *54:* (Suppl): 14, 1993.
Price L H, Charney D S, Heninger G R: Variability of response to lithium augmentation in refractory depression. Am J Psychiatry *143:* 1387, 1986.
Quitkin F M, McGrath P J, Stewart J W, Harrison W, Tricamo E, Wager S G, Ocepek-Welikson K, Nunes E, Rabkin J G, Klein D F: Atypical depression, panic attacks, and response to imipramine and phenelzine. Arch Gen Psychiatry *47:* 935, 1990.
Ribeiro S C, Tandon R, Grunhaus L, Greden J F: The DST as a predictor of outcome in depression: A meta-analysis. Am J Psychiatry *150:* 1618, 1993.
Rouillon F, Phillips R, Serrurier D, Ansart E, Gerard M J: Recurrence of unipolar depression and efficacy of maprotiline. Encephale *15:* 527, 1989.
Rouillon F, Serrurier D, Miller H D, Gerard M J: Prophylactic efficacy of maprotiline on unipolar depression relapse. J Clin Psychiatry *52:* 423, 1991.
Schou M: Relapse prevention in manic depressive illness: Important and unimportant factors. Can J Psychiatry *36:* 502, 1991.
Shea M T, Pilkonis P A, Beckham E, Collins J F, Elkin I, Sotsky S M, Docherty J P: Personality disorders and treatment outcome in the NIMH treatment of depression collaborative research program. Am J Psychiatry *147:* 711, 1990.
*Suppes T, Baldessarini R J, Faedda G L, Tohen M: Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry *48:* 1082, 1991.
Thase M E, Frank E, Mallinger A G, Hamer T, Kupfer D J: Treatment of imipramine-resistant recurrent depression: III. Efficacy of monoamine oxidase inhibitors. J Clin Psychiatry *53:* 5, 1992.
White K, Simpson G: Combined MAOI-tricyclic antidepressant treatment: A reevaluation. J Clin Psychopharmacol *1:* 264, 1981.

16.8 MOOD DISORDERS: PSYCHOSOCIAL TREATMENTS

ROBERT M. A. HIRSCHFELD, M.D.
M. TRACIE SHEA, Ph.D.

INTRODUCTION

Although psychoanalytic approaches were the predominant mode of treatment for depression in the early to middle part of this century, now many types of psychotherapy based on a variety of concepts are in use. Psychotherapeutic approaches have been developed specifically for depression that aim to correct specific manifestations, including cognition, behavior, and affect. In general, those treatments are short-term and seek to alleviate the depressive condition, not to change the character of the patient.

PSYCHOANALYSIS AND PSYCHOANALYTIC APPROACHES

THEORETICAL CONCEPTS The interpersonal nature of depression was noted and emphasized in the earliest psychoanalytic writings on depression, as was the centrality of the regulation of self-esteem. In *Mourning and Melancholia* Sigmund Freud stated that a vulnerability to depression caused by an interpersonal disappointment early in life led to future love relationships marked by ambivalence. Actual or threatened interpersonal losses in adult life trigger a self-destructive struggle in the ego that is manifested as depression. That theory was significantly refined by later psychoanalysts who described the depression-prone personality as one needing constant reassurance, love, and admiration, and as being dependent on others for narcissistic gratification and maintenance of self-esteem. Frustration of those dependency needs leads to a plummet in self-esteem and to subsequent depression. That notion was later expanded to include any person with a fragile self-esteem system. Another dynamic approach focuses on the cognitive aspects of depression, highlighting the recognition of the disparity between one's actual and idealized situation. That realization leads to a sense of helplessness and powerlessness and ultimately to depression.

GOALS All psychoanalytic contributions to studies of depression derive from the theory that a disturbance in interpersonal relations in early childhood, usually involving a loss or disappointment, impairs subsequent interpersonal relations. The affected person is especially vulnerable to interpersonal disappointments and losses later in life, which may result in depressive illness. The goal of traditional psychoanalytic psychotherapy is to elicit changes in personality structure, not simply to alleviate symptoms. It aims to improve the patient's potential for interpersonal trust, intimacy, and generativity; coping mechanisms, the ability to experience a wide range of emotions; and the capacity to grieve. Treatment may often require the patient to experience heightened anxiety and distress during the course of therapy, which usually continues for several years. Early psychoanalytic treatments were of short duration compared with current practice, usually lasting no more than a few months. Freud, for example, cured the composer Gustav Mahler of a sexual problem in one four-hour session. Psychoanalytic treatment lengthened in duration as the development and interpretation of the transference relationships became the core of the therapy and as the therapists became more passive in their behavior. Several clinicians, including Franz Alexander in Chicago, attempted to reverse those trends, but have had relatively little impact on their colleagues. In the past two decades, however, several specific short-term psychoanalytic approaches have evolved that are applicable to the treatment of depression. These approaches seek to reduce symptoms, resolve neuroses, and improve the patient's quality of life. Perhaps the most seminal work was by Michael Balint and his colleagues in the 1950s at the Tavistock Clinic in London. Since the death of Balint, David Malan has continued that work. Other contributors include Habib Davanloo in Montreal, Peter Sifneos in Boston, Hans Strupp in Tennessee, and Lester Luborsky in Philadelphia (Table 16.8-1).

Short-term psychoanalytic therapies for depression are distinguished from other psychotherapeutic approaches by the use of the transference relationship. The therapeutic relationship has two aspects: the real and the transferred. The real relationship refers to thoughts, feelings, and behaviors that are relevant and appropriate to the current interaction between patient and therapist. The transferred aspect is used to identify and reexperience

TABLE 16.8-1
Features of Short-Term Psychoanalytic Approaches

Name	Treatment Duration (No. of Sessions)	Specific Time Limit	Indications	Notes
Brief psychotherapy (Malan)	20-40	Yes	Patients with a focal life problem who respond to trial interpretations	Significant personality changes in suitable patients
Short-term dynamic psychotherapy (Davanloo)	15-30	No	Oedipal problems; neurotic problems where the focus is loss; obsessional and phobic neuroses; long-standing, characterological problems without a single focus	Highly confrontational, recommended for resistant patients; not recommended for patients with significant dependency or separation problems
Short-term anxiety provoking psychotherapy (Sifneos)	12-15	No	Oedipal triangular interpersonal problems	Avoids regression into pregenital characterological issues; change attributed to interpretation of Oedipal issues
Time-limited dynamic psychotherapy (Strupp)	<25	Yes	Avoidant, dependent, compulsive, and passive-aggressive personality disorders associated with depression, anxiety, and resentment	Focus on interpersonal themes, use of transference in a here-and-now way, not genetically
Supportive-expressive treatment (Luborsky)	12-25	Yes	Broad range of problems from mild situational maladjustments to borderline psychotic	Techniques flexible so that a wide range of patients can benefit from treatment

problems and patterns that developed in important relationships early in life and have been re-created in current important relationships. Transference is considered to be the key to all psychoanalytic approaches. The various treatments differ in how they deal with transference, although most relate patterns of therapist-patient interactions to current interpersonal situations. The development of a transference neurosis in which there is a regression into early childhood relationships is usually discouraged in those short-term therapies.

The short-term treatments depart in other ways from classic psychoanalytic practice. All involve active participation by the therapist and discourage free-association techniques. In general, they identify and emphasize a single focal issue. That issue, usually an interpersonal problem, is selected, and both the patient and therapist agree to deal primarily with the one problem. That focus is considered dynamic because it is used as a link with core conflicts arising from early life. The current conflict becomes a microcosm for the patient's earlier, more substantial, and long-lasting conflicts.

Active collaboration between patient and therapist involves the establishment of a working alliance. The therapist seeks to convey interest in the patient's problems, respect, and warmth, and attempts to elucidate explanations from the patient regarding behavior and feelings in addition to using interpretations.

Most short-term psychoanalytic approaches discourage regression, principally because emergence of such material as pregenital characterological issues often leads to a significant therapeutic impass that may not be resolved in a short period of time.

Identification of suitable patients for the short-term psychoanalytic therapies is given preeminence by all proponents. Patient selection criteria are similar, although there are some differences among the therapies. The patients selected should be intelligent; be capable of introspection; be able to see a connection among thoughts, feelings, and behavior; have a strong motivation for change; and be flexible. Motivation can be tested by assessment of the patient's responsiveness to interpretations early in therapy. A capacity for meaningful human relationships must have been demonstrated at some time during life. Finally, the capacity to tolerate anxiety and frustration is required. Obviously, those criteria exclude a significant proportion of psychiatric patients, leaving only the most desirable, verbal therapy candidates. Nonetheless, the proponents of these therapies point out that, for such patients, serious personality problems can be addressed in a relatively short time.

STRATEGIES AND TECHNIQUES Among the specific techniques used in the short-term approaches are the active interpretation of the transference, the identification of and emphasis on the specific dynamic focus, the active collaboration between patient and therapist, and the discouragement of regression.

In the short-term approaches, the transference is actively developed and interpreted, often from the outset of therapy. That approach is illustrated in an excerpt from an initial session with Davanloo in which he immediately challenges a patient's passivity.

Therapist: How do you feel about talking to me about yourself?
Patient: I feel uncomfortable. I have never done this before, so I don't really, you know . . . I feel I don't really know how to answer some of your questions.
Therapist: Um-hum. But have you noticed that in your relationship here with me you are passive, and I am the one who has to question you repeatedly?
Patient: No.
Therapist: Um-hum. What do you think about this? Is this the way it is with other people, or is it only here with me? . . . This passivity, lack of spontaneity.

Another vignette illustrates the interpretation of the transference relationship.

Patient: Since we talked about it last week, I've been noticing how much I try to impress people at work.
Therapist: Can you describe any of those times from last week?
Patient: Well, when I went to lunch with a colleague, I was continually telling him about all my latest accomplishments in an attempt to impress him. It's sort of how I feel in here sometimes.
Therapist: So sometimes when we're talking you find yourself thinking about how I feel about you, and whether I am impressed with you?
Patient: Yes.
Therapist: Why do you suppose that matters to you?
Patient: I guess because I want you to like me.
Therapist: Do you remember when you first had this feeling with another person?
Patient: Yes. I remember I felt this way when I talked to my father. He was always putting me down when I talked. I remember how I was constantly trying to impress him with the things I did like playing sports and bringing home good grades, but nothing I ever did seemed to be good enough for him.
Therapist: It is interesting that you are doing the same things with me to impress me that didn't work with your father.

In his manual, Strupp describes a married woman in her 30s who sought treatment for recurrent depressive episodes. The

Alkermes, Ex. 1060

woman's manner in the interview was aloof and curt, which led the therapist to want to discuss facts rather than elicit feelings. When this inclination was pointed out to her, the patient responded that she could not imagine that anything she said could be of interest to anyone, and acted in this way to protect herself from being hurt. The dynamic focus then became an exploration of her expectation that she was of no interest to anyone. A link was subsequently made with the patient's childhood, during which her parents seemed to prefer her sisters to her.

Sifneos gives an example of a patient who became angry and demanding about making up a canceled session. Instead of encouraging associations to childhood orality and dependency the therapist confronted the patient's maladaptive and self-destructive current behavior and encouraged the patient to request an extra session rather than being angry and withdrawn.

EFFICACY Eleven studies of brief psychodynamic psychotherapy in the treatment of depression have been reported in the past 15 years. Most included the psychodynamic treatments as controls, not as the experimental groups. In one study dynamic therapy was reported to have a better outcome than a waiting list control. In four studies the outcome for dynamic psychotherapy was found to be no different than that for cognitive therapy, behavior therapy, or pharmacotherapy. In one study psychodynamic therapy was less efficacious than combined pharmacotherapy and cognitive therapy; in three studies it was less efficacious than behavior therapy and cognitive therapy. All studies were published prior to 1988 (most were considerably earlier).

INTERPERSONAL THERAPY

THEORETICAL CONCEPTS Interpersonal therapy (IPT) was developed by Gerald Klerman and Myrna Weissman as part of their extensive research on the nature and treatment of depression over the past two decades. The theoretical basis of IPT includes the work of Adolf Meyer and Harry Stack Sullivan. In contrast with the predominantly intrapsychic orientation of classic psychoanalysis and Emil Kraepelin's biomedical model, Meyer's psychobiological approach emphasizes the interaction between the individual and the psychosocial environment over the patient's entire life course. The patient's current interpersonal experiences and attempts to adapt to environmental change and stress are seen as critical factors in psychiatric illness. Sullivan's interpersonal theory, which views interactions between people as the focus for study and treatment in psychiatry, draws heavily from the social sciences, including anthropology and sociology. A second major influence comes from John Bowlby's studies of attachment. These studies demonstrate the importance of attachment and social bonding to human functioning and the connection between disruption of these bonds and vulnerability to depression.

IPT conceptualizes depression from a medical model: depression is something that happens to the person that requires treatment. The depressed person is allowed to assume the "sick role" and is not blamed for the affliction any more than someone would be blamed for having cancer, heart disease, or pneumonia. The issue of attribution of blame is important. Many other approaches view depression as something the patient has brought on and must end by his or her own efforts.

The IPT approach to depression involves three interacting components: symptom formation, social and interpersonal experiences, and enduring personality patterns. Medication may be recommended for symptom reduction; psychotherapy focuses on improving the patient's interpersonal functioning. Although the causes of depression may vary with regard to a person's biological vulnerability, personality predispositions, or psychosocial precipitants, depression always occurs in a psychosocial and interpersonal context. Depression can predispose a patient to interpersonal problems, or interpersonal problems can precipitate depression. An interpersonal focus in the treatment process is thus presumed as essential for recovery.

GOALS IPT sets two therapeutic goals. The first is to reduce the patient's depressive symptoms and improve self-esteem. The second is to help the patient develop more effective strategies for dealing with current social and interpersonal relations. As a short-term psychotherapy, IPT does not attempt to restructure the patient's personality. IPT does, however, recognize the importance of early developmental experiences and assumes that historical conflicts are manifested in current relationships.

GENERAL CONSIDERATIONS IPT, a short-term psychotherapy, normally consisting of 12 to 16 weekly sessions, was developed specifically to treat nonbipolar, nonpsychotic ambulatory patients suffering depressive disorders. It is characterized by an active approach on the part of the therapist and by an emphasis on current issues and social functioning in the life of the patient. Intrapsychic phenomena such as defense mechanisms or internal conflicts are not addressed. Discrete behaviors such as lack of assertiveness, social skills, or distorted thinking may be addressed, but only in the context of their meaning or effect on interpersonal relationships.

STRATEGIES AND TECHNIQUES

General strategies For goal 1, reduction of symptoms, an educational approach is used. The patient is told about the clinical syndrome of depression, including its components and course. The therapist reviews the symptoms with the patient, gives a sense of optimism and hope, and emphasizes that depression is a common disorder with a good prognosis. Pharmacotherapy may be considered for symptom reduction if appropriate.

For goal 2, IPT defines four major problem areas commonly presented by depressed patients: grief, interpersonal role disputes, role transitions, and interpersonal deficits (Table 16.8-2). Associated therapeutic goals and recommended treatment strategies are outlined for each.

The choice of specific IPT strategies and techniques depends on the problem area defined as most salient for the patient. The four areas are not mutually exclusive, and patients may have multiple problems in more than one area; however, only one or two current interpersonal problems are selected for focus in order to set realistic goals and productive treatment strategies.

Cases of abnormal grief may involve delayed or distorted mourning, or both. The following example is cited in the IPT manual. A 68-year-old woman became depressed following the death of her husband, who had suffered a long course of physical and mental deterioration that resulted in considerable constraints and isolation on the part of the patient. Her symptoms included pervasive sadness and preoccupation with feelings of guilt and hopelessness. The first aim of treatment was to help the patient successfully mourn the loss, as the mourning process had been blocked by anger. The second aim was to help her to reestablish interests and relationships to substitute for what she had lost.

Interpersonal issues in a troublesome and conflicted marriage may include role disputes or role transitions. The choice between the two problem areas depends on whether the patient believes that the marriage is salvageable and whether the patient wants to stay in the marriage. If the patient decides to leave the marriage and the problem area is defined as role transition, the therapist will attempt to help the patient make that transition. That goal may include working on identifying

TABLE 16.8-2
Focal Problem Areas of Interpersonal Therapy

Problem Areas	Definition	General Goals and Strategies
Grief	Abnormal grief reactions occur because of failure to go through normal mourning following the death of a person important to the patient	Facilitate the mourning process; help reestablish interests and relationships to substitute for the loss
Interpersonal role disputes	Nonreciprocal expectations are occurring in patient's relationships with others	Help patient identify the dispute, guide in choices as to plans of action, encourage modification of maladaptive communication patterns, encourage reassessment of expectations
Role transitions	Feeling of inability to cope with change in life role (may be experienced as threatening to self-esteem, sense of identity, or both)	Help patient regard role in a more positive and less restrictive manner, restore self-esteem by helping patient develop sense of mastery with regard to demands of new role
Interpersonal deficits	History of inadequate or unsustaining interpersonal relationships	Reduce patient's social isolation by focusing on past relationships and relationship with therapist and by helping patient form new relationships

new sources of emotional support, overcoming irrational fears and regarding the new role more positively, and helping the patient master the demands of the new role. Alternatively, if the problem area is defined as a role dispute, the treatment strategies will include identifying the dispute and working toward its resolution, improving communication patterns, examining appropriateness of expectations, outlining various options, and deciding on a plan of action.

The interpersonal deficit problem area is appropriate for patients who are socially isolated or who have a sufficient number of relationships but feel unable to enjoy them. Interpersonal deficits may exist in patients who are chronically depressed and experience chronically impaired interpersonal functioning. Problems with social isolation may be long-standing or temporary; for each, treatment strategies aim to reduce social isolation. In the absence of current relationships discussion of positive and negative features of past relationships may be used as a model for the development of new relationships. Treatment may also focus on the relationship between therapist and patient.

An example of an interpersonal deficit cited by the IPT manual is as follows:

> A 22-year-old unmarried man became severely depressed one month after the breakup of a three-year relationship with his girlfriend. The patient, a part-time student employed as a cook, lived with his mother, who had stopped working after being hospitalized for physical problems, and subsequently, he had become depressed. Discussion of the patient's current relationship revealed that he felt close to no one except to his mother.
>
> The patient's history revealed inadequate social relationships and lack of interpersonal skills. Treatment focused on past significant relationships and on conflicts over his relationship with his mother. The patient-therapist relationship provided a direct source of information about the patient's style of relating to others, and that information was used to modify maladaptive interpersonal patterns and improve his ability to form relationships with others.

Specific techniques The specific techniques used in IPT may be applied to any of the four interpersonal problem areas. In the general order of their use in the course of treatment, they are (1) exploratory techniques, (2) encouragement of affect, (3) clarification, (4) communication analysis, (5) use of therapeutic relationship, and (6) behavior change techniques (Table 16.8-3).

TABLE 16.8-3
Interpersonal Therapy Techniques

Techniques	Definition
Exploratory techniques	Collect (by directive or nondirective methods) information about the patient's symptoms and problems
Encouragement of affect	Help patient recognize and accept painful affects, help patient use and manage affects positively in interpersonal relationships, encourage expression of suppressed affect
Clarification	Restructure and feed back patient's communications
Communication analysis	Identify maladaptive communication patterns, help patient communicate more effectively
Use of therapeutic relationship	Examine patient's feelings and behaviors in therapeutic relationship as model of patient's interactions in other relationships
Behavior change	Use to help patient solve simple life problems, teach patient to consider range of options for solving problems, use role playing to explore and understand patient's relationship with others and train patient in new ways of interacting with others

EFFICACY The efficacy of IPT has been tested in two large controlled studies. The first involved four groups (approximately 25 outpatients) treated by IPT alone, IPT plus amitriptyline (Elavil), amitriptyline alone, and a nonscheduled treatment comparison group. All active treatment groups, including that using IPT alone, were significantly more effective at reducing depressive symptoms than nonscheduled treatment; the combination of IPT and amitriptyline proved most effective. In addition, the IPT conditions had much lower dropout rates than did those without IPT.

In the second study, the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program, 250 outpatients with major depressive disorder were randomly assigned to one of four 16-week treatment conditions: IPT, cognitive-behavioral therapy, imipramine (Tofranil) with clinical management (IMI-CM), and placebo with clinical management (PLA-CM). In this study all four treatment conditions significantly reduced depressive symptoms. For severely depressed patients IPT was significantly more effective than PLA-CM in achieving remission of symptoms at 16 weeks. IMI-CM, however, tended to have the best outcome, particularly for patients with impairment in functioning. Imipramine was more rapid in its effects, with significantly better outcome than all other conditions at 12 weeks.

BEHAVIORAL APPROACHES

THEORETICAL CONCEPTS Although there are a number of behavioral approaches to depression, each with somewhat different theoretical assumptions and specific treatment methods, they have a common source in the work of B. F. Skinner, who incorporated the principles of classical and operant conditioning in an empirical analysis of behavior. Skinner's research provides the basic framework, methodology, and assumptions for the current behavioral theories and their clinical applications. Application of that model to complex human behavior led some theorists to expand the framework. For

example, social learning theory includes cognitive phenomena, such as emphasizing the role of subjective expectations and value in reinforcement. Although interested in the role of cognition, behavioral theorists assume that cognitions follow the same laws of learning as do more observable behavioral events and, while related, do not determine behavior in a causal sense. This assumption distinguishes behavioral approaches from the cognitive-behavioral approach described later. Despite some differences in focus, behavior therapies are commonly characterized by an emphasis on (1) the links between an observable or operationally definable behavior and the conditions that control or determine it and (2) the role of rewards or reinforcement as determinants of behavior and behavioral change.

The application of the behavioral approach to depression first occurred in 1965 with an analysis of depression by Charles B. Ferster, who proposed that depression is caused by a person's loss of positive reinforcement (for example, through separation, death, or sudden environmental change), which results in reduction of the entire behavioral repertoire, depressed behavior, and dysphoric feelings. That concept of depression is central to all behavioral approaches. A change in the rate of reinforcement is believed to be a key factor in the origin and maintenance of depression (through lack of available reinforcers or when the available reinforcers are not contingent on the person's behavior) and also in its reversal. Ferster also proposed that a social skills deficit—characterized by difficulty in obtaining social reinforcement—might increase a person's difficultly in coping with the loss of the usual supply of reinforcement.

GOALS The goals of the behavior therapies are to increase the frequency of the patient's positively reinforcing interactions with the environment and to decrease the number of negative interactions. Some behavioral treatments aim also at improving social skills. Alteration of personal behavior is believed to be the most effective way to change the associated depressed thoughts and feelings.

GENERAL CONSIDERATIONS Several behavior therapies devised to treat depression are characterized by overlapping behavioral and cognitive intervention strategies. One extensively studied approach was developed by Peter Lewinsohn on the basis of social learning theory. In addition to the individual-based social learning approach, Lewinsohn developed a "Coping with Depression Course" designed to deliver the specific behavioral strategies in a group format. The focus of Lewinsohn's approach, whether in individual or group format, is on increasing pleasant activities and interactions with the environment. A second prominent behavioral approach, based on a self-control model of behavior, was developed by Lynn Rehm to treat depression. Key components of this approach include techniques designed to correct deficits in the patient's ability to realistically and productively self-monitor, self-evaluate, and self-reinforce. A third approach focuses on the training of social skills in parents to increase positive social interactions and reinforcements (Table 16.8-4). These therapies share certain assumptions and strategies:

1. The treatment program is highly structured and generally short term.
2. The principle of reinforcement is seen as the key element in depression.
3. Changing behavior is considered to be the most effective way to alleviate depression.
4. The focus is on the articulation and attainment of specific goals.

Some behavioral treatments combine a variety of behavioral techniques and tailor the techniques to the individual needs of

TABLE 16.8-4
Behavioral Approaches to Depression

Treatment Approach	Basic Approach and Strategies	Tactics
Self-control therapy (Rehm)	Self-monitoring—gain control over and increase positive activities Self-evaluation—learn to set realistic goals; learn to make more accurate attributions regarding causes of successes and failures Self-reinforcement—learn to increase and maintain level of positive activities	Monitor mood Schedule pleasurable activities Set realistic goals and operational subgoals Schedule activities related to goals and monitor progress Learn to make correct self-attributions Construct individualized self-reinforcement programs to increase and maintain level of positive activities
Social learning therapy (Lewinsohn)	Initial two-week diagnostic phase leading to behavioral diagnosis Treatment designed to increase activity level and enhance social skills	Home observation Daily monitoring of mood and activity Increased participation in pleasant events Environmental interventions (environmental shifts, change consequences of certain behaviors) Assertion training through modeling and rehearsal Set goals for increasing social activities Relaxation training Time management Cognitive techniques (including thought interruption, worrying time, disputing irrational thoughts, noticing accomplishments, and positive self-rewarding thoughts)
Social skills training (Michel Hersen, Alan S. Bellack)	Skills training—patient is taught positive assertion, negative assertion, and conversational skills Social perception training—patient learns to attend to relevant context and cues of interpersonal interactions Practice—newly learned responses are carried out in the natural environment Self-evaluation and self-reinforcement—patient is trained to evaluate responses more positively and to provide self-reinforcement	Didactic instruction Modeling, guided practice of skills Role playing Homework assignments Monitoring and recording of homework performance by patient Patient's evaluation of role-playing responses with letter grade; therapist's correction of inappropriately low responses; therapist's modeling of positive self-statement

Alkermes, Ex. 1060

each patient. Normally, there are core ingredients in conjunction with a number of optional techniques.

STRATEGIES AND TECHNIQUES Although the major behavioral approaches to depression vary in their focus and emphasis in treatment and in the frequency of use of specific techniques, the following eight strategies are commonly used. Detailed manuals specify treatment regimes for most of these approaches.

Maintain records Recording mood and activities, both positive and negative, is essential to most behavioral therapies. Patients may also monitor the immediate and long-term consequences of specific behavior.

Increase general activity level, particularly pleasant events On the basis of the daily mood and activity recordings, the therapist encourages the patients to increase their participation in those activities rated as most pleasant by demonstrating a relationship between increased pleasant activities and lower levels of depression.

Decrease or manage unpleasant events From the daily ratings, negative interactions or situations that trigger feelings of depression are identified. Patients learn to avoid and decrease unpleasant events when possible. Patients are also taught to manage their reactions to negative events by learning to substitute more positive thoughts, to prepare for unpleasant events, and to prepare for failure.

Develop new self-reinforcement patterns Patients learn to reward themselves or to increase goal-related activities with material rewards or activities.

Enhance social skills Deficits in social skills and interaction patterns may be addressed through assertiveness training, modeling, and role playing with feedback and rehearsal or by providing graduated performance assignments to promote rewarding social interaction and to decrease social avoidance. A combination of approaches can be used. Group therapy sessions may be used to improve communication skills or to resolve specific interpersonal problems.

Relaxation training Relaxation techniques may aid in achievement of other goals, such as increasing social interaction, reducing the aversiveness of unpleasant situations, or producing a mood state incompatible with depression. Patients are taught relaxation of the major muscle groups; they are encouraged to practice relaxation twice a day and are instructed to keep a written log of relaxation activity.

Time management Training patients to plan ahead and make preparations necessary to participate in pleasant events (for example, obtaining a baby-sitter) is part of time management. An effort is made to work out an appropriate balance between activities that the patients want to do and activities they feel they have to do.

Cognitive skills training Cognitive skills training is generally geared toward decreasing negative thinking and increasing positive thinking. Patients are taught to monitor their thinking and to discriminate between positive and negative thoughts, necessary and unnecessary thoughts, and constructive and destructive thoughts. Specific techniques include thought-stopping, disputing irrational thoughts, and correcting errors in attribution regarding causes of successes and failures.

EFFICACY Behavior therapy has been tested in a number of studies of depressed subjects. Eight published studies involve random assignment and either a waiting list or nonspecific treatment group as control. Behavior therapy methods significantly reduced depressive symptoms in three quarters of the studies.

COGNITIVE-BEHAVIORAL THERAPY

THEORETICAL CONCEPTS Cognitive-behavioral therapy stems from four major previous theories: psychoanalytic theory, phenomenological philosophy, cognitive psychology, and behavioral psychology. One salient common feature is the recognition of the importance of the subjectiveness of conscious experience (one's perceptual experience of reality rather than the objective reality); another is the recognition of the emotional consequences of irrational beliefs and thoughts.

Aaron Beck, the originator of cognitive-behavioral therapy, developed a comprehensive, structured theory of depression. According to this theory, depression is associated with negative thought patterns, specific distorted schemas, and cognitive errors or faulty information processing (Table 16.8-5). Such cognitive dysfunctions form the core of depression while affective and physical changes and other associated features of depression are its consequences.

Cognitive theory conceptualizes depression as involving negative cognitions regarding the cognitive triad (ideas of oneself, the world, and one's future). The self is perceived as being defective, inadequate, deprived, worthless, and undesirable. The world appears as a negative, demanding, and defeating place, and one expects failure and punishment, continued hardship, suffering, deprivation, and failure in the future. Underlying the negative conditions are stable cognitive structures, called schemas, that include core beliefs or assumptions through which one interprets experience. Schemas associated with depression are analogous to viewing the world through dark glasses (for example, the core belief that one is unlovable). Cognitive errors, or systematic errors in thinking, allow the persistence of negative schemas despite contradictory evidence. A cognitive error frequently associated with depression is dichotomous thinking, the tendency to view one's experiences as black or white without shades of gray, or to believe that people

TABLE 16.8-5
Elements of Cognitive Theory

Element	Definition
Cognitive triad	Beliefs about oneself, the world, the future
Schemas	Ways of organizing and interpreting experiences
Cognitive distortions	
Arbitrary inference	Drawing a specific conclusion without sufficient evidence
Specific abstraction	Focus on a single detail while ignoring other more important aspects of an experience
Overgeneralization	Forming conclusions based on too little and too narrow experience
Magnification and minimization	Over- or undervaluing the significance of a particular event
Personalization	Tendency to self-reference to external events without a basis
Absolutist, dichotomous thinking	Tendency to place experience into all-or-none categories

are either all bad or all good. Symptoms of depression follow from the cognitive error. For example, apathy and low energy are results of the individual's expectation of failure in all areas. Similarly, a paralysis of will stems from the individual's pessimism and feelings of hopelessness.

GOALS The goal of cognitive-behavioral therapy is to change the way a person thinks and, subsequently, to alleviate the depressive syndrome and prevent its recurrence. This is accomplished by helping the patient (1) identify and test negative cognitions; (2) develop alternative, more flexible schemas; and (3) rehearse both new cognitive and new behavioral responses.

GENERAL CONSIDERATIONS Cognitive-behavioral therapy is a short-term, structured therapy that involves active collaboration between the patient and the therapist toward achieving set goals. It is oriented toward current problems and their resolution. Therapy is usually conducted on an individual basis, although group techniques have been developed and tested. Cognitive-behavioral therapy may be used in conjunction with pharmacotherapy.

STRATEGIES AND TECHNIQUES As with other psychotherapies, the attributes of the therapist are fundamental to successful cognitive-behavioral therapy. Therapists must be empathatic, able to understand the life experience of each patient, and capable of being genuine and honest with themselves and their patients. Therapists also must be able to relate skillfully to patients in their own experiential world in an interactive way. As a highly structured therapeutic approach, cognitive-behavioral therapy involves setting the agenda at the beginning of each session, assigning homework to be performed between sessions, and teaching specific new skills. The active collaboration between the therapist and the patient provides a genuine sense of teamwork.

Cognitive-behavioral therapy has three basic components: didactic aspects, cognitive techniques, and behavioral techniques (Table 16.8-6).

Didactic aspects The didactic aspects include explaining to the patient the nature of the cognitive triad, schemas, and faulty logic. The therapist informs the patient that they will formulate hypotheses together and will test them over the course of treatment. The therapist presents a full explanation of the relationship between depression and thinking, affect, and behavior, as well as the rationale for all aspects of the treatment. This contrasts with the more psychoanalytically oriented therapies in which very little explanation is involved.

TABLE 16.8-6
Components of Cognitive Behavioral Therapy

Didactic issues
Learning rationale and strategy of the therapy
Cognitive techniques
Eliciting automatic thoughts
Testing automatic thoughts
Identifying maladaptive underlying assumptions
Analyzing validity of maladaptive assumptions
Behavioral techniques
Scheduling activities
Mastery and pleasure
Graded task assignment
Cognitive rehearsal
Self-reliance training
Role playing
Diversion techniques

Cognitive techniques The cognitive approach has four strategies: eliciting automatic thoughts, testing automatic thoughts, identifying maladaptive underlying assumptions, and testing the validity of maladaptive assumptions.

ELICITING AUTOMATIC THOUGHTS Automatic thoughts are cognitions that intervene between external events and the individual's emotional reaction to the event. For example, a person invited to go bowling may think, negatively, "everyone is going to laugh at me when they see how badly I bowl," before he actually bowls with this group of people. Another example is when a person thinks "he doesn't like me" if someone passes the person in the hall without saying hello.

TESTING AUTOMATIC THOUGHTS The therapist, acting as a teacher, helps the patient test the validity of the automatic thought. The goal is to encourage the patient to formulate alternative possible interpretations and reject inaccurate or exaggerated automatic thoughts, after carefully examining them. For example, patients often set unrealistic expectations for themselves, then blame themselves when they are unable to live up to these expectations. The case of a 32-year-old depressed computer programmer with self-denigrating thoughts about his ability to complete homework assignments illustrates this point.

Patient: I don't know what's been wrong with me this week. I just don't seem to be as interested in doing my homework assignments. I don't know if I'm ever going to get better.
Therapist: Can you think of a specific time this week that you had problems doing homework because of disinterest?
Patient: Yes, on Thursday I tried to do my relaxation exercises, but I eventually gave up.
Therapist: Can you tell me what you were thinking at the time?
Patient: Well, I started doing my breathing, but I couldn't calm my thoughts and stop thinking about other things, like the instructions in the manual said. Then I started thinking about how long I've been working on this and how I should know how to do it by now.
Therapist: And how long have you been working on the breathing technique?
Patient: Uh, one week.
Therapist: Let's review the evidence that supports your statement that you should be performing this exercise with no problems at this time.

In this example, when the patient and therapist carefully reviewed the situation, it became apparent that the patient's expectation that he should be able to perform this exercise perfectly after one week of practice was unreasonable. On consideration that the ability to breathe and maintain calm thoughts is a skill that normally takes many weeks to perfect, the patient realized that his belief about his inability to learn was distorted and incorrect.

Generating alternative explanations is another technique used to undermine inaccurate and distorted automatic thoughts.

A 29-year-old secretary with a two-year history of depression reported that she frequently experienced feelings of sadness and hurt at work because of the curt and gruff manner in which her boss interacted with her. The automatic thought that she reported following one interaction with her boss—in which he stated "I wish things around here ran smoother"—was "He doesn't like me. He doesn't think I'm doing a good job." The therapist helped the patient generate a list of other interpretations of her employer's statement and behavior including the possibility that he interacted with all people this way, that he was a generally unhappy person, that he did not like his job and was allowing his unhappiness about his work situation to influence how he interacted with the patient, and that he was having personal problems that were preoccupying him and causing him to be unhappy at work and inattentive to the manner in which he interacted with his employees.

IDENTIFYING MALADAPTIVE ASSUMPTIONS As the patient and therapist continue to identify automatic thoughts, patterns usu-

ally become apparent, representing underlying rules or maladaptive general assumptions that guide the patient's life. Examples of such rules include, "To be happy, I must be perfect" or "If everyone doesn't like me, I'm not lovable." Such rules inevitably lead to disappointment, to failure, and subsequently to depression.

ANALYZING MALADAPTIVE ASSUMPTIONS Similar to testing the validity of automatic thoughts is testing the accuracy of maladaptive assumptions. One particularly effective technique is for the therapist to ask the patient to defend the validity of an assumption.

Patient: I guess I believe that I should always work up to my potential.
Therapist: Why is that?
Patient: Otherwise I would be wasting time.
Therapist: What is the long-range goal in working up to your potential?
Patient: I've never really thought about that. I've just assumed that I should.
Therapist: Are there any positive things you give up by always having to work up to your potential?
Patient: I suppose it makes it hard to relax or take a vacation.
Therapist: What about living up to your potential to enjoy yourself and relax? Is that important at all?
Patient: I've never really thought of it that way.
Therapist: Maybe we can work on giving yourself permission not to work up to your potential at all times.

In this example, the therapist is helping the patient recognize how maladaptive it is to strive to work up to one's potential at all times.

Behavioral techniques Behavioral techniques are used conjointly with cognitive techniques to test and change maladaptive or inaccurate cognitions in order to help patients understand the inaccuracy of their cognitive assumptions and to learn new strategies and ways of dealing with issues. A repertoire of behavioral techniques are utilized in cognitive-behavioral therapy.

1. Among the first things done is to schedule activities on an hourly basis. The patient keeps a record of these activities and reviews it with the therapist.
2. Patients are asked to rate the amount of mastery of and pleasure derived from those activities; they are often surprised at how much more mastery and pleasure they gain from the activities than they had otherwise believed.
3. To simplify the situation and allow for mini-accomplishments, tasks are often subdivided into subtasks, as in graded task assignments, to demonstrate to patients that they can succeed.
4. Cognitive rehearsal involves having the patient imagine the various steps involved in meeting and mastering a challenge and rehearsing the various aspects of it.
5. Self-reliance training involves encouraging patients to become more self-reliant, by doing such simple things as making their own beds, doing their own shopping, or preparing their own meals, rather than relying on other people.
6. Role playing is a particularly powerful and useful technique used to elicit automatic thoughts and learn new behaviors.
7. Diversion techniques are useful in helping patients get through particularly difficult times by means of physical activity, social contact, work, play, or visual imagery.

The techniques used are highly structured and goal oriented and require active collaboration between the therapist and the patient. Emphasis is on identifying maladaptive, inaccurate cognitions in various forms, seeking alternative explanations, and learning new behaviors to reverse the affective and drive disturbances and other associated features of depression and, it is hoped, help prevent their recurrence.

EFFICACY Cognitive therapy has been studied extensively in the treatment of outpatients with major depressive disorder. Of 34 such reports nine included a pill placebo, waiting list, or nonspecific treatment as a control group. In most studies, cognitive-behavioral therapy was superior to the control group in reducing depressive symptoms. The one notable exception is the NIMH Treatment of Depression Collaborative Research Program (TDCRP), in which cognitive-behavioral therapy did not differ significantly from the placebo clinical management condition (see prior section on IPT). Compared with pharmacotherapy alone, cognitive-behavioral therapy was found to be superior in two studies conducted in the 1970s. In three more recent studies, including the TDCRP, there were no differences in efficacy between antidepressant medication and cognitive-behavioral therapy. In six studies that compared cognitive-behavioral therapy with that therapy plus pharmacotherapy, five found no differences between the two outcomes and one found that the combined treatment was superior to cognitive-behavioral therapy alone.

In summary, cognitive-behavioral therapy has been shown to be an effective treatment for many outpatients with major depressive disorder. It is particularly effective among mild to moderately depressed patients and may be less effective than pharmacotherapy among more severely depressed patients.

DISCUSSION

Several issues influence the choice of treatment for depression, the duration of treatment, and whether or not to use more than one treatment modality at the same time. These issues include the phase of illness, diagnosis and patient characteristics, the presence of chronicity and dysthymia, the presence of bipolar disorder, and use of combined pharmacological-psychotherapeutic treatments.

PHASE OF ILLNESS Nearly all studies of psychosocial treatments for depression have focused on the acute phase of treatment; that is, they have tested the performance of a specific psychotherapeutic approach in resolving depressive symptoms within 12 to 16 weeks. These studies have generated considerable evidence of the efficacy of IPT, cognitive-behavioral therapy, and behavioral therapy in certain groups of patients during this time period. An episode of depression, however, does not necessarily end when the acute symptoms have abated. In fact, a relapse of symptoms may occur if treatment is discontinued too soon after the initial control of symptoms. That happens presumably because the acute treatment (especially pharmacotherapy) has not cured the illness, but rather ameliorated or reduced the symptoms temporarily. This situation is analogous to the effect of insulin on diabetes mellitus. Depression is now recognized as a recurrent, and often chronic, illness. Therefore, withdrawal of the treatment may result in return of illness.

An important consequence of our recognition of the long-term nature of the illness is the need for treatment beyond the acute phase and into the continuation and maintenance phases. Continuation treatment is the ongoing treatment from the point of clinical remission to the point at which spontaneous remission is expected to occur in untreated patients (that is, to the putative true end of an untreated episode). For depression, the continuation phase in pharmacological treatments generally

Alkermes, Ex. 1060

lasts approximately six to nine months following acute treatment. Maintenance treatment is longer-term, and is intended to prevent future depressive episodes or decrease their intensity. The model for psychotherapeutic treatments, in contrast, is that the strategies and techniques change maladaptive patterns that are linked to depression, and thus should result in a reduced risk for future episodes or symptoms of depression.

There are two sets of questions with regard to continuance of short-term psychotherapies over the long term. First, do the therapies confer a prophylactic effect in the future? Second, is it helpful to continue the treatments following a positive response into the continuation and maintenance phases?

Prophylactic effect of short-term therapies Follow-up studies of patients responding positively to acute treatment for depression have attempted to address the question of whether treatment offers long-term prophylactic effects.

For IPT, one study reported no differences in relapse or recurrence at a one-year follow-up between patients in a 16-week clinical trial treated with IPT, amitriptyline, amitriptyline plus IPT, and nonscheduled treatment in terms of relapse or recurrence. However, patients treated with IPT did have better social functioning at the one-year reevaluation point.

The majority of the follow-up studies have examined relapse rates in patients successfully treated with cognitive therapy or antidepressant medication. Those studies have shown a clear pattern of lower relapse rates for patients treated with cognitive-behavioral therapy than for those treated with short-term pharmacotherapy. However, the naturalistic designs of these studies precludes conclusions regarding the reasons for the differences found (that is, whether the results represent some enduring effects of the cognitive therapy, or to differences in risk for relapse among patients who respond to drugs versus psychotherapy).

Despite the positive findings for short-term psychotherapy in terms of decrease in symptoms and the possibly lower relapse rates with use of cognitive-behavioral therapy, the success of these approaches, as a well as of pharmacological treatments, depends on how outcome is defined. When outcome is defined optimally as complete remission of symptoms and maintenance of symptom-free remission for an extended period following treatment, it becomes clear that 12 to 16 weeks of treatment (with psychotherapy or pharmacotherapy) is insufficient for the majority of patients who present with major depression. This is illustrated by findings from the NIMH TDCRP, which reported the proportion of all patients starting treatment who achieved this stringently defined outcome. Complete remission (at least 8 weeks without symptoms) at the end of treatment and maintenance of remission for 18 months following treatment was achieved by 30 percent of patients after cognitive-behavioral therapy, by 26 percent after IPT, by 19 percent after imipramine with clinical management, and by 20 percent after placebo with clinical management. Considering outcome in this optimal way highlights the need for longer periods of treatment for full recovery as well as the need for continuation and maintenance treatments.

Treatment during the continuation phase Does continuing treatment after successive resolution of symptoms help to prevent relapses and recurrences? This clinically important question has received relatively little attention, but has been addressed in one study on cognitive-behavioral therapy. Forty-two subjects who received acute therapy were followed for one year. At three months into the follow-up study, half of those who responded to treatment were given additional treatment ("booster" sessions) until completion of the study while the other half of the responder group was given no additional treatment. The authors found no difference in relapse rates or depressive symptoms between the two groups at one year, suggesting that continued treatment with cognitive therapy after successful resolution of symptoms does not improve outcome. It must be emphasized that this is a single study and further research is needed. There are no studies on the use of IPT or behavior therapy in the continuation phase.

Treatment during the maintenance phase Does therapy continued a year or more after successive treatment help to prevent the occurrence of new episodes? In a landmark study by Ellen Frank and colleagues, a group of 128 patients with recurrent major depressive disorder who had responded to a combined short-term and continuation treatment of imipramine and IPT were randomly assigned to different maintenance treatment groups. Those treated with IPT alone had a significantly lower relapse rate than those receiving placebos. However, those treated with imipramine, with or without IPT, did significantly better than the IPT without imipramine groups. This study strongly supports continued treatment, especially pharmacotherapy, over a long period in time of patients with a history of recurrent episodes of depression.

There is some evidence that, in patients with recurrent depression, long-term treatment is useful in delaying or preventing recurrences. However, the value of continuation and maintenance treatment with psychotherapy remains unresolved and awaits further research.

DIAGNOSIS AND PATIENT CHARACTERISTICS The psychotherapeutic treatment approaches described above were developed for use with outpatients with nonbipolar, nonpsychotic depression. They should generally not be used as a sole treatment for severely depressed inpatients or for patients with bipolar depression, although their use when combined with pharmacotherapy for such patients has begun to be evaluated.

Whether these treatment approaches should be used without medication for outpatients with major depressive disorder has been controversial. The general clinical belief is that antidepressants should be part of the treatment when patients are more severely depressed, or have endogenous depressions. Findings from the NIMH Treatment of Depression Collaborative Research Program have suggested that IPT may be effective for at least some of the more severely depressed outpatients, and thus may be a feasible treatment for such patients if an alternative to medication is needed or desired. Endogenous depression was not found to differentially predict outcome in this study. Findings from other studies regarding endogenous depression have been mixed, but most do not find that outpatients with endogenous depression (as defined by the Research Diagnostic Criteria) respond better to pharmacotherapy than to psychotherapy. Treatment for patients meeting criteria for melancholia, however, should typically include medication.

Other findings from the NIMH Treatment of Depression Collaborative Research Program regarding patient characteristics and treatment outcome included better outcomes with IPT for patients with less impairment in social functioning, and better outcome with cognitive-behavioral therapy and with imipramine for patients with less distortion in cognitions (dysfunctional attitudes). Other studies have also shown that high scores on measures of dysfunctional attitudes predict a poorer outcome in cognitive-behavioral therapy. Together, these findings suggest that patients may require a minimal level of proficiency in the area of functioning that the treatment targets in order to

benefit from the treatment (at least in the short term). That is an important question for future research.

Some patient characteristics have been found to be predictive of response across treatments in general. Longer duration of the current episode, and also the diagnosis of dysthymic disorder prior to the onset of the major depressive disorder (double depression) have been shown to predict a poorer response; higher expectations of improvement have been associated with a better outcome to different forms of treatment.

The beliefs and expectations of the patient regarding depression and treatment should also be considered. Some patients who consider depression to be a psychological disorder that should be amenable to psychotherapeutic approaches are resistant to using medication. Others consider their depression to be a biochemical disturbance that will require medication if it is to be corrected, and not psychotherapy. A good therapist may be able to modify such expectations when necessary, but a positive attitude toward treatment on the part of the patient may be significantly important to a successful outcome.

In general, the therapist should be cautious in making attributions about premorbid personality problems during the depressed phase. Many interpersonal and cognitive styles may appear different to the patient and the therapist after the acute phase of the disorder has been alleviated. Nonetheless, several studies have found that the presence of a personality disorder is associated with a slower or generally worse response to treatment. For depression, such patients are likely to need longer periods of treatment.

DYSTHYMIC DISORDER AND CHRONICITY Most of our knowledge on the treatment of depression comes from the study of patients with acute major depression, and we know far less about the treatment of chronic depression. This is unfortunate, given the prevalence of dysthymic disorder. Over 3 percent of adults in the United States suffer from dysthymic disorder during any six-month period, according to the Epidemiologic Catchment Area (ECA). In addition, approximately one third of psychiatric outpatients suffer from dysthymic disorder. Nearly one in five patients with a major depressive episode fails to recover and becomes chronically depressed.

The importance and potential usefulness of psychosocial treatments for such patients is demonstrated by (1) the notable morbidity and impairment of quality of life associated with dysthymic disorder, which has been shown to exceed that associated with most medical illnesses; (2) the fact that a substantial proportion of patients with dysthymic disorder either fail to respond to medication or cannot tolerate the side effects; and (3) with or without medication, the long-standing patterns of social withdrawal; lack of assertiveness; impairment in family, marital, and occupational functioning; and chronic pessimism and hopelessness associated with dysthymic disorder need to be addressed. When depression is severe, pharmacological treatments are encouraged to alleviate suffering and increase the ability of the person to engage in the therapy. There are no controlled studies of the effectiveness of this treatment approach; however two naturalistic follow-up studies have suggested that long-term analytic therapy can have long-term beneficial effects.

More recent developments in the treatment of dysthymic disorder include the modification of psychotherapeutic approaches specifically for the treatment of dysthymic disorder, as well as preliminary open trial studies investigating the effectiveness of the modified psychotherapies for dysthymic patients. The chronic interpersonal and social deficits associated with dysthymic disorder provide a strong rationale for the use of IPT with dysthymic patients, and a manual has recently been developed. Aspects of dysthymic disorder that distinguish it from acute depression, requiring modification of IPT, include the lack of an acute precipitant, the characterological features often associated with the presence of a chronic mood disorder (such as paucity of interpersonal relationships, lack of self-assertion, poor social skills), and the lack of euthymic memories. Given the typical absence of an acute precipitant in dysthymic disorder the choice of a focus of treatment becomes more difficult. While all of the four IPT problem areas do occur in dysthymic patients, their frequency as a primary focus differs from acute depression. Grief is rarely the primary focus, whereas interpersonal deficits more frequently are. The frequent absence of interpersonal relationships in the patient's life requires an increased focus on the therapeutic relationship, which is used as a model for other interpersonal interactions. Social isolation is addressed by encouraging occupational and social activities involving contact with others. Participation in activities are used to examine social behaviors, expectations, and desires.

When relationships do exist, they are often unsatisfactory, in light of the difficulty these individuals have in asserting themselves, expressing anger, or setting limits. IPT for these patients emphasizes exploration of what the patient desires from the relationships and of what options are available to alter the relationships. The patient is helped to begin to identify personal needs, to begin to assert them, and to set limits. The expression of anger is encouraged and supported. Preliminary support for the use of IPT for dysthymic disorder has been provided by a nonrandomized pilot study of 19 patients treated with IPT, desipramine (Norpramin), or both.

Another psychotherapeutic approach that has recently been developed specifically for the treatment of dysthymic disorder is the Cognitive-Behavioral Analysis System of Psychotherapy (C-BASP). The focus of this treatment approach is on problematic cognitive and behavioral patterns associated with dysthymic disorder. A situational analysis procedure that includes performance feedback is a central part of the approach. Patients are taught to evaluate the adequacy of their behavior in various situations, particularly those involving interactions with others, and to target and modify self-defeating behaviors. Beliefs of helplessness and absence of control are challenged by the experience of mastery in producing desired outcomes. The treatment is conducted in stages, with the requirement that the patient demonstrates mastery at each stage before moving on to the next. The duration of treatment thus differs for different patients, but is typically short-term (less than six months). Ten dysthymic patients treated in a naturalistic study were reported as having a successful outcome, with nine of these remaining in remission for dysthymic disorder at follow-up of two years or more.

Despite these important recent advances, it is clear that controlled studies are needed to more clearly determine the nature, degree, and duration of benefits derived from these psychotherapeutic approaches in the treatment of dysthymic disorder and chronic depression.

PSYCHOSOCIAL TREATMENT OF BIPOLAR DISORDER

The clinical and research literature on major depressive disorder is replete with both psychotherapeutic and psychopharmacologic approaches. In sharp contrast is the literature on treatment of bipolar disorder, which focuses almost exclusively on psychopharmacology and, specifically, on the use of lithium carbonate (Eskalith) as the overwhelming treatment of choice. The introduction of lithium has influenced the diagnostic system, the clinical practice, and the therapeutic outcome of patients

Alkermes, Ex. 1060

with bipolar disorder for 20 years. It is as close to a wonder drug as has been experienced in psychiatry.

However, lithium is not the absolute cure for bipolar disorders. About one third of patients either do not respond or only partially respond to lithium. Even for those who respond fully, many serious social, occupational, familial, and marital problems often remain. Psychological and behavioral problems are frequently associated with bipolar disorder, and alcohol and substance abuse, violence, and suicide can result from inadequate treatment. Psychotherapeutic interventions may be particularly relevant for these problems.

Another major rationale for adjunctive psychotherapy is to improve medication compliance. An estimated 20 to 50 percent of patients with bipolar disorder who are on a prescribed medication regimen either do not fully comply with their doctor's instructions or discontinue treatment altogether. Physical side effects, as well as the psychological unwillingness to take pills, adds to the noncompliance problem. Lithium noncompliance or discontinuation increases relapse. Psychotherapy combined with lithium may result in increased medication compliance and a better clinical outcome.

Adjunctive psychotherapy can also be used to provide important educational benefits. It can help the patient and family members to learn to identify early warnings of an impending mania so that more rapid interventions can occur, and to identify problems that exacerbate or precipitate episodes.

Treatments Little has been written about the psychotherapeutic treatment of bipolar disorders since the report of 12 cases by Mabel Blake Cohen in 1954. In recent years, however, several approaches have been developed for psychosocial and psychotherapeutic treatment of bipolar disorder. Unfortunately there is no empirical research published on the efficacy of these approaches as yet, but they are sufficiently important that a description of each is included here.

These approaches, designed as short-term, outpatient interventions, were inspired by the well-documented success of similar programs used with schizophrenic patients.

Miklowitz and Goldstein The first treatment package, developed by David J. Miklowitz and Michael J. Goldstein, is based on behavioral family management techniques. Based on the premise that the same family attributes thought to be important in predicting the course of schizophrenia are also associated with the course of bipolar disorders, the focus of the program is on educating the family about bipolar disorders and aiding in the development of communication and problem-solving skills. This approach (like all psychosocial approaches for bipolar disorders) is not intended to serve as a substitute for a traditional medication regimen but rather as adjunctive therapy. The program for patients recently discharged after an episode of hypermania includes 21 one-hour sessions conducted in the patient's home over a nine-month period. These sessions are divided into seven sessions dealing with family education, seven on communication skills training, and seven on problem-solving skills training.

In a pilot trial with nine patients, only one patient relapsed over the nine-month posthospitalization period during which treatment was implemented. In comparison, a 61 percent relapse rate was reported from a naturalistic outcome study using traditional medication regimens without family management.

Basco and Rush The second treatment package, developed by Monica R. Basco and A. John Rush, is designed around four goals: (1) to educate the patient regarding bipolar disorder; (2) to teach cognitive-behavioral skills for coping with the psychosocial stressors, as well as the cognitive and behavioral problems associated with manic and depressive symptoms; (3) to facilitate compliance with a prescribed medication regimen; and (4) to monitor the occurrence, severity, and course of manic and depressive symptoms. The protocol is divided into three phases corresponding with these goals. The first phase, consisting of one-hour sessions, once a week for five weeks, educates the patient about the causes, symptoms, and treatment of bipolar disorder. The second phase, which teaches cognitive-behavioral skills, consists of weekly sessions lasting approximately 75 to 90 minutes. The third phase—maintenance—provides an opportunity to monitor the patient's symptoms, reinforce skills, and facilitate medication compliance. This final phase is held in one-hour sessions no less than once a month and no more than four times a month.

The treatment protocol is highly structured. Each session covers one component of the treatment package, and includes (1) a summary of the intention and direction of the session, (2) background information about the intervention technique, (3) goals of the session, (4) a step-by-step description of the intervention procedures, and (5) a homework assignment to reinforce what was learned in the session or to prepare for the next session.

COMBINED PHARMACOLOGIC-PSYCHOTHERAPEUTIC TREATMENT It is common practice for many psychiatrists to provide combined pharmacotherapy and psychotherapy for their patients with nonbipolar depression. The prevailing clinical opinion is that antidepressant medication is most effective for depressive symptoms, especially such vegetative symptoms as sleep disturbance, appetite disturbance, and loss of interest, whereas psychotherapy targets and improves marital and family relationships, social functioning, and occupational performance. However, the empirical evidence supporting this belief is minimal.

Is combined treatment more efficacious than either treatment modality alone? And does combined therapy treat a broader range of outcomes than either modality alone? Research addressing these questions is fraught with methodologic difficulties. Nonetheless, nearly 15 studies on combined therapy have been completed over the past 20 years. In general they have not found substantial increased efficacy of combined treatment over either treatment alone.

Seven studies of combined treatment with cognitive therapy have been conducted. These have all involved tricyclic antidepressants. Several compared the combined treatment with both medication alone and psychotherapy alone. Others compared the combined treatment against only one modality. Overall the results are inconsistent and do not demonstrate the superiority of combined treatment over that using a single modality. Three studies of combined behavior therapy and tricyclic antidepressants versus either medication alone or psychotherapy alone found no differences between the combined and single-modality treatments. Two studies of combined IPT and amitriptyline are also inconsistent, with one showing a trend for better outcome for the combined treatment, and the other showing no differences between outcomes of combined and single-modality treatments. As noted, Frank and colleagues, studying combined imipramine and maintenance IPT in patients with severe recurrent depression, found that imipramine with or without maintenance IPT was clearly superior to all other treatment modalities in the maintenance phase of the illness. However, in addition to studying a different phase of treatment, this study addressed a different sample (patients with highly recur-

rent disease who were responsive to combined treatment) than the other studies of combined treatment.

SUGGESTED CROSS-REFERENCES

Information regarding related aspects of mood disorders are discussed further in Chapter 16. Chapter 31 on psychotherapies also outlines behavioral and cognitive therapies and other psychosocial treatments. Psychiatric treatments of adolescents are reviewed in Chapter 46 and treatments in the elderly population are included in Section 49.7. Application of psychosocial treatment to schizophrenia may be found in Section 14.9.

REFERENCES

Basco M R, Rush A J: Cognitive-behavioral therapy for bipolar disorder. In *Cognitive Behavioral Treatment of Manic Depressive Disorder*. Guilford, New York, 1995.

Beck A T, Rush A J, Shaw B F, Emery G: *Cognitive Therapy of Depression*. Guilford, New York, 1979.

Bellack A S, Hersen M, Himmelhoch J S: Social skills training for depression: A treatment manual. Cat Sel Doc Psychol *10:* 2156, 1980.

Bemporad J R: Long-term analytic treatment of depression. In *Handbook of Depression*, Beckham E E, Leber W R, editors, p. 82. Dorsey, Homewood, IL: 1985.

Crits-Christoph P: The efficacy of brief dynamic psychotherapy: A meta-analysis. Am J Psychiatry *149:* 151, 1992.

Conte H R, Karasu T B: A review of treatment studies of minor depression: 1980–1991. Am J Psychother *46:* 58, 1992.

Davanloo H: *Short-Term Dynamic Psychotherapy*, vol 1. Aronson, New York, 1980.

Elkin I, Parloff M B, Hadley S W, et al: NIMH treatment of depression collaborative research program: Background and research plan. Arch Gen Psychiatry *42:* 305, 1985.

*Elkin I, Shea M T, Watkins J T, Imber S D, Sotsky S M, Collins J F, Glass D R, Pilkonis P A, Leber W R, Docherty J P, Fiester S J, Parloff M B: National Institute of Mental Health Treatment of Depression Collaborative Research Program: General effectiveness of treatments. Arch Gen Psychiatry *46:* 971, 1989.

Evans, M D, Hollon S D, DeRubeis R J, Piasecki J M, Grove W M, Garvey M J, Tuason V B: Differential relapse following cognitive therapy and pharmacotherapy for depression. Arch Gen Psychiatry *49:* 802, 1992.

Ferster C B: A functional analysis of depression. Am Psychol *10:* 857, 1973.

*Frank E, Kupfer D J, Perel J M, Cornes C, Jarrett D B, Mallinger A G, Thase M E, McEachran A B, Grochocinski V J: Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry *47:* 1093, 1990.

*Frank E, Kupfer D J, Wagner E F, McEachran A B, Cornes C: Efficacy of interpersonal psychotherapy as a maintenance treatment of recurrent depression. Arch Gen Psychiatry *48:* 1053, 1991. [Contributing factors (published erratum) Arch Gen Psychiatry *49:* 401, 1992.]

Gaylin W, editor: *The Meaning of Despair*. Aronson, New York, 1968.

Jarrett R B: Psychosocial aspects of depression and the role of psychotherapy. J Clin Psychiatry *51:* 26, 1990.

Jarrett R B, Rush A J: Cognitive therapy for depression. *Directions Clin Psychol*, 1995.

Kavanagh D J, Wilson P H: Prediction of outcome with group cognitive therapy for depression. Behav Res Ther *27:* 333, 1989.

Kazdin A E: Comparative outcome studies of psychotherapy: Methodological issues and strategies. J Consult Clin Psychol *54:* 95, 1986.

Keitner G I, Miller I W: Combined psychopharmacological and psychosocial treatment of depression. RI Med J *76:* 415, 1993.

Klerman G L: Drugs and psychotherapy. In *Handbook of Psychotherapy and Behavior Change: An Empirical Analysis*, Garfield, A Bergin, editors. Wiley, New York, 1986.

Klerman G L, Dimascio A, Weissman M, Prusoff B, Paykel E S: Treatment of depression by drugs and psychotherapy. Am J Psychiatry *131:* 186, 1974.

Klerman G L, Weissman M W, Rounsaville B J, Chevron E S: *Interpersonal Psychotherapy of Depression*. Basic Books, New York, 1984.

Lewinsohn P M, Antonuccio D, Steinmetz J L, Teri L: *The Coping With Depression Course: A Psychoeducational Intervention for Unipolar Depression*. Castalia, Eugene, OR, 1984.

Lewinsohn P M, Sullivan J M, Grosscup S J: Changing reinforcing events: An approach to the treatment of depression. Psychother Theor, Res Pract *17*, Fall 1980.

Luborsky L: *Principles of Psychoanalytic Psychotherapy—A Manual for Supportive-Expressive Treatment*. Basic Books, New York, 1984.

Malan D H: *Individual Psychotherapy and the Science of Psychodynamics*. Butterworth, London, 1979.

Markowitz J C, Klerman G L: *Manual for Interpersonal Therapy With Dysthymic Patients*. Payne Whitney Clinic, New York, 1991.

McCullough J P: Psychotherapy for dysthymia: A naturalistic study of ten patients. J Nerv Ment Dis *179:* 734, 1991.

Miklowitz D, Goldstein M, Neuchterlein K, Snyder K, Mintz J: Family factors and the course of bipolar affective disorder. Arch Gen Psychiatry *45:* 225, 1988.

Moreau D, Mufson L, Weissman M M, Klerman G L: Interpersonal psychotherapy for adolescent depression: Description of modification and preliminary application. J Am Acad Child Adolesc Psychiatry *30:* 642, 1991.

Rehm L P: Self-management therapy for depression. Adv Behav Res Ther *6:* 83, 1984.

Rush A J, Beck A T, Kovacs M: Comparative efficacy of cognitive therapy and pharmacotherapy in the treatment of depressed outpatients. Cogn Ther Res *I*: 17, 1977.

Rush A J, editor: *Short-Term Psychotherapies for Depression*. Guilford, New York, 1982.

*Rush A J: Short-term psychotherapeutic approaches to depression. *The Medical Psychotherapist*, 1995.

Shea M T, Elkin I, Hirschfeld, R M A: Psychotherapeutic treatment of depression. In *Review of Psychiatry*, R E Frances, A J Hales, editors. American Psychiatric Press, Washington, DC, 1988.

*Shea M T, Elkin I, Imber S D, Sotsky S M, Watkins J T, Collins J F, Pilkonis P A, Beckham E, Glass D R, Dolan R T, Parloff M B: Course of depressive symptoms over follow-up: Findings from the National Institute of Mental Health treatment of depression collaborative research program. Arch Gen Psychiatry *49:* 789, 1992.

Sifneos P E: *Short-Term Dynamic Psychotherapy: Evaluation and Technique*, ed 2. Plenum, New York, 1987.

Simons A D, Murphy G E, Levine F L, et al: Cognitive therapy and pharmacotherapy for depression: Sustained improvement over one year. Arch Gen Psychiatry *43:* 43, 1986.

Sotsky S M, Glass D R, Shea M T, Pilkonis P A, Collins J F, Elkin I, Watkins J T, Imber S D, Leber W R, Moyer J, Oliveri M E: Patient predictors of response to psychotherapy and pharmacology: Findings in the NIMH Treatment of Depression Collaborative Research Program. Am J Psychiatry *148:* 997, 1991.

Strupp H, Binder J L: *Psychotherapy in a New Key: A Guide to Time-Limited Dynamic Psychotherapy*. Basic Books, New York, 1984.

Thase M E: Long-term treatments of recurrent depressive disorders. J Clin Psychiatry: 32, 1992.

Watkins J T, Leber W R, Imber S D, Collins J F, Elkin I, Pilkonis P A, Sotsky S M, Shea M T, Glass D R: Temporal course of change of depression. J Consult Clin Psychol *61:* 858, 1993.

Weissman M M, Jarrett R B, Rush A J: Psychotherapy and its relevance to the pharmacotherapy of major depression: A decade later (1976–1985). In *Psychopharmacology: The Third Generation of Progress*, H Meltzer, editor, p 1059. Raven, New York, 1987.

Weissman M M, Klerman G L, Prusoff B A, Sholomskas D, Padian N: Depressed outpatients: Results one year after treatment with drugs and/or interpersonal therapy. Arch Gen Psychiatry *38:* 1981.

Weissman M M, Prusoff B A, Dimascio A, Neu C, Goklaney M, Klerman G L: The efficacy of drugs and psychotherapy in the treatment of acute depressive episodes. Am J Psychiatry *136:* 555, 1979.

Wells K B, Stewart A, Hays, R D: The functioning and well-being of depressed patients: Results from the Medical Outcomes study. JAMA *262:* 914, 1989.